

Official Title: A Phase Ib/II, Open-Label, Multicenter, Randomized Umbrella Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatment Combinations in Patients with Metastatic Non-Small Cell Lung Cancer (Morpheus-Lung)

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PROTOCOL

TITLE: A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER (MORPHEUS-LUNG)

PROTOCOL NUMBER: BO39610

VERSION NUMBER: 21

TEST PRODUCTS: Atezolizumab (RO5541267), Evolocumab, Linagliptin, Docetaxel, Sacituzumab Govitecan, Bevacizumab (RO4876646), Tiragolumab (RO7092284), Camonsertib (RO7616992), and XL092

STUDY PHASE: Ib/II

REGULATORY AGENCY IDENTIFIER NUMBERS: IND Number: 134,543
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PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	Date Final	Country	Version	Date Final
21	See electronic date stamp on final page of this document.	—	—	—
19	23 March 2023	France	20	11 September 2023
17	18 March 2022	France	18	18 March 2022
13	23 March 2021	France	16	15 July 2021
		Spain	15	12 April 2021
		France	14	6 May 2021
10	25 August 2020	Spain	12	22 December 2020
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PROTOCOL AMENDMENT, VERSION 21: RATIONALE

Protocol BO39610 has primarily been amended to add two new treatment arms: atezolizumab plus bevacizumab plus camonsertib (Atezo+Bev+Camon) and atezolizumab plus bevacizumab plus tiragolumab (Atezo+Bev+Tira). Additionally, risks and management guidelines for atezolizumab have been updated to align with the latest Atezolizumab Investigator's Brochure (Version 20). Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The following treatment arms for Stage 1 have been removed because all patients in these arms have completed treatment and more than 80% of them have completed survival follow-up (Sections 1.3, 3.1.1, 4.1.1.3, 4.1.2, 4.3.1, 5.3.5.12, and 5.7; Tables 1, 4, 5, 6, and 7; Figure 3; Appendices A16-4.1.3, A16-6, and 23; and previous Section 4.1.2.7)
 - Atezolizumab plus ipatasertib (previously Appendix 11)
 - Atezolizumab plus docetaxel for Stage 1 (Appendix 16; still remains open for Stage 2)
- The following treatment arms have been added (Sections 3.1.1, 3.1.3, 4.1.2.6, and 4.1.2.7; Figure 3; and Tables 4 and 7):
 - Atezo+Bev+Camon (new Appendix 14)
 - Atezo+Bev+Tira (new Appendix 15)
- Table 4 has been updated to indicate that if clinical activity is observed in an experimental arm during the preliminary phase, approximately 25–40 additional patients may be enrolled in that arm during the expansion phase (Section 3.1.1).
- The approximate total number of patients enrolled during Stage 1 has been changed based on the approximate enrollment of patients in the new treatment arms (Sections 3.1.1 and 6.1).
- The eligibility criteria have been updated to reflect the removal of old treatment arms and the inclusion of new treatment arms (Section 4.1).
- For patients in Cohort 2, the inclusion criteria have been adapted to allow only patients with a secondary (acquired) checkpoint inhibitor resistance to be enrolled (Section 4.1.1.1).
- The following exclusion criteria for Stage 1 have been clarified:
 - Patients with prior treatment with TROP-2 targeting agents are excluded but only if an anti-TROP-2 agent-containing arm is open for enrollment (Section 4.1.2.1).
 - For patients in Cohort 2, prior treatment with anti-TIGIT antibodies has been removed to account for potential new treatment options in the first-line setting of non-small cell lung cancer (Section 4.1.2.1).

- An exclusion criterion for the atezolizumab in combination with tiragolumab and XL092 (Atezo+Tira+XL092) and the atezolizumab in combination with camonsertib (Atezo+Camon) arms has been amended to delete the 10-day window for screening ECGs prior to first dose of study treatment because the 10 days are not mandatory, thus allowing more flexibility for study sites to perform the assessment (Sections 4.1.2.4 and 4.1.2.5; Appendix 2, Table 1).
- To avoid inconsistencies, the exclusion criterion regarding last systemic treatment line for the Atezo+Camon arm has been updated to exclude last systemic treatment line other than platinum-containing therapy and/or progressive disease as best response to platinum-containing therapy (Section 4.1.2.5).
- It has been made explicit that expedited safety reports will be notified to regulatory authorities through applicable systems such as EudraVigilance (Section 5.7).
- Fasting chemistry panel, fasting lipid panel, and hemoglobin A_{1c} have been removed from Stage 1 screening assessments because treatment arms requiring these assessment have been closed for enrollment (Appendix 2).
- The ECG screening assessment for Cohort 1 (atezolizumab in combination with tiragolumab [Atezo+Tira] and Atezo+Tira+XL092 arms) has been revised to be a triplicate ECG to minimize cardiac risks (Appendix 2, Table 1).
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- The adverse event management guidelines for atezolizumab and tiragolumab have been updated to align with the Atezolizumab Investigator's Brochure, Version 20 (Appendix 6, Table A7-4).
- The tiragolumab drug product information has been aligned throughout the protocol (Appendices A7-4.1.1.2 and A8-4.1.1.2).
- The language regarding administration of study treatment initiation has been aligned throughout the protocol to read, "It is recommended that treatment be initiated no later than 7 days after randomization; however, the first dose of study treatment should not occur within 3 days after a core biopsy or other surgical procedure" (Appendices A7-4.1.2, A8-4.1.2, A9-4.1.2, A12-4.1.2, A13-4.1.2, and A18-4.1.2).
- The language for administration of first and subsequent atezolizumab infusions has been made consistent throughout the protocol (Table A7-2, Table A8-2, Table A9-4, Table A12-2, Table A13-2, Table A16-2, Table A17-2, Table A18-3, and Table A19-3).
- The language for administration of first and subsequent tiragolumab infusions has been made consistent throughout the protocol (Table A7-3 and Table A8-3).
- The sections on permitted local therapies in Appendices 7 and 8 have been adapted to align with the wording used in other appendices (Appendices A7-4.2.1 and A8-4.2.1).

- It has been clarified that metamizole is prohibited in treating atezolizumab-associated infusion-related reactions because of its potential for causing agranulocytosis (Appendices A7-4.2.1, A8-4.2.1, A12-4.2.1, A16-4.2.1, A18-4.2.1, and A19-4.2.1).
- For safety reasons, it has been clarified that the list of cautionary medications for each study treatment is not necessarily comprehensive and that the investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered. The Medical Monitor is available to advise as needed (Appendices A7-4.2.2.1, A8-4.2.2.1, A9-4.2.2.1, A12-4.2.2.1, A13-4.2.2.1, A16-4.2.2.1, and A17-4.2.2.1).
- It has been corrected that live, attenuated vaccines are prohibited for 90 days after the final dose of tiragolumab (Appendix A7-4.2.3).
- For contraception requirements for Atezo+Tira arm, the requirement for women to refrain from donating eggs has been removed because neither atezolizumab nor tiragolumab are expected to be genotoxic (Appendix A7-4.3).
- List of assessments for Days 8 and 15 of Cycle 1 have been removed from the schedule of activities for Atezo+Tira arm for alignment with most up to data study protocols of this combination (Appendix A7-6, Table A7-5).
- Information about clinical studies with XL092 has been updated to align with XL092 Investigator's Brochure, Version 5 (Appendices A8-2.6 and A8-3.3).
- For permitted therapy for Atezo+Tira+XL092 arm, palliative radiotherapy has been revised to state that treatment with XL092 should be held prior to scheduled radiation therapy (Appendix A8-4.2.1).
- It has been clarified that sufficient monitoring of hematologic parameters should be in place for continued study treatment during palliative radiotherapy to minimize safety risks (Appendices A8-4.2.1, A8-4.2.3, A9-4.2.1, A12-4.2.1, A17-4.2.1, A18-4.2.1, and A19-4.2.1).
- The section on concomitant herbal therapies for the Atezo+Tira+XL092 arm has been updated to clarify that concomitant medications with CYP-sensitive substrates must be used with caution, as XL092 might alter systemic exposure of these substrates (Appendix A8-4.2.2.2).
- Contraception requirements for the Atezo+Tira+XL092 arm have been updated to state that women of childbearing potential must supplement hormonal contraceptive methods with use of a barrier method because of potential drug-drug interactions. It has also been clarified that women must refrain from donating eggs during the treatment period and for 5 months after the final dose of atezolizumab, for 90 days after the final dose of tiragolumab, and for 186 days after the final dose of XL092 (Appendix A8-4.3).
- Associated risks for XL092 have been revised to include edema to align with XL092 Investigator's Brochure, Version 5 (Appendix A8-5.1.3.11).

- The guidelines for management of patients who experience adverse events in the Atezo+Tira+XL092 arm have been updated to include information on management of anemia, neutropenia, thrombocytopenia, and leukopenia to align with XL092 Investigator's Brochure, Version 5 (Appendix A8-5.1.6.3).
- Viral serology assessments have been deleted from schedule of activities for Atezo+Tira+XL092 arm because they are not applicable (Appendix A8-6).
- C-reactive protein assessments have been deleted from schedule of activities for Atezo+Tira+XL092 arm because they are not indicated (Appendix A8-6).
- Urinalysis and coagulation assessments have been added to schedule of activities for Atezo+Tira+XL092 arm for treatment discontinuation visit because they had been missing (Appendix A8-6).
- The wording around ECG assessments for the Atezo+Tira+XL092 arm has been adapted to provide more clarity (Appendix A8-6).
- Contraception requirements for the atezolizumab in combination with sacituzumab govitecan (Atezo+SG) arm have been clarified to state that women of childbearing potential must refrain from donating eggs during the treatment period and for 5 months after the final dose of atezolizumab and for 6 months after the final dose of sacituzumab govitecan (Appendix A12-4.3).
- The following information for Atezo+Camon arm has been updated to align with Camonsertib Investigator's Brochure, Version 5:
 - Information about clinical studies with camonsertib (Appendix A13-2.5.1)
 - Prohibited therapy (Appendix A13-4.2.3)
 - Safety plan (Appendix A13-5.1)
 - a) Based on totality of safety data, the Sponsor may recommend to lower the dose or change the schedule of camonsertib as needed (Appendices A13-3.2 and A13.5.1).
 - b) Decreased appetite is no longer considered a risk associated with camonsertib (Appendices A13-5.1.2 and A13-5.1.2.2).
 - c) No reproductive or teratogenicity studies in animals have been conducted with camonsertib (Appendix A13-5.1.2.3).
 - The management guidelines for adverse events associated with camonsertib (Appendix A13-5.1.4.3, Table A13-5)
- The following updates have been made to the schedule of activities for Atezo+Camon arm to correct inaccuracies (Appendix A13-6):
 - Chemistry assessment has been deleted for Day 8 of Cycles 2 and 3.
 - Coagulation assessment has been added on Day 1 of Cycles 2 and 3.
 - Review of concomitant medications has been added on Days 8 and 15 of Cycle 1 and Days 1 and 8 of Cycles 2 and 3.
 - Atezolizumab administration has been added on Day 1 of Cycles 2 and 3.

- Dispensing of camonsertib has been added on Day 1 of Cycles 2 and 3.
- It has been clarified that triplicate ECG should be performed at baseline prior to receiving study treatment on Day 1 of Cycle 1.
- It has been clarified that at a particular timepoint (if applicable) the mean QTcF is >500 ms and/or >60 ms longer than the baseline value, another ECG must be recorded more than 30 minutes apart to confirm the QTcF prolongation.
- It has been clarified that additional unscheduled ECGs may be either triplicate or single ECGs.
- It has been clarified that if clinically indicated, hematological testing may be required more frequently beyond Cycle 1.
- The safety plan for the Atezo+Camon arm was modified as follows: The stopping rule for non-hematological treatment related Grade 3 or 4 adverse events was modified to state that the study drug is to be put on hold if the toxicity does not resolve to Grade 1 or better (or baseline) within 2 weeks; instead of Grade 2 or better (Appendix A13-5.1).
- Background on bevacizumab has been updated to state that atezolizumab plus bevacizumab has been approved as the first-line standard of care for patients with metastatic hepatocellular carcinoma (Appendices A18-1.2 and A19-1.2).
- It has been clarified that bevacizumab will be administered at least 5 minutes after completion of the atezolizumab infusion on Day 1 of each cycle (Appendices A18-4.1.2.1 and A19-4.1.2.1).
- Because osteonecrosis of the jaw has been reported in patients receiving bevacizumab, bisphosphonates has been added as cautionary therapy (Appendices A18-4.2.2.3 and A19-4.2.2.3).
- For contraception requirements for Atezo+Bev arm, the requirement for women to refrain from donating eggs has been removed because neither atezolizumab nor bevacizumab are expected to be genotoxic (Appendix A18-4.3).
- The management guidelines for Atezo+Bev have been updated to align with the Bevacizumab Investigator's Brochure (Appendix A18-5.1.4.3, Table A18-5).
- The management guidelines for Atezo+Bev+RTx have been updated to align with the Bevacizumab Investigator's Brochure (Appendix A19-5.1.6.3, Table A19-6).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in *italics*. This amendment represents cumulative changes to the original protocol.

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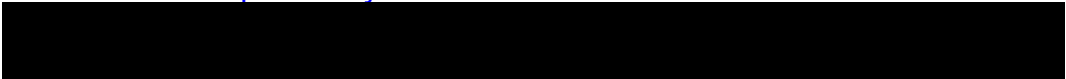
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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE: A PHASE Ib/II, OPEN-LABEL, MULTICENTER,
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SPONSOR: F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by Covance.

PROTOCOL SYNOPSIS

PROTOCOL TITLE: A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH METASTATIC NON–SMALL CELL LUNG CANCER (MORPHEUS-LUNG)

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NUMBERS: EU CT Number: 2023-504038-23-00
NCT Number: NCT03337698

STUDY RATIONALE

The purpose of this study is to evaluate the efficacy, safety, and pharmacokinetics of immunotherapy-based treatment combinations in patients with metastatic non–small cell lung cancer (NSCLC). This randomized Phase Ib/II umbrella study is designed to accelerate the development of cancer immunotherapy combinations by identifying early signals and establishing proof-of-concept clinical data in patients with NSCLC. Importantly, this study will assess the importance of simultaneously targeting multiple mechanisms of immune escape through immune cell priming and activation, tumor infiltration, and/or recognition of tumor cells for elimination in a population of patients with a high unmet clinical need.

OBJECTIVES AND ENDPOINTS

Table 1 Objectives and Corresponding Endpoints for Stage 1

Primary Efficacy Objective	Corresponding Endpoint
<ul style="list-style-type: none">• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	<ul style="list-style-type: none">• Objective response, defined as a complete response or partial response on two consecutive occasions ≥ 4 weeks apart during Stage 1, as determined by the investigator according to RECIST v1.1
Secondary Efficacy Objective	Corresponding Endpoints
<ul style="list-style-type: none">• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	<ul style="list-style-type: none">• PFS after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1• PFS at specific timepoints (e.g., 6 months)• OS after randomization, defined as the time from randomization to death from any cause• OS at specific timepoints (e.g., 6 months)• DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1• Disease control, defined as stable disease for ≥ 12 weeks or a complete or partial response, as determined by the investigator according to RECIST v1.1
Safety Objective	Corresponding Endpoints
<ul style="list-style-type: none">• To evaluate the safety of immunotherapy-based treatment combinations during Stage 1	<ul style="list-style-type: none">• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0• Change from baseline in vital signs and ECG parameters• Change from baseline in targeted clinical laboratory test results

ADA=anti-drug antibody; DOR=duration of response; eCRF=electronic Case Report Form; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1.

Table 2 Objectives and Corresponding Endpoints for Stage 2

Exploratory Efficacy Objective	Corresponding Endpoints
<ul style="list-style-type: none">• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 2	<ul style="list-style-type: none">• Objective response, defined as a complete response or partial response on two consecutive occasions ≥ 4 weeks apart during Stage 2, as determined by the investigator according to RECIST v1.1• PFS after initiation of Stage 2, defined as the time from initiation of Stage 2 to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1• DOR, defined as the time from the first occurrence of a documented objective response during Stage 2 to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1• Disease control, defined as stable disease for ≥ 12 weeks or a complete or partial response, as determined by the investigator according to RECIST v1.1
Safety Objective	Corresponding Endpoints
<ul style="list-style-type: none">• To evaluate the safety of immunotherapy-based treatment combinations during Stage 2	<ul style="list-style-type: none">• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0• Change from baseline in vital signs and ECG parameters• Change from baseline in targeted clinical laboratory test results

ADA=anti-drug antibody; DOR=duration of response; eCRF=electronic Case Report Form; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PFS=progression-free survival; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1.

OVERALL DESIGN AND STUDY POPULATION

This is a Phase Ib/II, open-label, multicenter, randomized, umbrella study in patients with metastatic NSCLC. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status). Two cohorts will be enrolled in parallel in this study: Cohort 1 will consist of patients with tumor PD-L1 expression (TPS or TCs $\geq 50\%$ or TC3, as determined by a documented local assessment using a health authority-approved PD-L1 immunohistochemistry assay), who have received no prior systemic therapy for metastatic NSCLC, and Cohort 2 will consist of patients who experienced disease progression during or following treatment with a platinum-containing regimen and a PD-L1/PD-1 checkpoint inhibitor, given in combination as one line of therapy or as two separate lines of therapy, regardless of PD-L1 expression. In each cohort, eligible patients will initially be assigned to one of several treatment arms (Stage 1). Patients who experience disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may be eligible to continue treatment with a different treatment regimen (Stage 2).

Because the treatment landscape for first-line metastatic NSCLC evolved since the initiation of this study, with new and highly effective treatment options being available in this setting, patient enrollment into Cohort 1 was suspended as of November 2018, and patients were no longer enrolled into Cohort 1. Patients already enrolled in Cohort 1 continued to be treated and monitored per protocol.

Several key aspects of the study design and study population are summarized below.

Table 3 Study Design and Study Population

Phase:	Phase Ib/II	Population Type:	Adult patients
Control Method:	Active comparator	Population Diagnosis or Condition:	Metastatic non–small cell lung cancer
Interventional Model:	Parallel	Population Age:	≥ 18 years
Test Compound{s):	Atezolizumab (RO5541267), Tiragolumab (RO7092284), Evolocumab, Linagliptin, Docetaxel, Sacituzumab Govitecan, Bevacizumab (RO4876646), Camonsertib (RO7616992), and XL092	Site Distribution:	Multi-site and multi-region
Active Comparator:	Atezolizumab (RO5541267) plus tiragolumab (RO7092284), Docetaxel	Study Intervention Assignment Method:	Randomization
Number of Arms:	11	Number of Participants to Be Enrolled:	Approximately 425–675

Stage 1

During Stage 1, patients in Cohort 1 will be randomly assigned to a comparator arm (atezolizumab [Atezo]+tiragolumab [Tira]) or an experimental arm consisting of atezolizumab in combination with tiragolumab and XL092 (Atezo+Tira+XL092) and patients in Cohort 2 will be randomly assigned to a control arm (docetaxel) or an experimental arm consisting of atezolizumab in combination with camonsertib (Atezo+Camo), *bevacizumab and camonsertib* (Atezo+Bev+Camo), *bevacizumab and tiragolumab* (Atezo+Bev+Tira), bevacizumab (Atezo+Bev), bevacizumab and radiotherapy (Atezo+Bev+RTx), sacituzumab govitecan (Atezo+SG), or evolocumab (Atezo+Evo).

Approximately 425–675 patients will be enrolled during Stage 1, excluding closed treatment arms and those that have already reported. Enrollment within the experimental arms will take place in two phases: a preliminary phase followed by an expansion phase.

The Sponsor may decide to delay or suspend enrollment within a given treatment arm.

The Sponsor may also decide to open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has qualified for the expansion phase.

Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion. Additional patients may be enrolled to ensure balance among treatment arms with respect to demographic and baseline characteristics, including potential predictive biomarkers, to enable further subgroup analyses. New experimental arms may be added during the study by amending the protocol.

Table 4 Stage 1 Treatment Regimens

Cohort (Enrollment Status)	Study Treatment	No. of Patients ^a	
		Preliminary Phase	Expansion Phase ^{b, c}
1 (enrolling ^d)	Atezo + Tira	Variable ^a	
	Atezo + Tira + XL092	40 ^e	25
2 (enrolling ^d)	Docetaxel	Variable ^a	
	Atezo + Evo	20 ^f	25
	Atezo + Bev	40 ^e	25–40
	Atezo + Bev + RTx	40 ^e	25–40
	Atezo + SG ^g	30 ^h	25
	Atezo + Camon	40 ^e	25–40
	<i>Atezo + Bev + Camon</i>	40 ^e	25–40
	<i>Atezo + Bev + Tira</i>	40 ^e	25–40

Atezo = atezolizumab; Bev = bevacizumab; *Camon* = camonsertib; Evo = evolocumab; PCSK9 = proprotein convertase subtilisin/kexin type 9; RTx = radiotherapy; SG = sacituzumab govitecan; Tira = tiragolumab; TROP-2 = trophoblast cell-surface antigen 2.

- ^a The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that no more than 50% of patients will be randomly allocated to a control arm.
- ^b If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25–40 additional patients may be enrolled in that arm during the expansion phase.
- ^c The Sponsor may open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase.
- ^d The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Thus, all listed experimental arms may not be open for enrollment at the same time.
- ^e Approximately 40 patients will be enrolled in the Atezo + XL092, the Atezo + Bev, the Atezo + Bev + RTx, the *Atezo + Bev + Tira*, the Atezo + Camon, and the *Atezo + Bev + Camon* arms.
- ^f Approximately 20 patients will be enrolled in the Atezo + Evo arm to ensure a sufficient number of patients with high PCSK9-expression (PCSK9-high) and low PCSK9 expression (PCSK9-low) to facilitate the evaluation of the benefit and risk in these subpopulations. Additional patients may be enrolled in the Atezo + Evo arm to ensure that at least 10 patients with high PCSK9 are included. No more than 30 patients will be enrolled in the Atezo + Evo arm in the preliminary phase.
- ^g This arm is closed and will be removed when the last patient discontinues from the study.
- ^h 30 patients will be enrolled in the Atezo + SG arm to ensure a sufficient number of patients with high, medium, and low TROP-2 expression to facilitate the evaluation of the benefit and risk of these subpopulations.

Stage 2

During Stage 1 in Cohort 2, patients who experience disease progression per RECIST v1.1, loss of clinical benefit as determined by the investigator (as described above), or unacceptable toxicity may be eligible to receive a different treatment combination during Stage 2, as outlined in Table 5, provided they meet the eligibility criteria and a Stage 2 arm is open for enrollment.

Patients in Cohort 2 who are eligible for more than one treatment arm will be assigned a treatment arm by the investigator.

Stage 2 treatment must begin within 3 months after a patient has experienced disease progression per RECIST v1.1 (docetaxel control arm), loss of clinical benefit (atezolizumab combination arms), or unacceptable toxicity and will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator. It is recommended that patients begin Stage 2 treatment as soon as possible.

Table 5 Stage 2 Treatment Regimens

Cohort (Enrollment Status)	Histologic Type	Study Treatment ^a
2	Non-squamous or squamous	Atezo + Docetaxel ^b
2 (not enrolling)		Atezo + Lina ^c

Atezo = atezolizumab; Lina = linagliptin.

^a The Sponsor may decide to delay or suspend enrollment within a given treatment arm.

^b Patients who are enrolled in the Docetaxel control arm are not eligible to receive this study treatment in Stage 2.

^c This arm is closed and will be removed when the last patient discontinues from the study.

The Sponsor may decide to discontinue enrollment in Stage 2 treatment arms on the basis of a review of safety data, preliminary efficacy data, and supportive information (e.g., biomarker research data), as appropriate.

STUDY TREATMENT

Table 6 Treatment Regimen for Atezo + Tira + XL092 Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none"> Atezolizumab 1200 mg IV on Day 1 of each cycle Tiragolumab 600 mg IV on Day 1 of each cycle XL092 100 mg PO QD

Atezo = atezolizumab; PO = by mouth, orally; QD = once a day; Tira = tiragolumab.

For management of drug related toxicities, the dose of XL092 can be reduced as outlined in Table 7.

Table 7 Suggested Dose Reductions for XL092

Drug	Initial Dose	First Dose Reduction	Second Dose Reduction
XL092	100 mg QD	60 mg QD	40 mg QD

QD = once a day.

Table 8 Treatment Regimen for Atezo + Evo Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	<ul style="list-style-type: none"> Atezolizumab 840 mg IV on Days 1 and 15 <i>of each cycle</i> Evolocumab 140 mg SC on Days 1 and 15 <i>of each cycle</i>

Atezo + Evo = atezolizumab plus evolocumab.

Table 9 Treatment Regimen for Atezo + SG Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none"> Sacituzumab govitecan 10 mg/kg by IV infusion on Days 1 and 8 of each cycle ^a Atezo 1200 mg IV on Day 1 of each cycle ^b

Atezo + SG = atezolizumab plus sacituzumab govitecan.

^a There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

^b The atezolizumab infusion should be initiated approximately 60 minutes following completion of the sacituzumab govitecan infusion.

For management of drug-related toxicities, the dose of sacituzumab govitecan can be reduced by 2.5 mg/kg (i.e., one dose level) up to two times, as outlined in Table 10.

Table 10 Suggested Dose Reductions for Sacituzumab Govitecan

	Initial Dose	First Dose Reduction	Second Dose Reduction
Sacituzumab govitecan	10 mg/kg	7.5 mg/kg	5 mg/kg

If further dose reduction is indicated for sacituzumab govitecan after two dose reductions, sacituzumab govitecan should be discontinued. After dose reduction, the dose of sacituzumab govitecan may not be escalated.

Table 11 Treatment Regimen for Atezo + Camon Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none"> Camonsertib [REDACTED] mg PO D1–3, D8–10; Q21D (<i>recommended starting dose/target dose</i>) Atezolizumab 1200 mg by IV infusion on Day 1 of each cycle

Atezo = atezolizumab; Camon = camonsertib; D = day; PO = by mouth, orally; Q21D = every 21 days.

For management of drug-related toxicities, the dose of camonsertib can be reduced by [REDACTED] mg (i.e., one dose level) one time, as outlined in Table 12.

Table 12 Suggested Dose Adjustment for Camonsertib

Dose Level	Dose
Recommended starting <i>dose/target dose</i>	[REDACTED] mg QD PO D1–3, D8–10; Q21D
First dose adjustment	[REDACTED] mg QD PO D1–3, D8–10; Q21D
Second dose adjustment	[REDACTED] mg QD PO D1–2, D8–9; Q21D

D = days; PO = orally, by mouth; QD = once a day; Q21D = every 21 days.

If further dose adjustment is indicated for camonsertib after two dose adjustments, camonsertib should be discontinued.

Table 13 Treatment Regimen for Atezo +Bev +Camon Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none"> • Camonsertib ■ mg PO D1–3, D8–10; Q21D for patients enrolled for the safety run-in period • Camonsertib ■ mg PO D1–3, D8–10; Q21D for patients enrolled after the safety run-in period • Atezolizumab 1200 mg by IV infusion on Day 1 of each cycle • Bevacizumab 15 mg/kg by IV infusion on Day 1 of each cycle

Atezo=atezolizumab; Bev =bevacizumab; Camon =camonsertib; D =day; PO =by mouth, orally; Q21D =every 21 days.

For management of drug-related toxicities, the dose of camonsertib can be reduced by ■ mg (i.e., one dose level) one time, as outlined in Table 14.

Table 14 Suggested Dose Adjustment for Camonsertib

Dose Level	Dose
Safety Run-In Period	
Initial Dose	
First dose adjustment	
Second dose adjustment	
Recommended target dose	
First dose adjustment	
Second dose adjustment	

D =days; PO =orally, by mouth; QD =once a day; Q21D =every 21 days.

Based on emerging data, the Sponsor may modify the study treatment (camonsertib and/or partner agent [s]) dose or schedule.

If further dose adjustment is indicated for camonsertib after two dose adjustments (where applicable), camonsertib should be discontinued.

Patients enrolled for the safety run-in period, receiving ■ mg of camonsertib QD PO D1–3, D8–10; Q21D, can also have their dose adjusted as per Table 14 or interrupted to manage specific adverse events as applicable.

Table 15 Treatment Regimen for Atezo +Bev +Tira Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none"> • Atezolizumab 1200 mg IV infusion on Day 1 of each cycle • Bevacizumab 15 mg/kg by IV infusion on Day 1 of each cycle ^a • Tiragolumab 600 mg by IV infusion on Day 1 of each cycle ^b

Atezo +Bev +Tira =atezolizumab plus bevacizumab plus tiragolumab;
IRR =infusion-related reaction.

^a On Day 1 of each cycle, bevacizumab will be administered at least 5 minutes after completion of the atezolizumab infusion.

^b [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED].

Table 16 Treatment Regimen for Atezo+Docetaxel Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none"> • Atezolizumab 1200 mg IV on Day 1 of each cycle • Docetaxel 75 mg/m² IV over 1 hour on Day 1 of each cycle

Atezo+Docetaxel=atezolizumab plus docetaxel.

The dose of docetaxel can be reduced to 55 mg/m² for management of drug-related toxicities. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m².

Table 17 Treatment Regimen for Atezo+Lina Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none"> • Atezolizumab 1200 mg IV on Day 1 of each cycle • Linagliptin 5 mg by mouth once daily

Atezo+Lina=atezolizumab plus linagliptin.

Table 18 Treatment Regimen for Atezo+Bev Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none"> • Atezolizumab 1200 mg IV infusion on Day 1 of each cycle • Bevacizumab 15 mg/kg by IV infusion on Day 1 of each cycle

Atezo+Bev=atezolizumab plus bevacizumab.

Table 19 Treatment Regimen for Atezo+Bev+RTx Arm

Radiotherapy	
Treatment Duration	Dose and Fractionation
Up to 21 days (± 5 days, including simulation, contouring, and planning)	8Gy \times 3
Systemic Therapy	
Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none"> Atezolizumab 1200 mg IV infusion on Day 1 of each cycle Bevacizumab 15 mg/kg by IV infusion on Day 1 of each cycle

Atezo+Bev+RTx=atezolizumab plus bevacizumab plus radiotherapy.

COMPARATORS

Table 20 Treatment Regimen for Atezo+Tira Arm (Comparator for Cohort 1)

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none"> Atezolizumab 1200 mg IV on Day 1 of each cycle Tiragolumab 600 mg IV on Day 1 of each cycle

Atezo=atezolizumab; Tira=tiragolumab.

Table 21 Treatment Regimen for Docetaxel Arm (Control for Cohort 2)

Cycle Length	Dose, Route, and Regimen
21 days	<ul style="list-style-type: none"> Docetaxel 75 mg/m² IV over 60 minutes on Day 1 of each cycle

The dose of docetaxel can be reduced to 55 mg/m² (e.g., for management of drug-related toxicities). If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose will not be escalated during subsequent administrations.

DOSE MODIFICATIONS

There will be no dose modifications for atezolizumab, tiragolumab, evolocumab, linagliptin, or bevacizumab in this study. All other dose modifications are described in the appropriate tables above.

DURATION OF PARTICIPATION

Participants will be treated until disease progression per RECIST v1.1, unacceptable toxicity, or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease), whichever occurs first. The total duration of study participation for each individual is expected to range from 1 day to approximately 3 to 4 years.

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Internal Monitoring Committee and Scientific Oversight Committee

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody, also known as anti-therapeutic antibody
ASTCT	American Society for Transplantation and Cellular Therapy
Atezo	atezolizumab
AUC	area under the concentration–time curve
<i>Bev</i>	<i>bevacizumab</i>
BP	blood pressure
<i>Camon</i>	<i>camonsertib</i>
CCOD	clinical cutoff date
CEA	carcinoembryonic antigen
CIT	cancer immunotherapy
Cobi	cobimetinib
COVID-19	coronavirus disease 2019
CrCL	creatinine clearance
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DL _{co}	diffusion capacity of the lung for carbon monoxide
DOR	duration of response
DPP-4	dipeptidyl peptidase-4
EBV	Epstein-Barr virus
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
Evo	evolocumab
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GI	gastrointestinal
<i>HbA_{1c}</i>	<i>hemoglobin A_{1c}</i>
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HeFH	heterozygous familial hypercholesterolemia
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio

Abbreviation	Definition
ICH	International Council for Harmonisation
IFN	Interferon
IHC	immunohistochemistry
<i>IL</i>	<i>interleukin</i>
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent-to-treat (<i>population</i>)
IxRS	interactive voice or web-based response system
LDL-C	LDL bound cholesterol
LDLR	LDL receptor
Lina	linagliptin
LMWH	low-molecular-weight heparin
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MBP	microprecipitated bulk powder
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
<i>nab</i>	<i>nanoparticle albumin-bound</i>
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE v4.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PC	Proprotein convertase
PCR	polymerase chain reaction
PCSK9	proprotein convertase subtilisin/kexin type 9
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
Q2W	every 2 weeks

Abbreviation	Definition
Q3W	every 3 weeks
Q4W	every 4 weeks
QD	once daily
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RET	rearranged during transfection
ROS1	c-ROS oncogene 1
RTx	radiotherapy
RVO	retinal vein occlusion
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBRT	stereotactic body radiotherapy
SOC	Scientific Oversight Committee
SG	sacituzumab govitecan
T3	triiodothyronine
T4	thyroxine
TC	tumor cell
TCR	T-cell receptor
<i>Tira</i>	<i>tiragolumab</i>
TNF	tumor necrosis factor
TPS	tumor proportion score
TROP-2	trophoblast cell-surface antigen 2
ULN	upper limit of normal
VCA	viral capsid antigen
WBRT	whole-brain radiotherapy
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON LUNG CANCER

Lung cancer remains the leading cause of cancer deaths worldwide; it is the most common cancer in both men and women and accounted for approximately 13% of all new cancers in 2008 (Jemal et al. 2011). In 2012, it was estimated that there were 313,000 new cases of lung cancer and 268,000 lung cancer deaths in Europe (GLOBOCAN 2012). In the United States, there were an estimated 221,200 new cases of lung cancer and 158,040 lung cancer deaths in 2015 (Siegel et al. 2015).

Non-small cell lung cancer (NSCLC) is the predominant subtype of lung cancer, accounting for approximately 85% of all cases (Howlader et al. 2015). NSCLC can be divided into two major histologic types: adenocarcinoma and squamous cell carcinoma (Travis et al. 2011). Adenocarcinoma histology accounts for more than half of all NSCLC, while squamous cell histology accounts for approximately 25% of NSCLC (Langer et al. 2010). There are recognized clinical differences in disease characteristics between adenocarcinoma and squamous NSCLC. First, squamous tumors commonly present in the central airways and typically remain localized in the bronchial epithelium (Hirsch et al. 2008), whereas non-squamous tumors are more commonly located in the lung parenchyma distal to the central airways. The remaining cases of NSCLC are represented by large cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and poorly differentiated histology.

Genetic changes that have prognostic and/or predictive significance in NSCLC include mutations in the *EGFR* gene, rearrangements in the *ALK* gene, and mutations in the *KRAS* gene. The rates of these mutations differ between squamous cell carcinoma and adenocarcinoma. For example, *EGFR* kinase domain mutations have been reported in 10%–40% of patients with adenocarcinoma NSCLC but are infrequently observed in squamous NSCLC (Herbst et al. 2008). Similarly, the *ALK* fusion oncogene, recognized as a driver of lung tumorigenesis, is observed in approximately 7% of patients with adenocarcinoma but is very rare in the squamous histology (Herbst et al. 2008; Langer et al. 2010). In addition, *KRAS* mutations are very rare in squamous NSCLC, while they can be observed in up to 30% of cases of adenocarcinoma NSCLC (Travis et al. 2011).

The overall 5-year survival rate for advanced disease is 2%–4%, depending on geographic location (Cetin et al. 2011). Poor prognostic factors for survival in patients with NSCLC include advanced-stage disease at the time of initial diagnosis, poor performance status, and history of unintentional weight loss. More than half of patients with NSCLC are diagnosed with distant disease, which directly contributes to poor survival prospects. Therefore, there is a high unmet need for improved medical intervention.

1.2 TREATMENT FOR NSCLC

1.2.1 Previously Untreated NSCLC without an *EGFR* Mutation or *ALK* Rearrangement

For patients without a driver mutation that confers sensitivity to a targeted agent, the globally recognized standard of care for inoperable Stage IIIB or IV NSCLC is platinum-based chemotherapy for four to six cycles followed by maintenance treatment until progression. This standard of care applies to both non-squamous and squamous NSCLC (Pfister et al. 2004; D'Addario et al. 2010; de Marinis et al. 2011; National Comprehensive Cancer Network [NCCN] 2014). Agents that have been partnered with either cisplatin or carboplatin include taxanes (paclitaxel or docetaxel), vinorelbine, gemcitabine, pemetrexed, and bevacizumab. Combinations of these drugs with platinum analogs are superior to single-agent therapy and have been shown to prolong survival (Azzoli et al. 2009).

In a Phase III Eastern Cooperative Oncology Group (ECOG) study of four platinum-based doublets (gemcitabine + cisplatin, docetaxel + cisplatin, paclitaxel + carboplatin, and paclitaxel + cisplatin) in patients with Stage IIIB or IV NSCLC who had not previously received chemotherapy (Schiller et al. 2002), the median survival rate was approximately 8 months for all four arms. Paclitaxel + carboplatin was chosen as the reference regimen for ECOG's future studies because of its more favorable toxicity profile. The benefit conferred by platinum-based chemotherapy regimens appears to have reached a plateau in objective response rate (ORR) (approximately 15%–25%) and median survival (7–11 months).

Immune checkpoint inhibitors, including PD-L1/PD-1 blocking antibodies, have emerged as a therapeutic option for first-line treatment of metastatic NSCLC. Pembrolizumab, a PD-1 inhibitor, is approved for the first-line treatment of metastatic NSCLC in patients whose tumors have PD-L1 expression on at least 50% of tumor cells (TCs; tumor proportion score [TPS] $\geq 50\%$) with no *EGFR* or *ALK* gene aberrations. In a Phase III study (KEYNOTE-024), the estimated rate of overall survival (OS) at 6 months was 80.2% for patients receiving pembrolizumab monotherapy compared with 72.4% for patients receiving platinum-based chemotherapy; the median OS was not reached in either group. OS was significantly longer in the pembrolizumab arm than in the chemotherapy arm (hazard ratio [HR]=0.60; $p=0.005$) (Reck et al. 2016). In an updated analysis published by Reck and colleagues (Reck et al. 2019), the median OS was 30.0 months (95% CI: 18.3 months to not reached) with pembrolizumab and 14.2 months (95% CI: 9.8 to 19.0 months) with chemotherapy (HR=0.63; 95% CI: 0.47 to 0.86), with an adjusted HR for OS for pembrolizumab versus chemotherapy of 0.49 (95% CI: 0.34 to 0.69).

These results were confirmed by KEYNOTE-042, a randomized, open-label, Phase III study that recruited 1274 patients (902 men, 372 women, median age of 63 years with a PD-L1 TPS of 1% or greater). Patients were allocated to pembrolizumab ($n=637$) or

chemotherapy (n=637). A total of 599 (47%) patients had a TPS of 50% or greater and 818 patients (64%) had a TPS of 20% or greater. As of 26 February 2018, the median follow-up was 12.8 months. OS was significantly longer in the pembrolizumab group than in the chemotherapy group in all three TPS populations ($\geq 50\%$ HR=0.69, 95% CI: 0.56 to 0.85, p=0.0003; $\geq 20\%$ HR=0.77, 95% CI: 0.64 to 0.92, p=0.0020, and $\geq 1\%$ HR=0.81, 95% CI: 0.71 to 0.93, p=0.0018). The median OS by TPS population were 20.0 months (95% CI: 15.4 to 24.9 months) for pembrolizumab versus 12.2 months (95% CI: 10.4 to 14.2 months) for chemotherapy, 17.7 months (95% CI: 15.3 to 22.1 months) versus 13.0 months (95% CI: 11.6 to 15.3 months), and 16.7 months (95% CI: 13.9 to 19.7 months) versus 12.1 months (95% CI: 11.3 to 13.3 months), respectively. Treatment-related adverse events of Grade 3 or worse occurred in 113 (18%) of 636 treated patients in the pembrolizumab group and in 252 (41%) of 615 treated patients in the chemotherapy group and led to death in 13 (2%) and 14 (2%) patients, respectively (Mok et al. 2019).

Pembrolizumab as a single agent was thus approved by the U.S. Food and Drug Administration (FDA) for the first-line treatment of patients with NSCLC expressing PD-L1 (TPS $\geq 1\%$), as determined by an FDA-approved test, with no *EGFR* or *ALK* genomic tumor aberrations.

Recently, Herbst and colleagues published the final analysis of the IMpower110 study, an open-label, Phase III trial that randomized patients with PD-L1 expression on greater than or equal to 1% of TCs or immune cells to receive atezolizumab or platinum-based chemotherapy (Herbst et al. 2020). Overall, 572 patients were enrolled. In the subgroup of patients with *EGFR* and *ALK* wild-type tumors who had the highest expression of PD-L1 (205 patients), the median OS was longer by 7.1 months in the atezolizumab group than in the chemotherapy group (20.2 months vs. 13.1 months; HR for death=0.59; p=0.01). Among all the patients who could be evaluated for safety, adverse events occurred in 90.2% of the patients in the atezolizumab group and in 94.7% of those in the chemotherapy group. Grade 3 or 4 adverse events occurred in 30.1% and 52.5% of the patients in the respective groups. Atezolizumab was approved by the FDA and European Medicines Agency for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained $\geq 50\%$ of TC [TC $\geq 50\%$] or PD-L1 stained tumor-infiltrating immune cells covering $\geq 10\%$ of the tumor area [immune cells $\geq 10\%$]), with no *EGFR* or *ALK* genomic tumor aberrations.

The combination of pembrolizumab with carboplatin/cisplatin and pemetrexed was approved by the FDA for patients with non-squamous NSCLC based on the Phase II study KEYNOTE-021. The results have been confirmed for patients with non-squamous NSCLC in the Phase III study KEYNOTE-189. The triplet combination demonstrated a significantly longer median OS in the intent-to-treat (ITT) population than chemotherapy alone (HR=0.49; $p < 0.0001$). Median progression-free survival (PFS) was also significantly longer for the experimental arm (8.8 months vs. 4.9 months; HR=0.52, $p < 0.0001$) (Gandhi et al. 2018).

In the Phase III study KEYNOTE-407, the combination of pembrolizumab with carboplatin plus either paclitaxel or nanoparticle albumin-bound (nab)-paclitaxel demonstrated a statistically significant OS benefit as compared with the control arm of carboplatin plus nab-paclitaxel (HR=0.64; 95% CI: 0.49 to 0.85; $p < 0.001$). The OS benefit was consistent across all levels of PD-L1 expression. The median PFS was 6.4 months (95% CI: 6.2 to 8.3 *months*) in the pembrolizumab combination group and 4.8 months (95% CI: 4.3 to 5.7 *months*) in the placebo combination group (HR=0.56; 95% CI: 0.45 to 0.70; $p < 0.001$) (Paz-Ares et al. 2018). On the basis of these results, the U.S. FDA has approved the combination of pembrolizumab plus carboplatin plus nab-paclitaxel for the first-line treatment of patients with squamous NSCLC.

More recently, in the Phase III IMpower150 study, the combination of atezolizumab and bevacizumab plus carboplatin and paclitaxel demonstrated a significant increase in PFS compared with bevacizumab plus carboplatin and paclitaxel in patients with metastatic non-squamous NSCLC (ITT population: HR=0.62; 95% CI: 0.52 to 0.74; $p < 0.001$). Furthermore, a significant and clinically meaningful improvement in median OS was observed for the atezolizumab-containing group at the second interim analysis (19.2 months vs. 14.7 months; stratified HR=0.78; 95% CI: 0.64 to 0.96; $p = 0.02$) (Socinski et al. 2018).

For most patients with previously untreated, advanced-stage, NSCLC with low PD-L1 expression (TPS < 50%), the standard of care is now the combination of a PD-(L)1 checkpoint inhibitor with a platinum-based chemotherapy, with or without bevacizumab.

1.2.2 Previously Treated NSCLC

With the approval of immune checkpoint inhibitors as first-line treatment of advanced NSCLC in patients with high PD-L1 expression, the treatment algorithm for this patient population is changing. Platinum-based chemotherapy will increasingly be used as second-line treatment for patients who experience disease progression during or following treatment with an immune checkpoint inhibitor. Furthermore, immune checkpoint inhibitors combined with platinum-based chemotherapy are expected to be used for patients with low PD-L1 expression or an unknown PD-L1 status who experienced disease progression during or following treatment with a platinum doublet.

To date, three immune checkpoint inhibitors have been approved for patients with metastatic NSCLC who experience disease progression during or following platinum-containing chemotherapy: nivolumab (PD-1 inhibitor), pembrolizumab (PD-1 inhibitor), and atezolizumab (PD-L1 inhibitor). Pembrolizumab is approved for patients whose tumors express PD-L1 (TPS \geq 1%), whereas PD-L1 expression is not a requirement for patients receiving treatment with nivolumab and atezolizumab. For nivolumab, the median OS was 9.2 months for patients with squamous histology and 12.2 months for patients with non-squamous histology (Opdivo® U.S. *Prescribing Information*). For pembrolizumab, the median OS was 10.4 months for patients treated at 2 mg/kg every 3 weeks (Q3W) and 12.7 months for patients treated at 10 mg/kg Q3W (squamous and non-squamous histology combined) (Keytruda® U.S. *Prescribing Information*). For atezolizumab, the median OS was 13.8 months (squamous and non-squamous histology combined) (Tecentriq® U.S. *Prescribing Information*).

In addition to immune checkpoint inhibitors and platinum-based chemotherapy, docetaxel and pemetrexed are approved for patients with metastatic NSCLC who experience disease progression during or following prior chemotherapy. Docetaxel was associated with an estimated median OS of 6–10 months (Stinchcombe and Socinski 2008; Ramlau et al. 2012). Pemetrexed had improved PFS and OS compared with docetaxel in patients with non-squamous histologies, thus limiting its approval to patients with non-squamous NSCLC (Scagliotti et al. 2009).

The choice of agent in the second- or third-line setting depends on a number of factors, including tumor histology, comorbidities, toxicity from previous treatments, toxicity profile for a given agent, smoking history, and patient preference. Overall, the benefit–risk profile of these therapies has been disadvantaged both by limited survival benefit and significant toxicities such as myelosuppression and neuropathy (docetaxel) and diarrhea (pemetrexed) (Stinchcombe and Socinski 2008).

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

This study will enroll two patient populations with metastatic NSCLC and significant unmet medical need: patients with tumor PD-L1 expression (TPS or TCs \geq 50% or TC3), who have received no prior systemic therapy for metastatic NSCLC (Cohort 1) and

patients who experienced disease progression during or following treatment with a platinum-containing regimen and a PD-L1/PD-1 checkpoint inhibitor, given in combination as one line of therapy or as two separate lines of therapy, regardless of PD-L1 expression (Cohort 2). While single-agent immune checkpoint inhibitors have shown superiority over platinum-based chemotherapy in previously untreated patients whose tumors have high PD-L1 expression, less than half of these patients experience an objective response (Reck et al. 2016). The combination of agents targeting different immune evasion mechanisms may increase response rates in this population. Given the relatively poor prognosis, limited treatment options, and potential toxicities associated with treatments for patients in Cohort 2, this population is in need of treatment options and therefore considered appropriate for trials of novel therapeutic candidates.

Cancer immunotherapy (CIT) has demonstrated clear clinical efficacy, with significant survival benefit observed across multiple advanced malignancies. Currently, the prevailing CIT approach is to circumvent immune evasion mechanisms and reinvigorate anti-tumor responses by targeting T-cell inhibitory factors such as PD-L1/PD-1. While these targets have resulted in remarkable clinical therapeutic success for various cancer indications, ongoing research indicates that a series of stepwise events is necessary for the generation of a continuous anti-tumor immune response (Chen and Mellman 2013). Each event is critical for an effective response, and each is also susceptible to several tumor immune-evasion mechanisms. Thus, the need to identify and circumvent the various factors that account for the absence of, or escape from, an effective anti-cancer immune response will be critical for propagating cancer immunity and advancing the field of CIT, most likely through combined CIT regimens.

This randomized Phase Ib/II umbrella study is designed to accelerate the development of CIT combinations by identifying early signals and establishing proof-of-concept clinical data in patients with NSCLC. The study is designed with the flexibility to open new treatment arms as new treatment combinations become available and close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity. Enrollment of multiple experimental arms within a single study, rather than one or two experimental arms within multiple studies, will result in an overall reduction in the number of patients receiving control arm treatment. More importantly, this study will assess the importance of simultaneously targeting multiple mechanisms of immune escape through immune cell priming and activation, tumor infiltration, and/or recognition of TCs for elimination. To improve the confidence of clinical signal detection in the experimental arms, this study will include a comparator (Cohort 1)/control (Cohort 2) arm. Moreover, patients who experience disease progression with the initial treatment regimen in Cohort 2 Stage 1 may be eligible to continue treatment with a different treatment regimen (Stage 2), which may advance the scientific understanding of immune escape mechanisms in patients who fail to respond to, or experience disease progression during, treatment with a CIT or chemotherapy regimen.

The target and proposed mechanism-of-action classification for each experimental investigational medicinal product (IMP) is summarized in Table 1. The control and experimental treatment regimens are described in Section 3.1 (see Table 4 and Table 6). Background information and a rationale for each treatment combination, including a benefit–risk assessment for experimental agents, are provided in the respective appendix for that treatment arm, as outlined in Table 4 and Table 6.

Table 1 Target and Proposed Mechanism-of-Action Classification for Experimental Investigational Medicinal Products

Experimental IMP	Target	Proposed Mechanism-of-Action Classification
Atezolizumab	PD-L1	Immune checkpoint inhibitor
Tiragolumab	TIGIT	TIGIT antagonist; improves activation and effectiveness of T-cell and NK cell tumor-killing activity ^a
XL092	RTK	RTK inhibitor, targeting MET, VEGFR2, Tyro, AXL, and MER ^b
Linagliptin	DPP-4	DPP-4 inhibitor; restores intratumoral chemotactic gradients and immune cell recruitment ^c
Bevacizumab	VEGF	Angiogenesis inhibitor, recruitment of T cells to the tumor microenvironment ^d
Docetaxel	Tubulin	Anti-mitotic chemotherapy agent
Sacituzumab govitecan	TROP-2	Tumor cell-targeted topoisomerase-I inhibitor, causes tumor cell death ^e
Evolocumab	PCSK9	PCSK9 inhibitor, increases MHC-I expression on tumor cells ^f
Camonsertib	ATR	ATR inhibitor, targeting the DNA repair mechanism ^g

ATR=ataxia telangiectasia and Rad3-related protein; DPP-4=dipeptidyl peptidase-4; IMP=investigational medicinal product; MHC-I= major histocompatibility complex class-I; NK=natural killer; PCSK9=proprotein convertase subtilisin/kexin type 9; RTK=receptor tyrosine kinase; TIGIT=T-cell immunoreceptor with Ig and ITIM domains; TROP-2=trophoblast cell-surface antigen 2; VEGF=vascular endothelial growth factor; VEGFR2=vascular endothelial growth factor receptor 2.

^a Stanietzky et al. 2009; Yu et al. 2009; Johnston et al. 2014.

^b Hsu et al. 2023.

^c Barreira da Silva et al. 2015.

^d Wallin et al. 2016.

^e Heist et al. 2017.

^f Liu et al. 2020.

^g Roulston et al. 2022.

1.4 COVID-19 BENEFIT–RISK ASSESSMENT

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how

systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of SARS-CoV-2 infection.

A possible consequence of immune checkpoint inhibition may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses (Wykes and Lewin 2018). In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by CIT.

Severe SARS-CoV-2 infection appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN)- γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving immune checkpoint inhibitor therapies (e.g., atezolizumab). At this time, there is insufficient evidence for causal association between immune checkpoint inhibitor therapies and an increased risk of severe outcomes from SARS-CoV-2 infection.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with immune checkpoint inhibitor therapies and clinical and radiologic features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

There are limited data concerning the possible interactions between CIT treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).

Per recommendations of the NCCN COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors and chemotherapy), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving CIT (SITC 2020). For patients enrolling in this study and receiving CIT, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving CIT to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines.

When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section [4.4](#)).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of immunotherapy-based treatment combinations in patients with metastatic NSCLC. Specific objectives and corresponding endpoints for the study are outlined below for Stage 1 (see [Table 2](#)) and Stage 2 (see [Table 3](#)).

Table 2 Objectives and Corresponding Endpoints for Stage 1

Primary Efficacy Objective	Corresponding Endpoint
<ul style="list-style-type: none"> To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1 	<ul style="list-style-type: none"> Objective response, defined as a complete response or partial response on two consecutive occasions ≥ 4 weeks apart during Stage 1, as determined by the investigator according to RECIST v1.1
Secondary Efficacy Objective	Corresponding Endpoints
<ul style="list-style-type: none"> To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1 	<ul style="list-style-type: none"> PFS after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 PFS at specific timepoints (e.g., 6 months) OS after randomization, defined as the time from randomization to death from any cause OS at specific timepoints (e.g., 6 months) DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 Disease control, defined as stable disease for ≥ 12 weeks or a complete or partial response, as determined by the investigator according to RECIST v1.1
Safety Objective	Corresponding Endpoints
<ul style="list-style-type: none"> To evaluate the safety of immunotherapy-based treatment combinations during Stage 1 	<ul style="list-style-type: none"> Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 Change from baseline in vital signs and ECG parameters Change from baseline in targeted clinical laboratory test results

ADA=anti-drug antibody; DOR=duration of response; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see [Appendix 1](#)).

Table 2 Objectives and Corresponding Endpoints for Stage 1 (cont.)

Exploratory Pharmacokinetic Objectives	Corresponding Endpoints
<ul style="list-style-type: none"> To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1 	<ul style="list-style-type: none"> Plasma or serum concentration of each drug (as appropriate) at specified timepoints
<ul style="list-style-type: none"> To evaluate potential relationships between drug exposure during Stage 1 and the efficacy and safety of immunotherapy-based treatment combinations 	<ul style="list-style-type: none"> Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints
Exploratory Immunogenicity Objectives	Corresponding Endpoints
<ul style="list-style-type: none"> To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1 	<ul style="list-style-type: none"> For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory Immunogenicity Objectives (cont.)	Corresponding Endpoints (cont.)
<ul style="list-style-type: none"> To evaluate potential effects of ADAs during Stage 1 	<ul style="list-style-type: none"> For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	Corresponding Endpoint
<ul style="list-style-type: none"> To identify biomarkers during Stage 1 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology 	<ul style="list-style-type: none"> Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.6) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA=anti-drug antibody; DOR=duration of response; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see [Appendix 1](#)).

Table 3 Objectives and Corresponding Endpoints for Stage 2

Exploratory Efficacy Objective	Corresponding Endpoints
<ul style="list-style-type: none"> To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 2 	<ul style="list-style-type: none"> Objective response, defined as a complete response or partial response on two consecutive occasions ≥ 4 weeks apart during Stage 2, as determined by the investigator according to RECIST v1.1 PFS after initiation of Stage 2, defined as the time from initiation of Stage 2 to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 DOR, defined as the time from the first occurrence of a documented objective response during Stage 2 to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 Disease control, defined as stable disease for ≥ 12 weeks or a complete or partial response, as determined by the investigator according to RECIST v1.1
Safety Objective	Corresponding Endpoints
<ul style="list-style-type: none"> To evaluate the safety of immunotherapy-based treatment combinations during Stage 2 	<ul style="list-style-type: none"> Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 Change from baseline in vital signs and ECG parameters Change from baseline in targeted clinical laboratory test results
Exploratory Pharmacokinetic Objectives	Corresponding Endpoints
<ul style="list-style-type: none"> To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2 	<ul style="list-style-type: none"> Plasma or serum concentration of each (as appropriate) drug at specified timepoints
<ul style="list-style-type: none"> To evaluate potential relationships between drug exposure during Stage 2 and the efficacy and safety of immunotherapy-based treatment combinations 	<ul style="list-style-type: none"> Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints

ADA=anti-drug antibody; DOR=duration of response; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PFS=progression-free survival; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see [Appendix 1](#)).

Table 3 Objectives and Corresponding Endpoints for Stage 2 (cont.)

Exploratory Immunogenicity Objectives	Corresponding Endpoints
<ul style="list-style-type: none"> To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2 	<ul style="list-style-type: none"> For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline
<ul style="list-style-type: none"> To evaluate potential effects of ADAs during Stage 2 	<ul style="list-style-type: none"> For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK, endpoints
Exploratory Biomarker Objective	Corresponding Endpoint
<ul style="list-style-type: none"> To identify biomarkers during Stage 2 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology 	<ul style="list-style-type: none"> Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.6) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA=anti-drug antibody; DOR=duration of response; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PFS=progression-free survival; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see [Appendix 1](#)).

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase Ib/II, open-label, multicenter, randomized, umbrella study in patients with metastatic NSCLC. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status).

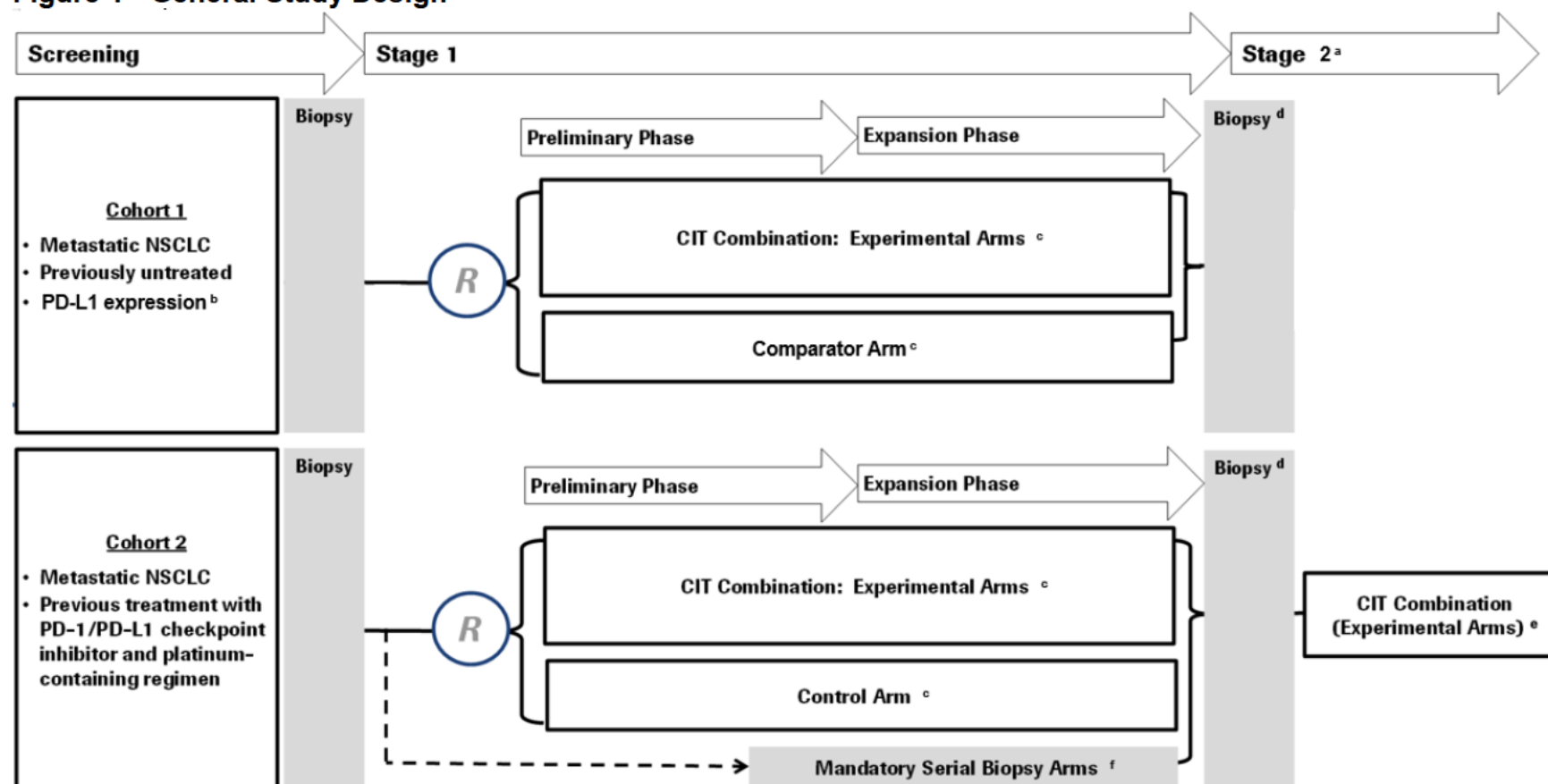
Two cohorts will be enrolled in parallel in this study: Cohort 1 will consist of patients with tumor PD-L1 expression (TPS or TCs $\geq 50\%$ or TC3, as determined by a documented local assessment using a health authority–approved PD-L1 immunohistochemistry [IHC] assay), who have received no prior systemic therapy for metastatic NSCLC, and Cohort 2 will consist of patients who experienced disease progression during or following treatment with a platinum-containing regimen and a PD-L1/PD-1 checkpoint inhibitor, given in combination as one line of therapy or as two separate lines of therapy,

regardless of PD-L1 expression (see [Figure 1](#)). In each cohort, eligible patients will initially be assigned to one of several treatment arms (Stage 1; see Section [3.1.1](#)). Patients who experience disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may be eligible to continue treatment with a different treatment regimen (Stage 2; see Section [3.1.4](#)).

Because the treatment landscape for first-line metastatic NSCLC evolved since the initiation of this study, with new and highly effective treatment options being available in this setting, patient enrollment into Cohort 1 was suspended as of November 2018, and patients were no longer enrolled into Cohort 1. Patients already enrolled in Cohort 1 continued to be treated and monitored per protocol.

From Protocol Version 19 *onward*, Cohort 1 is being reactivated with a comparator arm of patients who will receive a combination treatment consisting of Atezo+Tira.

Figure 1 General Study Design



CIT = cancer immunotherapy; IHC = immunohistochemistry; NSCLC = non-small cell lung cancer; R = randomization; TC = tumor cell; TPS = tumor proportion score.

^a Stage 2 does not apply to Cohort 1.

^b PD-L1 expression (TPS or TCs $\geq 50\%$ or TC3), as determined by a documented local assessment using a health authority-approved PD-L1 IHC assay.

^c Refer to [Table 4](#) for a summary of available Stage 1 treatment regimens in Cohorts 1 and 2.

- ^d A biopsy will be performed for patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1, or loss of clinical benefit as determined by the investigator (if deemed clinically feasible by the investigator).
- ^e Refer to [Table 6](#) for a summary of available Stage 2 treatment regimens in Cohort 2.
- ^f The Sponsor may open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase (see Section [3.1.2](#)).

3.1.1 Stage 1

During Stage 1, patients in Cohort 1 will be randomly assigned to a comparator arm (atezolizumab [Atezo]+tiragolumab [Tira]) or an experimental arm consisting of atezolizumab in combination with tiragolumab and XL092 (Atezo+Tira+XL092) and patients in Cohort 2 will be randomly assigned to a control arm (docetaxel, *if not paused*) or an experimental arm consisting of atezolizumab in combination with camonsertib (Atezo+Camon), bevacizumab and camonsertib (Atezo+Bev+Camon), bevacizumab and tiragolumab (Atezo+Bev+Tira), bevacizumab (Atezo+Bev), bevacizumab and radiotherapy (Atezo+Bev+RTx), sacituzumab govitecan (Atezo+SG), or evolocumab (Atezo+Evo) (see [Figure 2](#) and [Figure 3](#)). Details on the treatment regimens for Stage 1 are provided in [Appendix 7–Appendix 10](#), [Appendix 12–Appendix 15](#), [Appendix 18](#), and [Appendix 19](#) as specified in [Table 4](#). [Table 5](#) lists Stage 1 treatment arms for which enrollment and patient follow-up has been completed.

Approximately 425–675 patients will be enrolled during Stage 1, excluding closed treatment arms and those that have already reported (see [Table 5](#) for more details). Enrollment within the experimental arms will take place in two phases: a preliminary phase followed by an expansion phase.

In Cohort 2, approximately 40 patients will be enrolled in the bevacizumab- and the camonsertib-containing arms during the preliminary phase. Thirty patients will be enrolled in the Atezo+SG arm to ensure a sufficient number of patients with high, medium, and low trophoblast cell-surface antigen 2 (TROP-2) expression. Twenty patients will be enrolled in the Atezo+Evo arm to ensure a sufficient number of patients with high proprotein convertase subtilisin/kexin type 9 (PCSK9) expression (PCSK9-high) and low PCSK9 expression (PCSK9-low). Additional patients may be enrolled in the Atezo+Evo arm to ensure that at least 10 patients with high PCSK9 expression are included. No more than 30 patients will be enrolled in the Atezo+Evo arm in the preliminary phase. Fifteen patients will be enrolled in all other experimental arms during the preliminary phase. If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25–40 additional patients may be enrolled in that arm during the expansion phase. The Sponsor may decide to delay or suspend enrollment within a given treatment arm. The Sponsor may also decide to open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has qualified for the expansion phase (see [Section 3.1.2](#) for details). Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion. Additional patients may be enrolled to ensure balance among treatment arms with respect to demographic and baseline characteristics, including potential predictive biomarkers, to enable further subgroup analyses. New experimental arms may be added during the study by amending the protocol.

Patients will be randomly assigned to treatment arms, with the exception of the mandatory serial biopsy arms, and the randomization ratio will depend on the number of experimental arms that are available (e.g., if an arm is added or enrollment in an arm is suspended, pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control or comparator arm will be no more than 50%. Randomization will take into account arm-specific exclusion criteria. Patients will be ineligible for a specific arm if they meet any of the exclusion criteria outlined for that arm (see Section 4.1.2). Details on treatment assignment and randomization are provided in Section 4.2.

Table 4 Stage 1 Treatment Regimens

Cohort (Enrollment Status)	Study Treatment	No. of Patients ^a		Appendix
		Preliminary Phase	Expansion Phase ^{b, c}	
1 (enrolling ^d)	Atezo + Tira	Variable ^a		Appendix 7
	Atezo + Tira + XL092	40 ^e	25	Appendix 8
2 (enrolling ^d)	Docetaxel	Variable ^a		Appendix 10
	Atezo + Evo ^g	20 ^f	25	Appendix 9
	Atezo + Bev	40 ^e	25–40	Appendix 18
	Atezo + Bev + RTx	40 ^e	25–40	Appendix 19
	Atezo + SG ^g	30 ^h	25	Appendix 12
	Atezo + Camon	40 ^e	25–40	Appendix 13
	<i>Atezo + Bev + Camon</i>	40 ^e	25–40	Appendix 14
	<i>Atezo + Bev + Tira</i>	40 ^e	25–40	Appendix 15

Atezo = atezolizumab; Bev = bevacizumab; *Camon* = *camonsertib*; Evo = evolocumab; PCSK9 = proprotein convertase subtilisin/kexin type 9; RTx = radiotherapy; SG = sacituzumab govitecan; Tira = tiragolumab; TROP-2 = trophoblast cell-surface antigen 2.

^a The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that no more than 50% of patients will be randomly allocated to a control arm (see Section 4.2 for details).

^b If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25–40 additional patients may be enrolled in that arm during the expansion phase.

^c The Sponsor may open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase (see Section 3.1.2).

^d The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Thus, all listed experimental arms may not be open for enrollment at the same time.

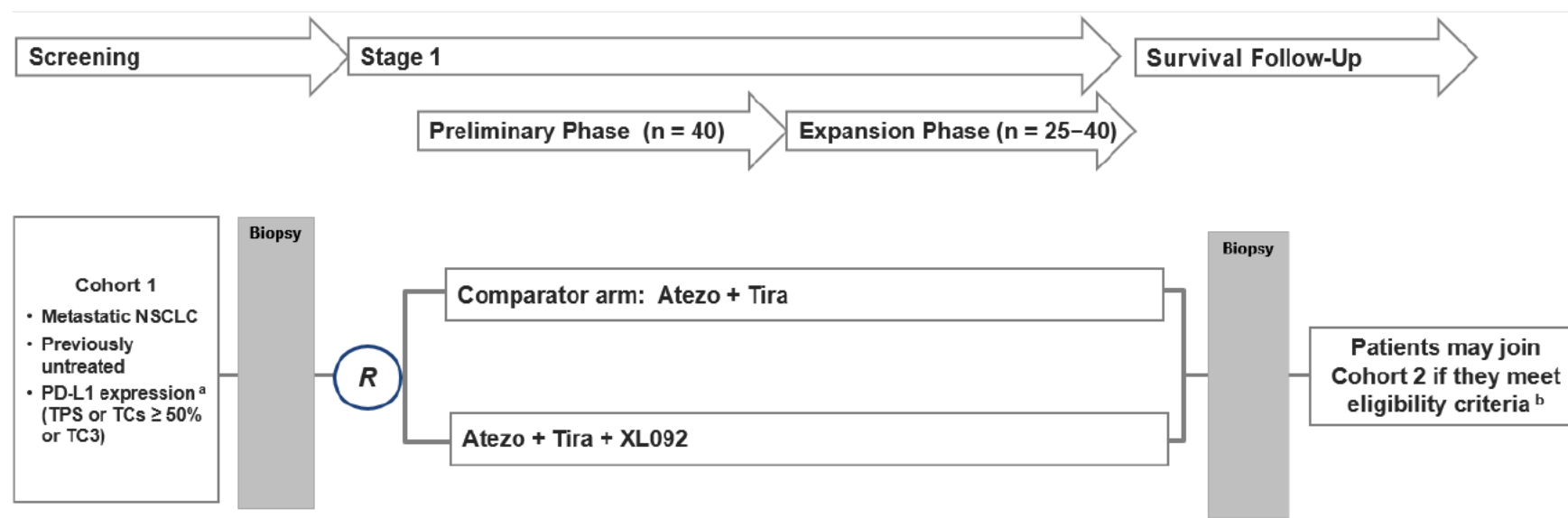
^e Approximately 40 patients will be enrolled in the Atezo + XL092, the Atezo + Bev, the Atezo + Bev + RTx, the *Atezo + Bev + Tira*, the Atezo + Camon, and the *Atezo + Bev + Camon* arms.

^f Approximately 20 patients will be enrolled in the Atezo + Evo arm to ensure a sufficient number of patients with high PCSK9-expression (PCSK9-high) and low PCSK9 expression (PCSK9-low) to facilitate the evaluation of the benefit and risk in these subpopulations. Additional patients may be enrolled in the Atezo + Evo arm to ensure that at least 10 patients with high PCSK9 are included. No more than 30 patients will be enrolled in the Atezo + Evo arm in the preliminary phase.

^g This arm is closed and will be removed when the last patient discontinues from the study.

^h Thirty patients will be enrolled in the Atezo + SG arm to ensure a sufficient number of patients with high, medium, and low TROP-2 expression to facilitate the evaluation of the benefit and risk of these subpopulations.

Figure 2 Detailed Study Design: Cohort 1

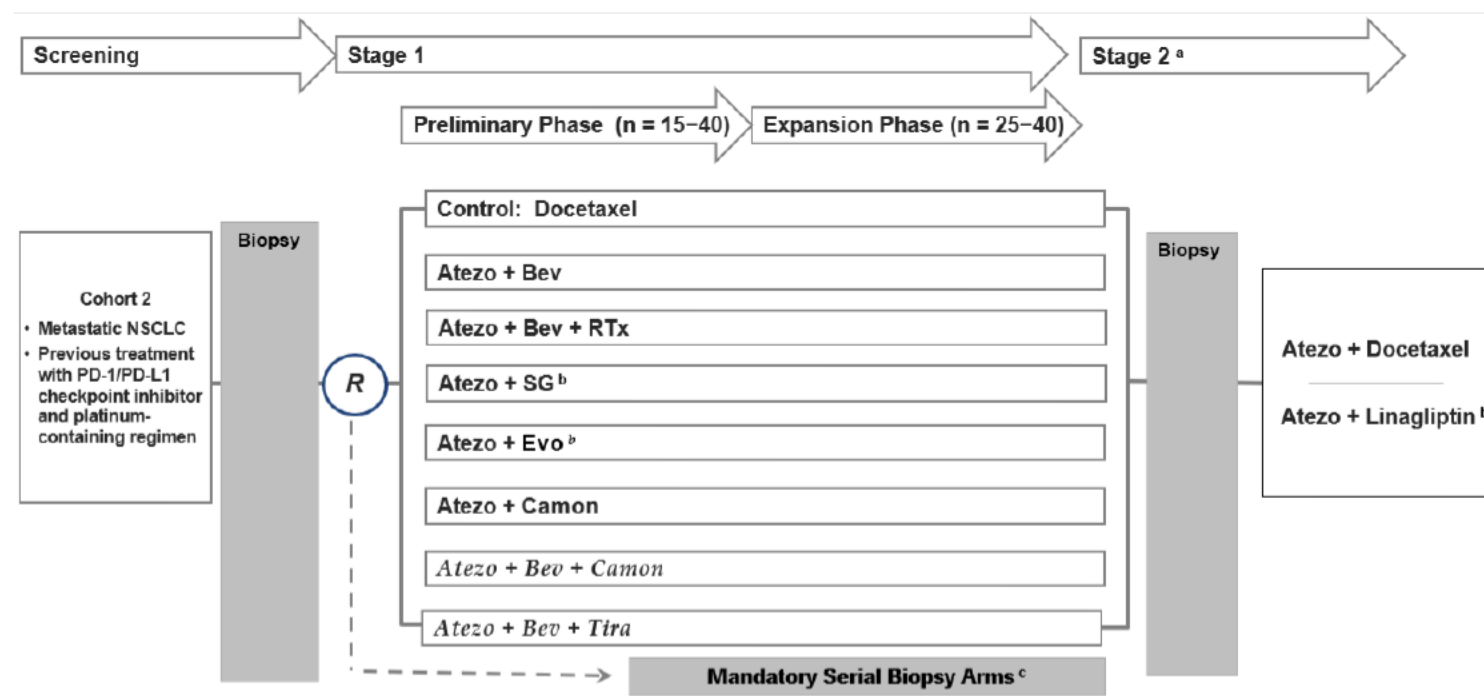


Atezo=atezolizumab; IHC= immunohistochemistry; n=number of patients; NSCLC=non-small cell lung cancer; R=randomization; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; TC=tumor cell; Tira=tiragolumab; TPS=tumor proportion score.

^a PD-L1 expression (TPS or TCs ³ 50% or TC3), as determined by a documented local assessment using a health authority-approved PD-L1 IHC assay.

^b Patients who experience disease progression per RECIST v1.1 or loss of clinical benefit as determined by the investigator (for details, see Section 3.1.1) during Cohort 1 treatment may be eligible to receive a different treatment in Cohort 2, provided they meet the eligibility criteria. Details are provided in the respective appendix for each treatment arm (see [Appendix 7–Appendix 10](#), [Appendix 12–Appendix 15](#), [Appendix 18](#), and [Appendix 19](#)).

Figure 3 Detailed Study Design: Cohort 2



Atezo=atezolizumab; Bev=bevacizumab; Camon=camonsertib; Evo=Evolocumab; Lina=linagliptin; n=number of patients; NSCLC=non-small cell lung cancer; R=randomization; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; RTx=radiotherapy; SG=sacituzumab govitecan; Tira=tiragolumab.

^a Patients who experience disease progression per RECIST v1.1, loss of clinical benefit as determined by the investigator (for details, see Section 3.1.1), or unacceptable toxicity during Stage 1 may be eligible to receive a different treatment combination during Stage 2, provided they meet the eligibility criteria. Details are provided in the respective appendix for each treatment arm (see [Appendix 7–Appendix 10](#), [Appendix 12–Appendix 15](#), [Appendix 18](#), and [Appendix 19](#)).

^b This arm is closed and will be removed when the last patient discontinues from the study.

^c The Sponsor may open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase (see Section 3.1.2).

Table 5 Closed and Reported Treatment Arms

Stage	Cohort	Study Treatment	No of Patients Enrolled		Protocol Versions Describing Arm
			Preliminary Phase	Expansion Phase	
1	1	Atezo + RO6958688	1	0	1–12
1	2	Atezo + RO6958688	1	0	1–12
1	2	Atezo + CPI-444	16	0	1–13
1	1	Atezo	3	NA	1–18
1	1	Atezo + Cobi	5	0	1–18
1	2	Atezo + Cobi	15	0	1–18
1	2	<i>Atezo + Ipat</i>	30	0	4–20
1	2	<i>Atezo + Docetaxel</i>	16	0	7–20
2	1	Atezo + Pem + Carbo	2	NA	1–18
2	1	Atezo + Gem + Carbo	0	NA	1–18

Atezo = atezolizumab; Carbo = carboplatin; Cobi = cobimetinib; Gem = gemcitabine;
Ipat = ipatasertib; NA = not applicable; Pem = pemetrexed.

Patients in the docetaxel control arm will continue to receive treatment until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; see [Appendix 1](#)). Patients in the atezolizumab combination arms will be treated until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Patients in the atezolizumab plus docetaxel arm will continue to receive docetaxel until unacceptable toxicity or disease progression per RECIST v1.1; atezolizumab can be continued until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudoprogression) with CITs (such as atezolizumab), radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet the criteria for disease progression per RECIST v1.1 while receiving treatment with a CIT drug will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values such as new or worsening hypercalcemia) indicating unequivocal progression of disease

- Absence of decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

3.1.2 Mandatory Serial Biopsy Arms at Participating Sites

If an experimental combination demonstrates clinical activity during the preliminary phase, the Sponsor may decide to test that same combination in a mandatory serial biopsy arm at the time that arm is open for expansion. This arm will consist of patients at participating sites who are willing to undergo an on-treatment biopsy.

Enrollment in a mandatory serial biopsy arm is contingent upon the review and approval of mandatory serial biopsies by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for mandatory serial biopsies, this section of the protocol (Section 3.1.2) will not be applicable at that site. The objective of the mandatory serial biopsy arms is to analyze serial tissue samples (including pretreatment, on-treatment, and post-progression samples) in an effort to better understand potential biological changes that occur during treatment with CIT combinations (including immune escape), provide evidence of pharmacodynamic effects, or confirm hypothesized mechanisms of action. Biomarkers may include those that inform stromal and immune biology (Turley et al. 2015).

Patients entering Stage 1 who are determined by the investigator to be eligible for serial biopsies may be enrolled in a mandatory serial biopsy arm rather than undergo random assignment to other arms that are open for enrollment. If more than one mandatory biopsy arm is open within Cohort 2, patients will be assigned to one of the available arms by the Sponsor.

Approximately 15 patients with serial biopsy samples will be enrolled in each mandatory serial biopsy arm. However, the number of patients will be reduced if optional on-treatment biopsies have been collected (and determined to be evaluable) from consenting patients treated with that same CIT combination during the preliminary phase, to limit on-treatment biopsy collection to a total of approximately 15 patients per CIT combination within each cohort.

Patients enrolled in a mandatory biopsy arm will undergo the same assessments as other patients receiving the same treatment combination but will have an additional mandatory on-treatment biopsy at Week 4 (± 1 week) after initiation of CIT combination treatment (if deemed clinically feasible by the investigator). Details about the timing of biopsy sample collection are provided in the schedule of activities for each arm (see [Appendix 7–Appendix 10](#), [Appendix 12–Appendix 15](#), [Appendix 18](#), and [Appendix 19](#)).

To be eligible for a mandatory serial biopsy arm, a patient should have at least two accessible tumors that are amenable to excisional, punch, or core-needle biopsy (a minimum of three cores, 18-gauge needle or larger [16-gauge needle preferred]) without unacceptable risk of a major procedural complication. If it is planned that more than one biopsy will be obtained from a single lesion, the lesion should be large enough to permit successive biopsies ≥ 1 cm apart.

Patients enrolled in a mandatory serial biopsy arm for whom three evaluable tissue samples cannot be obtained may continue to receive study treatment as scheduled.

3.1.3 Safety Evaluation Phase

To account for potential overlapping toxicities in the Atezo+Tira+XL092, Atezo+Camon, and the *Atezo+Bev+Camon* arms, enrollment within each arm will be suspended after approximately █ patients have been enrolled to allow for a safety evaluation. The safety evaluation will be based on safety data from a minimum of █ patients who have received at least █ of treatment (i.e., one dose of each agent for a given combination) and completed safety follow-up assessments during at least █ full treatment cycle (See Sections [A8–5.1](#), [A13–5.1](#), and [A14–5](#)). If a combination is determined to be sufficiently safe, enrollment will be resumed in that arm.

3.1.4 Stage 2

During Stage 1 in Cohort 2, patients who experience disease progression per RECIST v1.1, loss of clinical benefit as determined by the investigator (for details, see Section [3.1.1](#)), or unacceptable toxicity may be eligible to receive a different treatment combination during Stage 2 as outlined in [Table 6](#), provided they meet the eligibility criteria and a Stage 2 arm is open for enrollment. Details are provided in the respective appendix for each treatment arm (see [Appendix 7–Appendix 10](#), [Appendix 12–Appendix 15](#), [Appendix 18](#), and [Appendix 19](#)).

Study details specific to the Stage 2 treatment regimens are provided in [Appendix 16](#) and [Appendix 17](#) as specified in [Table 6](#).

Patients in Cohort 2 who are eligible for more than one treatment arm will be assigned a treatment arm by the investigator.

Stage 2 treatment must begin within 3 months after a patient has experienced disease progression per RECIST v1.1 (docetaxel control arm), loss of clinical benefit (atezolizumab combination arms), or unacceptable toxicity and will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator. It is recommended that patients begin Stage 2 treatment as soon as possible.

Table 6 Stage 2 Treatment Regimens

Cohort (Enrollment Status)	Histologic Type	Study Treatment ^a	Appendix
2	Non-squamous or squamous	Atezo + Docetaxel ^b	Appendix 16
2 (not enrolling)		Atezo + Lina ^c	Appendix 17

Atezo = atezolizumab; Lina = linagliptin.

^a The Sponsor may decide to delay or suspend enrollment within a given treatment arm.

^b Patients who are enrolled in the Docetaxel control arm are not eligible to receive this study treatment in Stage 2.

^c This arm is closed and will be removed when the last patient discontinues from the study.

The Sponsor may decide to discontinue enrollment in Stage 2 treatment arms on the basis of a review of safety data, preliminary efficacy data, and supportive information (e.g., biomarker research data), as appropriate.

3.1.5 Assessments and Monitoring

All patients will be closely monitored for adverse events throughout the study, and adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

Patients will undergo tumor assessments every 6 weeks (starting on Day 1 of Cycle 1) for the first 48 weeks and then every 6 or 12 weeks thereafter (see Section 4.5.5 and [Appendix 7–Appendix 19](#) for details). Response will be assessed by the investigator using RECIST v1.1 (see [Appendix 1](#)).

If clinical activity is demonstrated in an experimental arm, the Sponsor may request that tumor assessment scans for that arm and the corresponding control/comparator arm be submitted for evaluation by an independent review facility.

Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided the patient has not received any checkpoint inhibitor therapy since the time of the biopsy. For patients in Cohort 2 who received treatment with checkpoint inhibitor therapy beyond initial radiographic progression per RECIST v1.1, collection of tumor tissue may be discussed with the Medical Monitor. Tumor tissue will also be collected from patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1 (docetaxel control arm), or loss of clinical benefit as determined by the investigator (Atezo + Tira comparator arm and Atezo/Atezo + Tira-containing experimental arms).

(if deemed clinically feasible by the investigator). For patients enrolled in a mandatory serial biopsy arm at participating sites, an additional tumor tissue sample will be collected during treatment (if clinically feasible). These samples, as well as blood samples collected during the study, will be utilized for biomarker research (see rationale for biomarker assessments in Section 3.4.3 and details on tissue sample collection in Section 4.5.6).

To characterize the pharmacokinetic (PK) properties and/or immunogenicity of atezolizumab and other therapeutic agents, blood samples will be obtained at various timepoints before and during study treatment administration.

On the basis of a review of real-time safety data and available PK data, treatment regimens may be modified by the Sponsor as deemed appropriate.

The schedule of activities for each treatment arm is presented in [Appendix 7–Appendix 19](#).

3.1.6 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will monitor patient safety throughout the study. The IMC will include representatives from Clinical Science, Safety Science, and Biostatistics. In addition to the ongoing assessment of the incidence, nature, and severity of adverse events, serious adverse events, deaths, and laboratory abnormalities performed by the investigator and the Medical Monitor, the IMC will review all necessary cumulative data at regular intervals during the study. At the time of each review, the IMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, a treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities will be detailed in an IMC Charter.

3.1.7 Scientific Oversight Committee

A Scientific Oversight Committee (SOC) will act as a consultative body to the Sponsor, providing external expert opinions on the safety data collected during the study. This committee will consist of an external group of at least three oncology experts in CIT who will advise the Sponsor on the interpretation of study data. For this purpose, the SOC will evaluate aggregate safety data on a periodic basis, approximately every 6 months from the time the first patient is enrolled in the study. Members will follow a charter that outlines their roles and responsibilities. Data being evaluated by the SOC will include demographic, adverse event, serious adverse event, and relevant laboratory data. The SOC may review efficacy data if safety concerns necessitate benefit–risk assessments. The Sponsor will retain all decision-making authority for this study.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient completes the last visit, including survival follow-up visits conducted by telephone or on-site visit.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 8 years.

3.3 DURATION OF PARTICIPATION

Participants will be treated until disease progression per RECIST v1.1, unacceptable toxicity, or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease), whichever occurs first. The total duration of study participation for each individual is expected to range from 1 day to approximately 3 to 4 years.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Patient Population

Despite improvements in the first-line treatment of patients with metastatic NSCLC that have resulted in longer survival times and reduced disease-related symptoms, significant unmet medical need exists in this patient population as only a small fraction of patients derive benefit from these new treatment options.

The study will enroll two patient populations: patients with tumor PD-L1 expression (TPS or TCs $\geq 50\%$ or TC3, as determined by a documented local assessment using a health authority-approved PD-L1 IHC assay) who have received no prior systemic therapy for metastatic NSCLC (Cohort 1) and patients who experienced disease progression during or following treatment with a platinum-containing regimen and a PD-L1/PD-1 checkpoint inhibitor, given in combination as one line of therapy or as two separate lines of therapy, regardless of PD-L1 expression (Cohort 2).

Atezolizumab and pembrolizumab have shown comparable 12-month OS rates and ORRs in previously untreated as well as in previously treated patients expressing high levels of PD-L1 on their tumors (Garon et al. 2015; Garassino et al. 2017; Reck et al. 2016; Rittmeyer et al. 2017), while the combination of atezolizumab and tiragolumab seems to be superior compared with atezolizumab monotherapy in patients with high tumor PD-L1 expression (Cho et al. 2022). Cohort 1 will compare atezolizumab + tiragolumab-based CIT combinations with atezolizumab + tiragolumab in patients with tumor PD-L1 expression (TPS or TCs $\geq 50\%$ or TC3) who have received no prior systemic therapy for metastatic NSCLC. This design is expected to allow for rapid signal detection in a homogeneous patient population. Eligible patients will be required to have a high level of TC PD-L1 expression to ensure a population with a good probability of response.

Patients who experience progression during or following first-line treatment for metastatic NSCLC have an even more limited prognosis, with a median survival of approximately 8–9 months (Stinchcombe and Socinski 2008). Approved therapies are associated with significant toxicities (e.g., neuropathy, febrile neutropenia, myelosuppression, and alopecia) that negatively impact quality of life. Thus, there is a continuing need for more efficacious, better-tolerated treatments. Therefore, Cohort 2 will compare CIT combinations with docetaxel alone in patients who experienced disease progression during or following treatment with a platinum-containing regimen and a PD-L1/PD-1 checkpoint inhibitor, given in combination as one line of therapy or as two separate lines of therapy, regardless of PD-L1 expression. With the increasing use of checkpoint inhibitors as first-line or second-line therapy, this patient population is expected to increase over time and currently has no promising treatment options. It is therefore important to investigate a combination of agents targeting different tumor immune evasions mechanisms in this patient population.

3.4.2 Rationale for Immunotherapy-Based Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response has been termed pseudo-progression (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed immune cells and no viable cancer cells. Because of the potential for a response after pseudoprogression, this study will allow patients allocated to immunotherapy-based treatment arms to continue combination treatment after apparent radiographic progression per RECIST v1.1, provided the benefit–risk ratio is judged to be favorable by the investigator (see criteria in Section 4.6.1). Patients should be discontinued for unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1.1 for details).

3.4.3 Rationale for Biomarker Assessments

Blood samples for biomarker assessments will be collected at baseline, during the study, and at Stage 1 discontinuation due to unacceptable toxicity, disease progression per RECIST v1.1, or loss of benefit as determined by the investigator (see Section 3.1.1 for details) (if deemed clinically feasible by the investigator), to enable analysis of biomarkers related to resistance, disease progression, and clinical benefit of study treatments. Changes in biomarkers in blood may provide evidence of biologic activity of the specific treatment combinations. Correlations between surrogate biomarkers in blood (such as tumor burden markers, cytokines, chemokines, immune cell

subpopulations, gene expression, and circulating tumor DNA) and drug dose and efficacy and safety endpoints may allow for the development of a blood-based biomarker assay to help define future treatments and identify which patients are more likely to benefit from specific treatment combinations.

Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. Tumor tissue will also be collected for patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) (if deemed clinically feasible by the investigator), to enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of study treatments.

Tumor samples will be evaluated for biomarkers such as tumor-infiltrating immune cells, PD-L1, CD8, and expression of targets specific to each drug combination. Evaluation of the tumor microenvironment in response to treatment within each arm, including changes in the number and functional status of tumor-infiltrating immune cells, could provide validation of the postulated mechanism of action and confirmation that an appropriate dose and exposure for the specific treatment combination have been achieved.

Tumor tissue and blood samples may be analyzed through use of next-generation sequencing (NGS) and whole exome sequencing (WES) to identify somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet all of the criteria outlined in Sections 4.1.1.1 and 4.1.1.2 to qualify for Stage 1. Patients must meet all of the criteria outlined in Sections 4.1.1.2 and 4.1.1.3 to qualify for Stage 2.

4.1.1.1 Inclusion Criteria for Stage 1

Patients must meet all of the following criteria to qualify for Stage 1:

- Age \geq 18 years at the time of signing Informed Consent Form
- ECOG Performance Status of 0 or 1 (see Appendix 3)
- Life expectancy \geq 3 months, as determined by the investigator

- Histologically or cytologically confirmed metastatic, non-squamous or squamous NSCLC

Histologic classification may be based on tumor specimens collected prior to metastasis. Patients with tumors of mixed histology must be classified as non-squamous or squamous on the basis of the major histological component.

- For patients in Cohort 1: no prior systemic therapy for metastatic NSCLC

Patients who received chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease in the neoadjuvant or adjuvant setting are eligible for the study if therapy was completed at least 6 months prior to initiation of study treatment and if they did not develop disease progression or recurrence within ≤ 6 months of completion of therapy.

- For patients in Cohort 2: disease progression during or following treatment for metastatic or locally advanced, inoperable NSCLC that consisted of a platinum containing regimen and a PD-L1/PD-1 checkpoint inhibitor, given in combination as one line of therapy or as two separate lines of therapy (in either order), for a maximum of two prior lines of systemic therapy. Patients *who received checkpoint inhibitor containing systemic treatment for metastatic disease for less than 6 months or developed disease progression or recurrence within 6 months after initiation of checkpoint inhibitor based treatment for metastatic NSCLC* are not eligible for Cohort 2

Patients who received treatment with a checkpoint inhibitor in the adjuvant setting and developed disease progression or recurrence >12 weeks after discontinuation of adjuvant CPI therapy may be allowed to participate in Cohort 2.

Patients who received treatment with a checkpoint inhibitor in the neoadjuvant setting only resulting in a major pathologic response or better and developed disease progression or recurrence >12 weeks from the discontinuation of adjuvant CPI therapy may be allowed to participate in Cohort 2.

Patients who received treatment with a checkpoint inhibitor in the neoadjuvant setting resulting in a major pathologic response or better and continue CPI treatment into the adjuvant setting and developed disease progression or recurrence >6 months after starting adjuvant CPI therapy may be allowed to participate in Cohort 2.

Patients who received definitive therapy for locally advanced disease that included a combination of at least a platinum-based chemotherapy (for example, cisplatin or carboplatin) and PD-L1/PD-1 checkpoint inhibitor may be allowed to participate in Cohort 2 if they develop progressive disease or recurrence >6 months after completion of their definitive therapy for locally advanced disease.

Prior exposure to anti-CTLA-4 antibodies is allowed if used in combination with a PD-L1/PD-1 checkpoint inhibitor.

Patients who received first-line therapy with a platinum-containing regimen and a PD-L1/PD-1 checkpoint inhibitor, given in combination as one line of therapy, must not receive a systemic second-line treatment in order to be eligible for the study.

- Availability of a representative tumor specimen that is suitable for determination of PD-L1 and/or additional biomarker status by means of central testing

Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be used, provided the patient has not received any checkpoint inhibitor therapy since the time of the biopsy.

For patients in Cohort 2 who received treatment with checkpoint inhibitor therapy beyond initial radiographic progression per RECIST v1.1, collection of tumor tissue requires discussion with the Medical Monitor.

A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 15–16 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report to the designated central laboratory, once the patient is randomized. Refer to Section 4.5.6 for additional information on tumor specimens collected at screening.

- For patients in Cohort 1: Tumor PD-L1 expression, defined as TPS or TCs $\geq 50\%$ or TC3, as determined by a documented local assessment using a health authority-approved PD-L1 IHC assay

4.1.1.2 Inclusion Criteria for Stages 1 and 2

Patients must meet all of the following criteria to qualify for Stage 1 and to qualify for Stage 2:

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Measurable disease (at least one target lesion) according to RECIST v1.1
 - Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
 - ANC $\geq 1.5 \times 10^9/L$ ($1500/\mu L$) without granulocyte colony-stimulating factor support
 - WBC count $\geq 2.5 \times 10^9/L$ ($2500/\mu L$)
 - Lymphocyte count $\geq 0.5 \times 10^9/L$ ($500/\mu L$)
 - Platelet count $\geq 100 \times 10^9/L$ ($100,000/\mu L$) without transfusion

- Hemoglobin ≥ 90 g/L (9.0 g/dL)
Patients may be transfused to meet this criterion.
- For patients in Cohort 1: AST, ALT, and ALP $\leq 2.5 \times$ upper limit of normal (ULN) with the following exceptions:
Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN
Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
- For patients in Cohort 2: liver function test results that meet one of the following sets of criteria:
 - a) AST, ALT, and ALP $\leq 2.5 \times$ ULN
 - b) AST and ALT $\leq 1.5 \times$ ULN and ALP $\leq 5 \times$ ULN
- For patients in Cohort 1: bilirubin $\leq 1.5 \times$ ULN, with the following exception:
Patients with known Gilbert disease: bilirubin level $\leq 3 \times$ ULN
- For patients in Cohort 2: bilirubin $\leq 1.0 \times$ ULN, with the following exception:
Patients with known Gilbert disease: bilirubin level $\leq 3 \times$ ULN
- Albumin ≥ 25 g/L (2.5 g/dL)
- Creatinine clearance ≥ 40 mL/min (calculated using the Cockcroft-Gault formula)
- For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 ULN
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen during the 14 days prior to initiation of study treatment
- Negative HIV test at screening, with the following exception:
Patients with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count $\geq 200/\mu\text{L}$, and have an undetectable viral load.
Patients without a prior positive HIV test result will undergo an HIV test at screening, unless not permitted per local regulations.
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening
The HBV DNA test will be performed only for patients who have a positive total HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening
The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- Tumor accessible for biopsy

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as outlined for each specific treatment arm in [Appendix 7–Appendix 19](#)
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as outlined for each specific treatment arm in [Appendix 7–Appendix 19](#)

4.1.1.3 Inclusion Criteria for Stage 2

Patients must meet all of the following criteria to qualify for Stage 2:

- ECOG Performance Status of 0–2 (see [Appendix 3](#))
- Patients in the docetaxel control arm: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity or disease progression per RECIST v1.1 while receiving Stage 1 treatment
- Patients in an atezolizumab-containing experimental arm during Stage 1: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity not related to atezolizumab or loss of clinical benefit as determined by the investigator (see Section [3.1.1](#) for details) while receiving Stage 1 treatment
- Availability of a tumor specimen from a biopsy performed upon discontinuation of Stage 1 (if deemed clinically feasible by the investigator)

4.1.2 Exclusion Criteria

Patients will be excluded from enrollment during Stage 1 and Stage 2 if they meet any of the applicable criteria outlined in subsequent sections, as summarized by treatment arm in [Table 7](#). If a patient is eligible only for a control/comparator arm, the patient will not be enrolled in the study. Event grades in the exclusion criteria are based on NCI CTCAE v4.0.

Table 7 Arm-Specific Exclusion Criteria

Stage	Cohort	Treatment Arm	Applicable Exclusion Criteria
1	1	Atezo + Tira	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.3
		Atezo + Tira + XL092	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.4
	2	Docetaxel	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.8
		Atezo + Evo	Sections 4.1.2.1 and 4.1.2.2
		Atezo + Bev	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.9
		Atezo + Bev + RTx	Sections 4.1.2.1, 4.1.2.2, 4.1.2.9, and 4.1.2.10
		Atezo + SG	Sections 4.1.2.1 and 4.1.2.2
		Atezo + Camon	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.5
		<i>Atezo + Bev + Camon</i>	Sections 4.1.2.1, 4.1.2.2, 4.1.2.6, and 4.1.2.9
		<i>Atezo + Bev + Tira</i>	Sections 4.1.2.1, 4.1.2.2, 4.1.2.7, and 4.1.2.9
2	2	Atezo + Docetaxel	Sections 4.1.2.2 and 4.1.2.8
		Atezo + Lina	Sections 4.1.2.2 and 4.1.2.11

Atezo=atezolizumab; Bev=bevacizumab; *Camon* = camonsertib; Evo=evolocumab; Lina=linagliptin; RTx=radiotherapy; SG=sacituzumab govitecan; Tira=tiragolumab.

4.1.2.1 Exclusion Criteria for Stage 1

Patients who meet any of the following criteria will be excluded from Stage 1:

- Activating mutation in the *EGFR* gene or *ALK* gene rearrangement
Patients with tumors of non-squamous histology with unknown *EGFR* and/or *ALK* status will undergo testing at a local laboratory at screening, by health authority-approved testing, per the assay's intended use, according to local laws and regulations. Patients with tumors of squamous histology who have an unknown *EGFR* or *ALK* mutational status will not be required to be tested at prescreening/screening.
- Prior treatment with any of the protocol-specified study treatments (including TROP-2 targeting agents *if an anti-TROP-2 agent-containing arm is open for enrollment*), with the following exception:
Patients in Cohort 2 who received atezolizumab, bevacizumab, or tiragolumab for treatment of NSCLC as well as patients who received evolocumab for an approved indication are eligible for the study.
- For patients in Cohort 2: prior treatment with a T-cell co-stimulating therapy or an immune checkpoint inhibitor other than a PD-L1/PD-1 checkpoint inhibitor *and* anti-CTLA-4 antibodies
Patients who discontinued a PD-L1/PD-1 checkpoint inhibitor primarily for toxicity or intolerability are not eligible for the study.

- For patients in Cohort 2: immune checkpoint inhibitor or biologic treatment (e.g., bevacizumab) within 2 weeks prior to initiation of study treatment, or other systemic treatment for NSCLC within 2 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Eligibility only for the control/comparator arm
- Known targetable *ROS1*, *BRAF*^{V600E}, or *RET* proto-oncogene genomic aberrations

4.1.2.2 Exclusion Criteria for Stages 1 and 2

Patients who meet any of the following criteria will be excluded from Stage 1 and from Stage 2:

- Prior allogeneic stem cell or solid organ transplantation
- Treatment with systemic immunostimulatory agents (including, but not limited to, IFN and IL-2) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor- α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressant medication during study treatment, with the following exceptions:

Patients who received acute, low-dose, systemic immunosuppressant medications or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.

Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the *final* dose of atezolizumab
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

Use of an indwelling catheter (e.g., PleurX[®]) is allowed.
- Uncontrolled tumor-related pain

Patients requiring pain medication must be on a stable regimen at study entry.

Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.

- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected serum calcium > ULN)
- Symptomatic, untreated, or actively progressing CNS metastases

Patients with a history of CNS metastases treated with CNS-directed therapies (e.g., stereotactic body radiotherapy [SBRT], whole-brain radiotherapy [WBRT]) are eligible, provided that all of the following criteria are met:

- Measurable disease, per RECIST v1.1, must be present outside the CNS.
- The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
- Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
- There is no evidence of interim progression between completion of CNS-directed therapy and the screening brain scan.
- The patient has not received stereotactic radiotherapy within 7 days prior to initiation of study treatment or WBRT within 14 days prior to initiation of study treatment or neurosurgical resection within 28 days prior to initiation of study treatment.
- The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anti-convulsant therapy at a stable dose is permitted.

Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.

- History of leptomeningeal disease
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see [Appendix 4](#) for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study.

Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

- Rash must cover <10% of body surface area.
 - Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
 - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan
 - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
 - History of malignancy other than NSCLC within 2 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, nonmelanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
 - Active tuberculosis
 - Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety
 - Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
 - Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
 - Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
 - Grade ≥ 3 hemorrhage or bleeding event within 28 days prior to initiation of study treatment
 - Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study

Placement of central venous access catheter (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.

- Adverse events from prior anti-cancer therapy that have not resolved to Grade ≤ 1 or better, with the exception of alopecia of any grade, Grade ≤ 2 peripheral neuropathy, and immune checkpoint inhibitor-related hypothyroidism Grade ≤ 2
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies
- Known allergy or hypersensitivity to any of the study drugs or their excipients
- Patients entering Stage 2: inability to tolerate atezolizumab during Stage 1
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study

Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

4.1.2.3 Additional Exclusion Criteria for Atezo+Tira Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the Atezo+Tira arm during Stage 1:

- Known hypersensitivity to any component of atezolizumab or tiragolumab
- Acute Epstein-Barr virus (EBV) infection or known or suspected chronic active EBV infection at screening



- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease, or current alcohol abuse

4.1.2.4 Additional Exclusion Criteria for Atezo+Tira+XL092 Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the Atezo+Tira+XL092 arm *during Stage 1*:

- Patients who meet any of the exclusion criteria for Atezo+Tira arm listed under Section [4.1.2.3](#)
- Prior treatment with XL092
- Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before first dose of study treatment.

- Concomitant anticoagulation with oral anticoagulants (e.g., warfarin, direct thrombin, and Factor Xa inhibitors) and platelet inhibitors (e.g., clopidogrel)

Allowed anticoagulants are low-dose aspirin for cardioprotection (per local applicable guidelines) and *prophylactic use of* low-molecular-weight heparins (LMWHs).

Individualized therapeutic anticoagulation therapy with heparin or specified direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban is allowed if it can be provided safely and effectively.

- Patients with uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
 - Cardiovascular disorders:

Uncontrolled hypertension defined as sustained blood pressure (BP) > 140 mmHg systolic or 90 mmHg diastolic despite optimal antihypertensive treatment.

Stroke (including transient ischemic attack), myocardial infarction, or other ischemic event or pulmonary embolism within 6 months before the first dose of study treatment.

Patients with a diagnosis of incidental, subsegmental pulmonary embolism or deep vein thrombosis within 6 months of the first dose of study treatment are allowed if stable, asymptomatic, and treated with anticoagulation for at least 2 weeks before the first dose of study treatment. The Medical Monitor is available to advise as needed.
 - Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
 - Tumors invading the GI-tract from external viscera
 - Active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, or acute pancreatitis
 - Acute obstruction of the bowel, gastric outlet, or pancreatic or biliary duct within 6 months of the first dose of study treatment unless cause of obstruction is definitively managed and patient is asymptomatic
 - Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose of study treatment

Complete healing of an intra-abdominal abscess must be confirmed before first dose of study treatment.
 - Known gastric or esophageal varices
 - Clinically significant hematuria, hematemesis, or hemoptysis of >0.5 teaspoon (2.5 mL) of red blood, or other history of significant bleeding (e.g., pulmonary hemorrhage) within 12 weeks of the first dose of study treatment
 - Cavitating pulmonary lesion(s) or known endobronchial disease manifestation

- Lesions invading major blood vessel including, but not limited to, inferior vena cava, pulmonary artery, or aorta
Patients with intravascular tumor extension may be eligible. The Medical Monitor is available to advise as needed.
- Serious non-healing wound/ulcer/bone fracture.
Non-healing wounds or ulcers are permitted if due to tumor-associated skin lesions.
- Malabsorption syndrome
- Requirement for hemodialysis or peritoneal dialysis
- Major surgery (e.g., GI surgery, removal or biopsy of brain metastasis) within 8 weeks prior to first dose of study treatment; prior laparoscopic nephrectomy within 4 weeks prior to first dose of study treatment; or minor surgery (e.g., simple excision, tooth extraction) within 10 days of the first dose of study treatment
Complete wound healing from major or minor surgery must have occurred at least prior to first dose.
Fresh tumor biopsies should be performed at least 7 days before the first dose of study treatment. Patients with clinically relevant ongoing complications from prior surgical procedures, including biopsies, are not eligible.
- QT interval corrected through use of Fridericia's formula (*average* QTcF) >450 ms for males or >470 ms for females *within the screening period*.
- Inability to swallow study treatment formulation
- Radiation therapy for bone metastasis within 2 weeks of first dose of study treatment or any other radiation therapy within 4 weeks of the first dose of study treatment.
Patients with clinically relevant ongoing complications from prior radiation therapy are not eligible.

4.1.2.5 Additional Exclusion Criteria for Atezo+Camon Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the Atezo+Camon arm during Stage 1:

- Last systemic treatment line *other than platinum-containing therapy and/or progressive disease as best response to platinum-containing therapy*
- Prior therapy with an ATR or DNA-dependent protein kinase (DNA-PK) inhibitor

- No red blood cell or platelet transfusions, or growth factors within 14 days of first dose of study treatment and the following other hematologic criteria:
 - Hemoglobin: < 10 g/dL
 - Platelet count < 120,000 cells/mm
- Inadequately controlled hypertension (defined as systolic BP > 150 mmHg and/or diastolic BP > 100 mmHg), based on an average of ≥ 3 BP readings on ≥ 2 sessions, despite adequate treatment prior to first dose of camonsertib
- Moderate or severe hepatic impairment (i.e., Child-Pugh class B or C)
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, or recent history of myocardial infarction that in the opinion of the investigator will pose an increased risk of rhythm abnormalities
- *Confirmed* QTcF > 450 ms for males or > 470 ms for females within *the screening period*
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- History or current condition (such as transfusion-dependent anemia or thrombocytopenia), therapy, or laboratory abnormality that might confound the study results, or interfere with the patient's participation for the full duration of the study treatment
- Life-threatening illness, medical condition, or organ system dysfunction (such as coagulopathy, encephalopathy or ascites requiring drainage within 4 weeks prior to enrollment) or other reasons which, in the investigator's opinion, could compromise the patient's safety, or interfere with or compromise the integrity of the study outcomes
- Current treatment with medications that are well-known to prolong the QT interval (see [Appendix 21](#))
- History of myelodysplastic syndrome or acute myeloid leukemia diagnosis
- Patients who are receiving strong CYP3A inhibitors or inducers (see [Appendix 22](#)), P-glycoprotein inhibitors and/or breast cancer resistant protein (BCRP) inhibitors within 5 half-lives prior to first dose of study treatment
- Known hypersensitivity to any of the ingredients of camonsertib
- Patients with active, uncontrolled bacterial, fungal, or viral infection

4.1.2.6 Additional Exclusion Criteria for Atezo+Bev+Camon Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the Atezo+Bev+Camon arm during Stage 1:

- *Patients who meet any of the exclusion criteria for bevacizumab-containing arms listed in Section 4.1.2.9*
- *Patients who meet any of the exclusion criteria for the Atezo+Camon arm listed in Section 4.1.2.5*

4.1.2.7 Additional Exclusion Criteria for Atezo+Bev+Tira Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the Atezo+Bev+Tira arm during Stage 1:

- *Patients who meet any of the exclusion criteria for bevacizumab-containing arms listed in Section 4.1.2.9*
- *Patients who meet any of the exclusion criteria for the Atezo+Tira arm listed in Section 4.1.2.3*

4.1.2.8 Additional Exclusion Criteria for Docetaxel-Containing Arms during Stage 1 and Stage 2

Patients who meet any of the following criteria will be excluded from docetaxel-containing arms during Stage 1 and Stage 2:

- Prior treatment with docetaxel
- History of severe hypersensitivity to docetaxel or to other drugs formulated with polysorbate 80
- Grade ≥ 2 peripheral neuropathy
- Treatment with strong inhibitors or strong inducers of CYP3A4 within 14 days prior to initiation of study treatment or anticipation of need for such treatment during study treatment

4.1.2.9 Additional Exclusion Criteria for Bevacizumab-Containing Arms during Stage 1

Patients who meet any of the following criteria will be excluded from the bevacizumab-containing arms during Stage 1:

- Patients with squamous NSCLC
- Inadequately controlled hypertension (defined as systolic BP > 150 mmHg and/or diastolic BP > 100 mmHg), based on an average of ≥ 3 BP readings on ≥ 2 sessions
Anti-hypertensive therapy to achieve these parameters is allowed.
- History of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment

- History of hemoptysis (≥ 2.5 mL of bright red blood per episode) within 1 month prior to initiation of study treatment
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (≤ 10 days prior to initiation of study treatment) use of aspirin (> 325 mg/day) or clopidogrel (> 75 mg/day)

Note: The use of full-dose oral or parenteral anticoagulants for therapeutic purpose is permitted as long as the INR and/or aPTT is within therapeutic limits (according to institution standards) within 7 days prior to initiation of study treatment and the patient has been on a stable dose of anticoagulants for ≥ 2 weeks prior to initiation of study treatment. Prophylactic use of anticoagulants is allowed. However, the use of direct oral anticoagulant therapies, such as dabigatran (Pradaxa[®]) and rivaroxaban (Xarelto[®]), is not recommended due to bleeding risk.

- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to initiation of study treatment
- History of abdominal or tracheoesophageal fistula, GI perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment
- History of intestinal obstruction and/or clinical signs or symptoms of GI obstruction, including subocclusive or occlusive syndrome related to the underlying disease, within 6 months prior to initiation of study treatment or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding within 6 months prior to initiation of study treatment

Patients with signs or symptoms of subocclusive or occlusive syndrome or with intestinal obstruction at the time of initial diagnosis may be enrolled if they had received definitive (surgical) treatment for symptom resolution.

- Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure
- Serious, nonhealing or dehiscing wound, active ulcer, or untreated bone fracture
- Grade ≥ 2 proteinuria, as demonstrated by $\geq 2+$ protein on dipstick urinalysis and ≥ 1.0 g of protein in a 24-hour urine collection

All patients with $\geq 2+$ protein on dipstick urinalysis at screening must undergo a 24-hour urine collection for protein. Patients with $< 2+$ protein on dipstick urinalysis are eligible for the study.

- Metastatic disease that involves major airways or blood vessels, or centrally located mediastinal tumor masses (< 30 mm from the carina) of large volume
- History of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including, but not limited to, peptic ulcer disease, diverticulitis, or colitis
- Ablative radiotherapy within 28 days or abdominal/pelvic radiotherapy within 60 days prior to initiation of study treatment

- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to initiation of study treatment; or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 60 days prior to initiation of study treatment; or anticipation of need for major surgical procedure during the course of the study or non-recovery from side effects of any such procedure

4.1.2.10 Additional Exclusion Criteria for Radiotherapy-Containing Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the radiotherapy-containing arm during Stage 1:

- Patients who meet any of the exclusion criteria for bevacizumab-containing arms listed under Section [4.1.2.9](#)
- Lack of lesions where SBRT can safely be applied
- Serious medical comorbidities precluding radiotherapy. These include, but are not limited to, the following:
 - Interstitial lung disease in patients requiring thoracic radiation
 - Active Crohn disease in patients where the GI tract will receive radiotherapy, or active ulcerative colitis where the bowel will receive radiotherapy
 - Connective tissue disorders such as lupus or scleroderma
 - Known genetic disorders associated with increased toxicity to radiation therapy (e.g., ataxia telangiectasia)
- Substantial overlap with a previously treated radiation volume:

Prior radiotherapy in general is allowed, as long as the composite plan meets dose constraints herein.

For patients treated with radiation previously, biological effective dose calculations should be used to equate previous doses to the tolerance doses listed in the technical radiotherapy manual. All such cases must be discussed with the responsible radiotherapy investigator at the site. The Medical Monitor is available to advise as needed.

Lesions that have been treated with radiotherapy within the last 6 months should not be radiated.

4.1.2.11 Additional Exclusion Criteria for Atezo + Lina Arm during Stage 2

Patients who meet any of the following criteria will be excluded from the Atezo + Lina arm during Stage 2:

- Known diagnosis of Type 2 diabetes mellitus currently treated with a DPP-4 inhibitor
- Inability to swallow medication or malabsorption condition that would alter the absorption of orally administered medications

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and Stage 1 treatment assignment from the interactive voice or web-based response system (IxRS). Patients who enroll in Stage 2 will be assigned to treatment through use of the IxRS and will retain the same patient identification number that was assigned in Stage 1.

For Stage 1, this study will employ a permuted-block randomization method with dynamically changing randomization ratios to account for fluctuation in the number of treatment arms that are open for enrollment over the course of the study. The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control or comparator arm will be no more than 50%. The randomization ratios may be altered to increase enrollment in a particular arm.

Randomization will take into account general exclusion criteria and arm-specific exclusion criteria as outlined in Sections 4.1.1 and 4.1.2. For example, the Atezo+SG arm will be removed as an option for patients who are ineligible for that arm. If a patient is randomized to the Atezo+Bev+RTx arm but cannot start treatment with radiotherapy for clinical/technical reasons (e.g., contraindication for radiotherapy that is detected after randomization, e.g., during the radiotherapy planning process), this patient will be allowed to skip radiotherapy and start treatment with Atezo+Bev. The reason for skipping radiotherapy will be documented accordingly. If a patient is eligible for a control/comparator arm *only*, the patient will not be enrolled in the study.

If more than one mandatory serial biopsy arm is open for enrollment at a time, eligible patients (at participating sites) will be assigned to one of the available arms by the Sponsor.

Patients in Cohort 2 who are eligible for more than one Stage 2 treatment arm will be assigned a treatment arm by the investigator.

Patients who do not receive at least one dose of each drug for their assigned systemic treatment regimen will not be included in the efficacy analyses. Additional patients may be enrolled in Stage 1 to reach the target number of treated patients planned for analysis.

4.3 STUDY TREATMENT

Details on the therapeutic agents for each treatment arm are provided in the respective appendix for that treatment arm, as outlined in Table 4 for Stage 1 and Table 6 for Stage 2.

4.3.1 Investigational Medicinal Product Accountability

The IMPs for this study are atezolizumab, tiragolumab, XL092, docetaxel, linagliptin, bevacizumab, sacituzumab govitecan, evolocumab, and camonsertib. [Appendix 23](#) identifies all IMPs, non-investigational medicinal products, auxiliary medicinal products, and unauthorized auxiliary medicinal products for this study. All IMPs required for completion of this study will be provided by the Sponsor where required by local practices. The study site will acknowledge receipt of IMPs supplied by the Sponsor. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on a drug inventory log.

4.3.2 Post-Trial Access to Study Treatment

Currently, the Sponsor does not have any plans to provide study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing study treatments in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY AND PROHIBITED FOOD

Details on concomitant therapy, prohibited food, and additional restrictions for each treatment arm are provided in the respective appendix for that treatment arm (see [Appendix 7–Appendix 19](#)).

4.5 STUDY ASSESSMENTS

A schedule of activities to be performed during the study is provided for each treatment arm in [Appendix 7–Appendix 19](#). All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each infusion; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed

Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Written informed consent must also be obtained before performing screening evaluations and study-related procedures for Stage 2.

Screening evaluations for Stage 1 and Stage 2 are to be performed within 28 days prior to initiation of study treatment (Day 1). For the Atezo+Bev+RTx arm, screening evaluations are to be performed within 28 days prior to randomization. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment.

Patients who fail their first screening for study eligibility (Stage 1 or Stage 2) may qualify for re-screening opportunities at the investigator's discretion (up to two re-screenings per stage and cohort may be possible). Patients must re-sign the consent form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within a specified time prior to Day 1, or, for the Atezo+Bev+RTx arm, within a specified time prior to randomization (see the schedule of activities for screening in [Appendix 2](#)) may be used; such tests do not need to be repeated for screening or re-screening.

4.5.2 Medical History, Molecular Profile, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline.

The patient's molecular profile for lung cancer, if available, will be recorded at screening and whenever updated information becomes available during the study. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within a specified time prior to initiation of study treatment will be recorded (as outlined for each arm in [Appendix 7–Appendix 19](#)). At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions electronic Case Report Form (eCRF).

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic BP while the patient is in a seated position, pulse oximetry, and temperature.

Vital signs should be measured at specified timepoints, as outlined for each arm in the schedules of activities (see [Appendix 7–Appendix 19](#)), and as clinically indicated.

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 48 weeks following initiation of treatment and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1. However, patients in atezolizumab-containing arms who continue treatment after radiographic disease progression will undergo tumor assessments every 6 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see Section [3.1.1](#) for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new, non-protocol-specified anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.

All measurable and/or evaluable lesions should be assessed and documented at screening (in both Stage 1 and Stage 2). Brain metastases treated with radiotherapy or surgery will not be considered measurable or evaluable but will be documented at screening as a site of metastatic disease. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment, or, for the Atezo + Bev + RTx arm, within 28 days prior to randomization, do not have to be repeated at screening.

Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or magnetic resonance imaging (MRI) scans (with IV contrast) of the chest, abdomen, pelvis, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast

allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head should be performed. A CT scan with contrast or MRI scan with contrast of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if contrast is contraindicated). Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

All measurable and/or evaluable lesions identified at baseline should be re-assessed at each subsequent tumor evaluations according to the schedule above. Brain metastases treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). To facilitate evaluation of post-progression tumor changes while treatment is ongoing, tumor assessments must be continued after disease progression per RECIST v1.1 for patients who receive treatment beyond progression. This includes continued measurement of target lesions, evaluation of non-target lesions (including monitoring for further worsening of any non-target lesions that have shown unequivocal progression), and evaluation of any newly identified lesions (including measurements, if lesions are measurable) at all subsequent assessments.

Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see [Appendix 1](#)).

Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Available results must be reviewed by the investigator prior to treatment administration.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)

- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, amylase, and lipase in all arms and ferritin where applicable
- Fasting lipid panel (performed for specified arms only; details provided in schedules of activities; only if evolocumab-containing arm is open for enrollment)
- Coagulation: INR and aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- [REDACTED]:
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- HIV serology, unless not permitted per local regulations
- HBV serology: HBsAg, hepatitis B surface antibody, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. [REDACTED]

[REDACTED]
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- C-reactive protein
- LDH
- Pregnancy test

All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted
 For patients on a bevacizumab-containing arm, if urinary protein is $\geq 2+$ on dipstick, then a 24-hour urine collection is required to check the total urinary protein. If there is an explanation for the positive dipstick result (e.g., menses), it should be recorded and there is no need to perform further laboratory assessments.
- Determination of tumor PD-L1 expression (through a documented local assessment using a health authority-approved PD-L1 IHC assay) and *EGFR* and *ALK* status (not needed for patients with known status and patients with squamous NSCLC) through local testing performed on tumor tissue collected at baseline via health authority-approved testing, per the assay's intended use, according to local laws and regulations.
- Baseline tumor tissue samples from the primary lesion or a metastatic lesion will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be used, provided the patient has not received any checkpoint inhibitor therapy since the time of the biopsy. For patients in Cohort 2 who have received treatment with checkpoint inhibitor therapy beyond initial radiographic progression per RECIST v1.1, collection of tumor tissue may be discussed with the Medical Monitor.

A representative FFPE tumor specimen in a paraffin block (preferred) or at least 15–16 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report to the designated central laboratory, once a patient is randomized.

Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable TCs that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that requires decalcification is not acceptable.

Remaining archival tumor tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first.

Samples for the following laboratory test will be sent to a central laboratory or to the study site's local laboratory for analysis:

- Soluble CD25 (performed for specified arms only; details provided in the respective schedules of activities)

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Serum sample for analysis of autoantibodies: anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody in all arms and anti-citrullinated peptide antibody in specified arms only

Serum samples collected for the assessment of PK, anti-drug antibody (ADAs), or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.

- Plasma or serum samples for PK analysis (see [Appendix 7–Appendix 19](#))
- Plasma or serum samples for immunogenicity analysis (see [Appendix 7–Appendix 19](#))
- Plasma, serum, and peripheral blood mononuclear cell (PBMC) samples for exploratory research on biomarkers (see [Appendix 7–Appendix 19](#))
- Tumor tissue sample collected at baseline (as described above) for exploratory research on biomarkers
- Mandatory serial biopsy arms at participating sites (see Section [3.1.2](#)): tumor tissue sample collected 4 weeks (± 7 days) after initiation of Stage 1 treatment (if deemed clinically feasible by the investigator) for exploratory research on biomarkers

Patient should have at least two accessible tumors that are amenable to excisional, punch, or core-needle biopsy (a minimum of three cores, 18-gauge needle or larger [16-gauge needle preferred]) without unacceptable risk of a major procedural complication. If it is planned that more than one biopsy will be obtained from a single lesion, the lesion should be large enough to permit successive biopsies ≥ 1 cm apart.

The Informed Consent Form will contain a separate section that addresses the mandatory serial biopsy arms. A separate, specific signature will be required to document a patient's agreement to participate in one of these arms.

- Tumor tissue sample collected during Stage 1, at the time of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator (see Section [3.1.1](#) for details) (if deemed clinically feasible by the investigator) for exploratory research on biomarkers

Biopsies should be performed within 40 days after determination of unacceptable toxicity, disease progression, or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

Exploratory biomarker research may include, but will not be limited to, analysis of genes or gene signatures associated with tumor immunobiology, PD-L1, cytokines associated with T-cell activation, T-cell receptor repertoire, carcinoembryonic antigen, or density,

localization, and activation status of immune cells and their subsets. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of NGS of a comprehensive panel of genes. Genomic research with a focus on somatic variants may be conducted by comparing DNA extracted from blood or PBMCs with DNA extracted from tissue to distinguish somatic variants from germline variants. Genomic profiling may include whole genome sequencing (WGS) or WES of blood samples, with a focus on somatic variants.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.9), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum and plasma samples collected for PK analysis or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Plasma, serum, PBMC, blood, and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the exception of the samples that undergo WES, which will be stored until they are no longer needed or until they are exhausted. However, the storage period for the WES samples will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.7 Electrocardiograms

An ECG will be performed at screening, at specified timepoints for arms that require additional ECG monitoring, and as clinically indicated, as outlined for each arm in the schedules of activities (see [Appendix 7–Appendix 19](#)). ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.8 Optional Tumor Biopsies

Patients will be given the option of consenting to additional tumor biopsies. Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation, if deemed clinically feasible. In addition, patients who consent to optional biopsies may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

An Informed Consent Form with a separate, specific signature will be required to document a patient's agreement to undergo optional biopsies.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section [4.5.6](#). Refer to Section [4.5.6](#) for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.9 Optional Samples for Research Biosample Repository

4.5.9.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of biomarker assays, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker assays and establish the performance characteristics of these assays

4.5.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section [4.5.9](#)) will not be applicable at that site.

4.5.9.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to CIT or diseases:

- Blood samples collected on Day 1 of Cycle 1 during Stage 1 and Stage 2
- Leftover blood, serum, plasma, PBMC, and tissue samples (with the exception of leftover tissue from archival FFPE blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides) collected during Stage 1 or Stage 2 of the study, including leftover tissue samples from additional tumor biopsies or medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via WGS, NGS, or other genomic analysis methods.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.9.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.9.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.9.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from this study.

4.5.9.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Use of another non-protocol anticancer therapy
- Pregnancy

- Atezolizumab-containing arms: loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details)

For details on study treatment discontinuation in the atezolizumab plus docetaxel arm, see Section 3.1.1.

- Docetaxel control arm: radiographic disease progression per RECIST v1.1

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Patients will return to the clinic for a treatment discontinuation visit ≤ 30 days after the *final* dose of study treatment. The visit at which response assessment shows progressive disease or loss of clinical benefit may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities provided for each arm in [Appendix 7–Appendix 19](#).

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

A safety plan for each treatment arm, including a summary of risks and management guidelines for patients who experience specific adverse events, is provided in the respective appendix for that treatment arm ([Appendix 7–Appendix 19](#)).

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN- γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section [5.3.5.12](#).

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections [5.3.5.9](#) and [5.3.5.10](#), for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.

- Requires or prolongs inpatient hospitalization (see Section [5.3.5.11](#))

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for each treatment arm are listed in the respective appendix for that treatment arm (see Appendix 7–Appendix 19).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.3.5.12–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until 30 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 8 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 8 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living ^a
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living ^{b, c}
4	Life-threatening consequences or urgent intervention indicated ^d
5	Death related to adverse event ^d

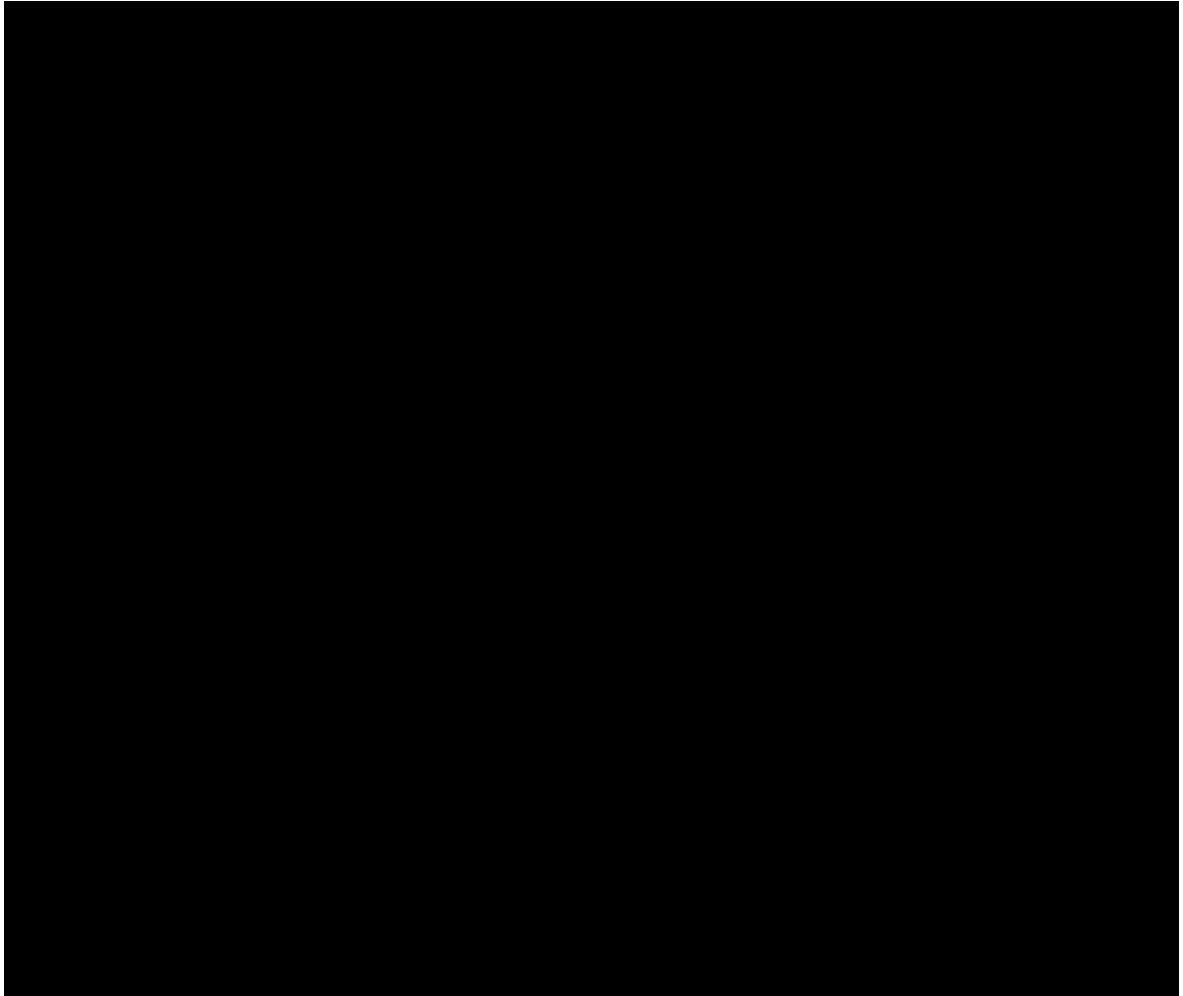
NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on NCI CTCAE (v4.0), which can be found at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- ^a Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- ^b Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
- ^c If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.
- ^d Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

The ASTCT CRS Consensus Grading Scale (Table 9) (Lee et al. 2019) should be used in addition to the NCI CTCAE v4.0 when reporting severity of CRS (see Section 5.3.5.1 for details on CRS reporting).



5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also [Table 10](#)):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event

- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

Table 10 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	<u>An adverse event will be considered related, unless it fulfills the criteria specified below.</u> Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related or Injection-Site Reactions and Cytokine Release Syndrome

There may be significant overlap in signs and symptoms of infusion-related reactions (IRRs) and CRS. While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, hemophagocytic lymphohistiocytosis, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion or injection should be captured on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction", "injection-site reaction", or "cytokine release syndrome"). Avoid ambiguous terms such as "systemic reaction." Cases of late-onset CRS should be reported as "cytokine release syndrome" on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated Infusion-Related, Injection Reaction eCRF, or

Cytokine Release Syndrome eCRF, as appropriate. If a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with associated signs and symptoms also recorded separately on the dedicated Infusion-Related, Injection Reaction eCRF, or Cytokine Release Syndrome eCRF.

NCI CTCAE v4.0 [REDACTED] should be used when reporting severity of CRS on the Adverse Event eCRF. NCI CTCAE v4.0 should be used when reporting severity of organ toxicities associated with CRS on the dedicated Cytokine Release Syndrome eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided [Appendix 6](#).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related or injection reactions (see Section [5.3.5.1](#)), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.

- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin $5 \times$ ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high BP), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3 \times$ baseline value) in combination with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of NSCLC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of NSCLC

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

The patient has not experienced an adverse event.

- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Reporting Requirements for Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose

- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

In some cases, a medication error may be intercepted prior to administration of the drug.

- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For atezolizumab (RO5541267), tiragolumab (RO7092284), XL092, camonsertib (RO7616992), evolocumab, linagliptin, docetaxel, sacituzumab govitecan, and bevacizumab (RO4876646), adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with atezolizumab, tiragolumab, XL092, camonsertib, evolocumab, linagliptin, docetaxel, sacituzumab govitecan, and

bevacizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list

of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, all adverse events will be reported until 30 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report

via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 135 days after the *final* dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

Reporting requirements for pregnancies are described for each treatment arm in the respective appendix for that treatment arm (see [Appendix 7–Appendix 19](#)).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 135 days after the *final* dose of study treatment or until initiation of new, non-protocol-specified systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Atezolizumab Investigator's Brochure
- Tiragolumab Investigator's Brochure
- Camonsertib Investigator's Brochure
- XL092 Investigator's Brochure
- Bevacizumab Investigator's Brochure
- Sacituzumab Govitecan Investigator's Brochure
- Summary of Product Characteristics for docetaxel, evolocumab, and linagliptin

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The final study analysis will be based on patient data collected through study discontinuation. If not otherwise specified, efficacy analyses will be based on the efficacy-evaluable population, defined as all patients who receive at least one dose of each drug for their assigned treatment regimen, and other analyses will be based on the safety-evaluable population, defined as all patients who receive any amount of study treatment.

The analysis results will be summarized by the treatment that patients actually received, and as well as by stage (Stage 1 or Stage 2). Data will be described and summarized as warranted by sample size. Continuous variables will be summarized through use of means, standard deviations, medians, and minimum and maximum values. Categorical variables will be summarized through use of counts and percentages. Listings will be used in place of tables in the event of small sample sizes.

New baseline values will be established for the Stage 2 efficacy and safety analyses. For evaluation of tumor response, new baseline tumor assessments will be established as described in Section 4.5.5. For other endpoints (e.g., change from baseline in vital signs or laboratory test results), the last non-missing value prior to the patient's first dose during Stage 2 will serve as the new baseline.

6.1 DETERMINATION OF SAMPLE SIZE

This study is not designed to make explicit power and Type I error considerations for a hypothesis test. Instead, this study is designed to obtain preliminary efficacy, safety, and PK data on immunotherapy-based treatment combinations when administered to patients with metastatic NSCLC.

Approximately 425–675 *patients* will be randomly allocated to the control/comparator and experimental arms during the study during Stage 1, excluding closed treatment arms and those that have already reported (see Table 5). Enrollment within the experimental arms will take place in two phases: a preliminary phase followed by an expansion phase.

Approximately 15 patients with serial biopsy samples will be enrolled in each mandatory serial biopsy arm.

However, the number of patients may be reduced if optional on-treatment biopsies have been collected (and determined to be evaluable) from consenting patients treated with that same CIT combination during the preliminary phase, to limit on-treatment biopsy collection to approximately 15 patients per CIT combination within each cohort.

With approximately 15 patients with serial biopsies in each arm, an 80% two-sided confidence interval for a 30% increase in CD8⁺ T cells in the center of the tumor would be 22.8%, 37.2%, assuming a standard deviation of 0.20 for the difference in CD8⁺ T cells between paired samples (i.e., baseline vs. on-treatment samples, baseline vs. post-progression samples, or on-treatment vs. post-progression samples).

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment will be summarized by region, country, and investigator by treatment arm within the two stages. Patient disposition will be summarized by treatment arm within each stage. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm within each stage.

For safety-evaluable patients, study drug administration data will be tabulated or listed by treatment arm within each stage, and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose and dose intensity for each study drug. Reasons for discontinuation of study drugs will also be tabulated.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, weight, malignancy duration, metastatic disease site, histology [squamous vs. non-squamous], and baseline ECOG Performance Status) will be summarized overall and by treatment arm within each stage.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is objective response during Stage 1, as defined in Section 2 (see [Table 2](#)). Patients with missing or no response assessments will be classified as non-responders.

ORR, defined as the proportion of patients with a complete or partial response, will be calculated for each arm, along with 95% confidence intervals (Clopper–Pearson method). The difference in ORR between the experimental arms and the corresponding comparator/control arm will also be calculated, along with 95% confidence intervals, using the Wald method with continuity correction.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are PFS, OS, and PFS and OS at specific timepoints (e.g., 6 months), duration of response (DOR), and disease control during Stage 1, as defined in Section 2 (see [Table 2](#)). PFS, DOR, and disease control are determined by the investigator according to RECIST v1.1.

DOR will be derived for efficacy-evaluable patients with a complete or partial response.

For patients who do not have documented disease progression or death in a study stage, PFS and DOR will be censored at the day of the last tumor assessment.

Patients who are still alive at the time of OS analysis will be censored at the last date they were known to be alive.

The Kaplan-Meier method will be used to estimate the median for PFS, OS, and DOR, with 95% confidence intervals constructed through use of the Brookmeyer and Crowley method. OS rate at specific timepoints will also be estimated through use of the Kaplan-Meier method, with 95% confidence intervals calculated on the basis of the Greenwood estimate for the variance.

Disease control rate, defined as the proportion of patients with stable disease for ≥ 12 weeks, a partial response, or a complete response, will be calculated for each treatment arm, with 95% confidence intervals estimated through use of the Clopper-Pearson exact method.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are objective response, PFS, DOR, and disease control during Stage 2, as determined by the investigator according to RECIST v1.1 (see [Table 3](#)).

Objective response, PFS, DOR, and disease control will be analyzed through use of the same methods described in Sections [6.4.1](#) and [6.4.2](#). DOR will be derived for efficacy-evaluable patients with a complete or partial response.

6.5 SAFETY ANALYSES

Verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v4.0, [REDACTED].

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs and ECGs, and exposure to study drugs. Exposure to combination treatment and length of safety follow-up will be summarized by treatment arm within each stage.

Treatment-emergent adverse events occurring after initiation of treatment will be summarized. For each patient, the maximum reported severity of each adverse event will be used in the summaries by severity grade. All treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of study treatment, Grade ≥ 3 adverse events, deaths, and causes of death will be listed and summarized by mapped term, appropriate thesaurus level, and NCI CTCAE severity grade.

Relevant laboratory, vital sign (pulse rate, respiratory rate, BP, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Sparse samples will be collected for potential PK analyses of atezolizumab (patients who receive at least one dose of atezolizumab) and specified drugs given in combination with atezolizumab (patients who receive at least one dose of the drug). Serum or plasma concentrations of the various study drugs will be reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by treatment arm, and by cycle and day when appropriate and as data allow. Individual and median serum or plasma concentrations of the various study drugs will be plotted by treatment arm and cycle and day. PK data for combination drugs may be compared with available historical data from internal and published previous studies. Atezolizumab concentration data may be pooled with data from other studies using an established population PK model to derive PK parameters such as clearance, volume of distribution, and area under the curve.

6.7 IMMUNOGENICITY ANALYSES

Immunogenicity may be assessed for atezolizumab and other study treatments as appropriate (refer to arm-specific appendices for details). The immunogenicity analyses will include all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

For atezolizumab, the numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after baseline (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or are missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be post-treatment-ADA negative if they are ADA negative or are missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

For other study treatments where ADA is tested, positivity will be determined according to standard methods established in previous studies of that drug.

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.8 BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of these biomarkers with response to study drugs, taking into account efficacy and safety endpoints.

6.9 INTERIM ANALYSES

It is anticipated that interim analyses will be conducted over the course of the study, with the earliest (Stage 1) interim analysis taking place when at least one experimental arm has completed enrollment in the preliminary phase, approximately 15 patients have been enrolled in the control arm for that same cohort, and patients have been followed for a minimum of 6 weeks for the primary endpoint analysis (ORR). If no complete or partial responses are observed in an experimental arm, enrollment in that arm will be stopped. Otherwise, a posterior probability may be used to guide further enrollment in a treatment arm based on an interim analysis of clinical activity in the experimental arm compared with the control arm.

If the interim analysis suggests that the activity in an experimental arm is higher than that in the control arm, there may be further enrollment of [REDACTED] additional patients in the experimental arm.

An interim analysis will also be conducted after approximately 15 patients have been enrolled in a Stage 2 treatment arm and followed for a minimum of 6 weeks. If no complete or partial responses are observed after at least 15 patients have been enrolled and followed for a minimum of 6 weeks in the Atezo + Lina arm, or the Atezo + Docetaxel arm (Stage 2), further enrollment in that arm will be stopped.

The interim analyses will be performed and interpreted by Sponsor study team personnel.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent

directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section [7.5](#).

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMPs, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Forms (and ancillary sample Informed Consent Forms such as a Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, they will be provided in a certified translation into the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal

health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient, last visit).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring. Screening and enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate patient safety throughout the study. An SOC will provide external expert opinions on the safety data collected during the study.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4). In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

<https://www.roche.com/innovation/process/clinical-trials/data-sharing/>

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1

Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.¹

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval ≤ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

¹ For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis \geq 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area (e.g., brain metastases) or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, because CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with prior studies, if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new

lesions on a different modality, because the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention because they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm \times 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm

but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non-lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes because they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well, and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non-lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis.

Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions
Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters in the study (including baseline)
In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedules of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

All lymph nodes must be non-pathological in size (< 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

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If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response.

This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as having "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy.

The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in [Table 1](#).

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCE

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.

Appendix 2

Schedules of Activities for Screening


Table 1 Schedule of Activities for Stage 1 Screening

Assessment/Procedure	Stage 1 Screening ^a (Day –28 to –1)
Informed consent	x ^b
Demographic data	x
Medical history and baseline conditions	x
Molecular profile of lung cancer (if available)	x
Vital signs ^c	x
Weight	x
Height	x
Complete physical examination ^d	x
ECOG Performance Status	x
ECG ^e	x
Hematology ^f	x ^g
Chemistry ^h	x ^g
Amylase, lipase	x ^g
Coagulation (INR, aPTT)	x ^g
TSH, free T3 (or total T3 ⁱ), free T4	x
Viral serology ^{j, k}	x
C-reactive protein	x
LDH	x ^g
Pregnancy test ^l	x ^g
Urinalysis ^m	x
Tumor biopsy ⁿ	x
Baseline tumor assessments ^{o, p}	x ^g
Concomitant medications ^q	x
Adverse events ^r	x

Atezo + Bev + RTx = atezolizumab plus bevacizumab plus radiotherapy; CT = computed tomography; EBNA = Epstein-Barr virus nuclear antigen; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FDG = fluorodeoxyglucose; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PCR = polymerase chain reaction; PET = positron emission tomography; QTcF = QT interval corrected through use of Fridericia's formula; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; VCA = viral capsid antigen.

Appendix 2: Schedules of Activities for Screening

Table 1 Schedule of Activities for Stage 1 Screening (cont.)

- ^a Patients who fail their first screening for study eligibility may qualify for re-screening opportunities at the investigator's discretion (up to two re-screenings per stage and cohort may be possible). Patients must re-sign the consent form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within a specified time prior to randomization may be used; such tests do not need to be repeated for screening or re-screening.
- ^b Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.
- ^c Includes respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.
- ^d Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.
- ^e *Patients should be resting in a supine position for at least 10 minutes prior to ECG; for all patients in Cohort 1, triplicate ECGs should be performed at screening. If triplicate ECGs cannot be performed due to logistical challenges, single ECGs are permitted; however, if the single ECG read shows QTcF > 460 ms, two additional ECGs must be performed to determine the average QTcF. For all patients in Cohort 2, single 12-lead ECGs should be performed. If QTcF is >450 ms for males or >470 ms for females, another ECG must be recorded more than 30 minutes apart to confirm the QTcF prolongation.*
- ^f Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
- ^g Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment (Cycle 1, Day 1). For the Atezo+Bev+RTx arm, screening laboratory test results must be obtained within 14 days prior to randomization.
- ^h Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.
- ⁱ TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4.
- ^j Patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- ^k 
- ^l All women of childbearing potential will have a serum pregnancy test at screening.

Appendix 2: Schedules of Activities for Screening

Table 1 Schedule of Activities for Stage 1 Screening (cont.)

- ^m Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. Patients with non-squamous NSCLC with $\geq 2+$ protein on dipstick urinalysis at screening must undergo a 24-hour urine collection for protein, but only if a bevacizumab-containing arm is open for enrollment.
- ⁿ Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided that the tissue was obtained from a biopsy performed within 6 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy. For patients in Cohort 2 who received treatment with checkpoint inhibitor therapy beyond initial radiographic progression per RECIST v1.1, collection of tumor tissue may be discussed with the Medical Monitor. Refer to Section 4.5.6 for tissue sample requirements.
- ^o All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment, or within 28 days prior to randomization for the Atezo + Bev + RTx arm, do not have to be repeated at screening. Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, pelvis, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast, if feasible) of the abdomen, pelvis, and head should be performed. A CT scan with contrast or MRI scan with contrast of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if contrast is contraindicated). Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.
- ^p For patients that are potentially eligible for radiotherapy-containing arm, pretreatment 18-FDG PET/CT imaging is strongly recommended. 18-FDG PET/CT imaging performed as standard of care prior to obtaining information consent and within 56 days prior to randomization do not need to be repeated at screening.
- ^q Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 7 days prior to initiation of study treatment.
- ^r After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

Appendix 2: Schedules of Activities for Screening

Table 2 Schedule of Activities for Stage 2 Screening

Assessment/Procedure	Stage 2 Screening ^a
Informed consent	x ^b
Molecular profile of lung cancer (if available)	x
Vital signs ^c	x
Weight	x
Complete physical examination ^d	x
ECOG Performance Status	x
ECG ^e	x
Hematology ^f	x ^g
Chemistry ^h	x ^g
Coagulation (INR, aPTT)	x ^g
TSH, free T3 (or total T3 ⁱ), free T4	x
Viral serology ^j	x
Pregnancy test ^k	x ^g
Urinalysis ^l	x ^g
C-reactive protein	x
LDH	x ^g
Tumor response assessments ^m	x ^{m, n}
Concomitant medications ^o	x
Adverse events ^p	x

CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; FDG=fluorodeoxyglucose; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone.

- ^a The visit at which response assessment shows progressive disease may be used as the Stage 2 screening visit. Patients who fail their first screening for study eligibility may qualify for re-screening opportunities at the investigator's discretion (up to two re-screens per stage and cohort may be possible). Patients must re-sign the consent form prior to re-screening.
- ^b Written informed consent must be obtained before performing screening evaluations for Stage 2 except as noted in footnote "n" below.
- ^c Includes respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

Appendix 2: Schedules of Activities for Screening

Table 2 Schedule of Activities for Stage 2 Screening (cont.)

- ^d Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.
- ^e Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.
- ^f Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
- ^g Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment (Cycle 1, Day 1).
- ^h Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.
- ⁱ TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4.
- ^j At screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- ^k All women of childbearing potential will have a serum pregnancy test.
- ^l Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ^m All measurable and evaluable lesions should be assessed and documented. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast, if feasible) of the abdomen, pelvis, and head should be performed. A CT scan with contrast or MRI scan with contrast of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if contrast is contraindicated). Bone scans and CT scans of the neck should be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.
- ⁿ Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.
- ^o Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 7 *days* prior to initiation of study treatment.

Table 2 Schedule of Activities for Stage 2 Screening (cont.)

- ^P After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

Appendix 3

ECOG Performance Status Scale

Grade	Description
0	Fully active; able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care; confined to a bed or chair >50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG=Eastern Cooperative Oncology Group.

Appendix 4

Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

<ul style="list-style-type: none"> • Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myelitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome 	<ul style="list-style-type: none"> • Crohn disease • Dermatomyositis • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Granulomatosis with polyangiitis • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease – chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis 	<ul style="list-style-type: none"> • Myasthenia gravis • Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthrititis • Polyglandular autoimmune syndrome • Primary biliary cholangitis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren's syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease
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Appendix 5

Anaphylaxis Precautions

EQUIPMENT NEEDED

- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Maintain an adequate airway.
3. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations.

Appendix 6

Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab

Toxicities associated or possibly associated with atezolizumab or tiragolumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology when clinically indicated.

Although most *immune-mediated* adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab and/or tiragolumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment-related.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections in this appendix or the treatment arm-specific appendices.

- In general, tiragolumab and atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.

- [REDACTED]

- [REDACTED]

- [REDACTED]

- [REDACTED]

Appendix 6: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events associated with Atezolizumab and/or Tiragolumab

The investigator should consider the benefit–risk balance for a given patient prior to further administration of atezolizumab and tiragolumab. Resumption of atezolizumab and tiragolumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab and tiragolumab should be based on the investigator's *benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies, such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Coronavirus disease 2019 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in [Table A6-1](#).

Table A6-1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
[Redacted]	
a	[Redacted]
b	
c	
d	

Table A6-1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

[illegible]

HEPATIC EVENTS

Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in [Table A6-2](#).

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in [Table A6-3](#).

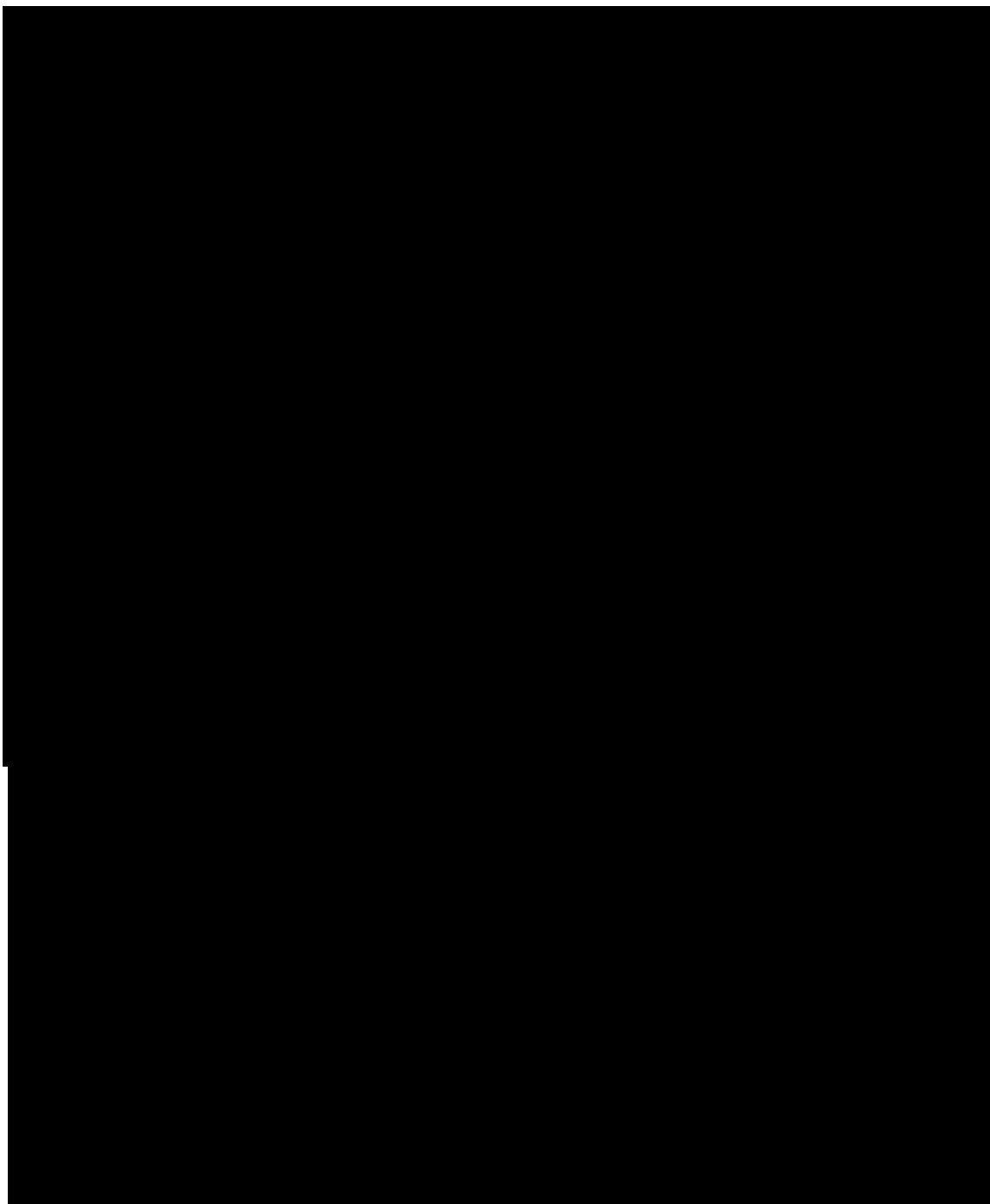
All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table A6-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management

[REDACTED]

Table A6-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)



ENDOCRINE EVENTS

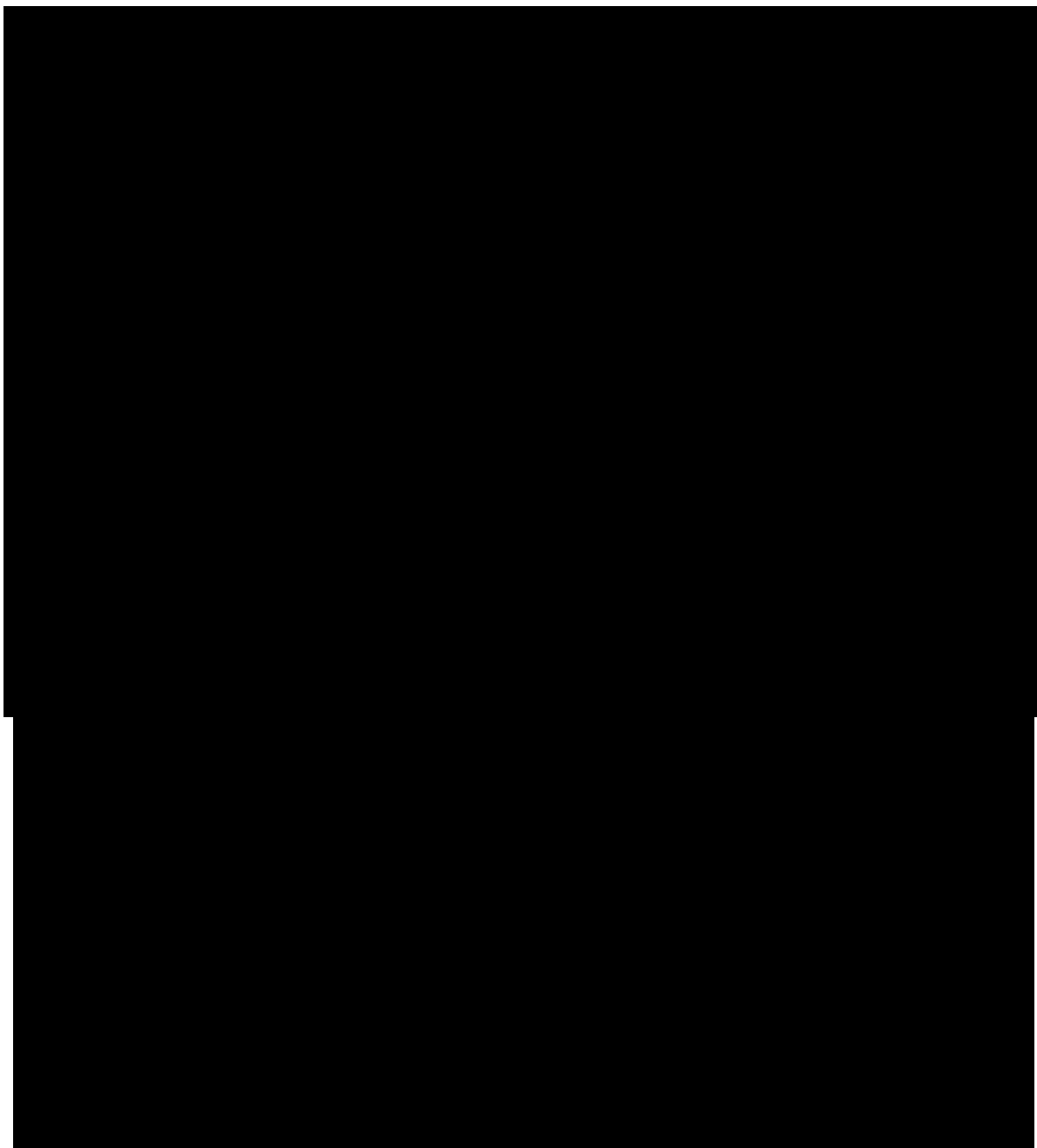
Management guidelines for endocrine events are provided in [Table A6-4](#).

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotrophic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table A6-4 Management Guidelines for Endocrine Events

Event	Management

Table A6-4 Management Guidelines for Endocrine Events (cont.)



Appendix 6: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events associated with Atezolizumab and/or Tiragolumab

Table A6-4 Management Guidelines for Endocrine Events (cont.)

Event	Management

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in [Table A6-5](#).

Table A6-5 Management Guidelines for Ocular Events

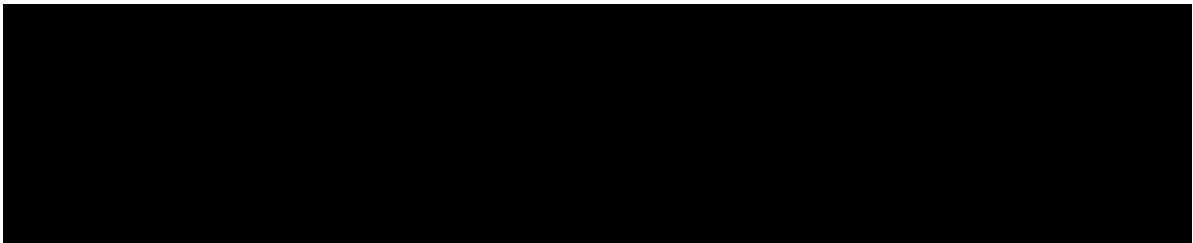
Event	Management
[Redacted content]	
[Redacted content]	

IMMUNE-MEDIATED CARDIAC EVENTS

In high-risk patients (including those with abnormal baseline cardiac troponin levels, when available), transthoracic echocardiogram (TTE) monitoring should be considered, as clinically indicated, and based on local clinical practice. Management guidelines for cardiac events are provided in [Table A6-6](#).

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., *troponin*, B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of *myositis* or associated with pericarditis (see section on *immune-mediated* pericardial disorders below) and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.



Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table A6-6](#).

IMMUNE-MEDIATED PERICARDIAL DISORDERS

[REDACTED]

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer (*e.g.*, metastatic disease), *cancer treatment* (*e.g.*, chest radiotherapy), cardiac injury (*e.g.*, *injury due to myocardial infarction or iatrogenesis*), and autoimmune disorders, and should be managed accordingly.

[REDACTED]

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table A6-6](#). Withhold treatment with atezolizumab and tiragolumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table A6-6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
[REDACTED]	

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

Appendix 6: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events associated with Atezolizumab and/or Tiragolumab

[REDACTED]

[REDACTED]

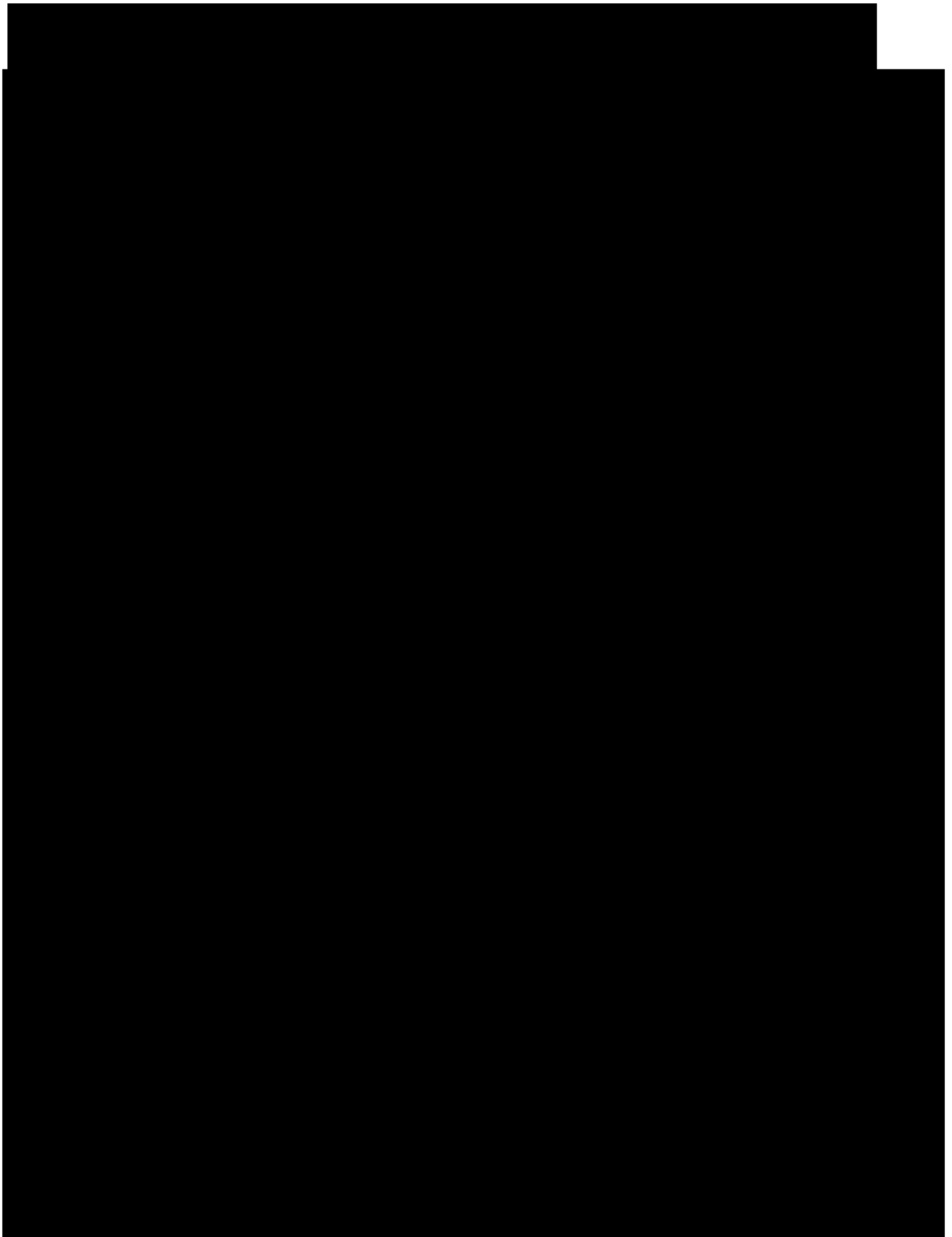
[REDACTED]

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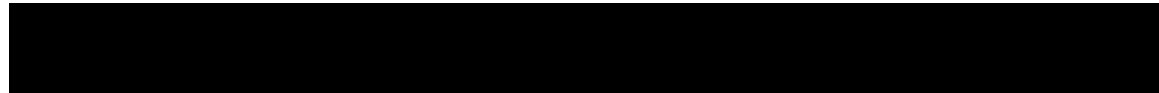
[REDACTED]

[REDACTED]

Appendix 6: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events associated with Atezolizumab and/or Tiragolumab



Appendix 6: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events associated with Atezolizumab and/or Tiragolumab

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Appendix 6: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events associated with Atezolizumab and/or Tiragolumab

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PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in [Table A6-8](#).

Table A6-8 Management Guidelines for Pancreatic Events, Including Pancreatitis

[illegible]

Table A6-8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

[illegible]

DERMATOLOGIC EVENTS

The majority of cases of rash reported with the use of atezolizumab and/or tiragolumab were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in [Table A6-9](#).

Table A6-9 Management Guidelines for Dermatologic Events

[illegible]

Appendix 6: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events associated with Atezolizumab and/or Tiragolumab

Table A6-9 Management Guidelines for Dermatologic Events (cont.)

Event	Management

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. *Myasthenia may be associated with myositis (see section on immune-mediated myositis) and patients should be managed accordingly.* Management guidelines for neurologic disorders are provided in [Table A6-10](#), with specific guidelines for myelitis provided in [Table A6-11](#).

Table A6-10 Management Guidelines for Neurologic Disorders

[illegible]

Appendix 6: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events associated with Atezolizumab and/or Tiragolumab

Table A6-10 Management Guidelines for Neurologic Disorders (cont.)[illegible]

Table A6-11 Management Guidelines for Immune-Mediated Myelitis

Event	Management
<div></div>	

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table A6-12](#).

Table A6-12 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management

RENAL EVENTS

Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Appendix 6: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events associated with Atezolizumab and/or Tiragolumab

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table A6-13](#).

Table A6-13 Management Guidelines for Renal Events

[illegible]

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase/*creatin*e phosphokinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. *Patients may initially present with low grade nondescript symptoms including mild pain and weakness; thus, there should be a low threshold for suspicion of myositis.* Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis (*see section on immune-mediated myocarditis*) and myasthenia gravis (*bulbar symptoms such as dysphagia, dysphonia, and dyspnea; see section on neurologic disorders*).

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table A6-14](#).

Table A6-14 Management Guidelines for Immune-Mediated Myositis

[illegible]

Appendix 6: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events associated with Atezolizumab and/or Tiragolumab

Table A6-14 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management

Table A6-14 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management

Appendix 6: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events associated with Atezolizumab and/or Tiragolumab

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Appendix 6: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events associated with Atezolizumab and/or Tiragolumab

[REDACTED]

[REDACTED]

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Appendix 7

Study Details Specific to Atezo+Tira Arm

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A7-1 BACKGROUND ON ATEZO+TIRA ARM

A7-1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab enhances the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, myocarditis, and nephritis, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma (in the European Union), non-small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer (in the European Union), hepatocellular carcinoma, melanoma (in the United States), and alveolar soft part sarcoma (in the United States).

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A7-1.2 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/κ monoclonal antibody that binds to T-cell immunoreceptor with Ig and ITIM domains (TIGIT) and prevents its interaction with CD155 (also known as poliovirus receptor [PVR]). Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of tumor-specific T-cell responses. This may result in improved meaningful anti-tumor activity when tiragolumab is used in combination with other cancer immunotherapies and administered with chemotherapy. The available

Appendix 7: Study Details Specific to Atezo + Tira Arm

nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in patients with cancer.

Refer to the Tiragolumab Investigator's Brochure for details on nonclinical and clinical studies.

A7-2 RATIONALE FOR ATEZO+TIRA ARM

A7-2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses by binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors, have had a significant impact on the treatment of patients with *NSCLC* in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active as monotherapy for many patients.

A7-2.2 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin super family (Yu et al. 2009). TIGIT is expressed on the surface of activated T-cell and natural killer (NK)-cell subsets and interacts with high affinity with CD155 (also known as PVR) (Yu et al. 2009). Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses in nonclinical models of autoimmune and viral infections, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; Johnston et al. 2014). TIGIT expression is elevated in the tumor microenvironment in many human tumors, is concordantly expressed with other checkpoint immune receptors such as PD-1 on the surface of T cells, and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014; Manieri et al. 2017). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017).

TIGIT is expressed by a wide variety of human tumors. It is expressed in most solid tumors, such as NSCLC, breast cancer, head and neck cancer, and melanoma, as well as in hematologic tumors, such as multiple myeloma and non-Hodgkin lymphoma. Fluorescence activated cell-sorting analysis of T cells isolated from fresh tumor samples revealed that TIGIT and PD-1 are also co-expressed on tumor-infiltrating T cells (Johnston et al. 2014; Yadav et al. 2016; Yang 2016; Guilleroy et al. 2018). TIGIT was expressed in 30%–80% of tumor-infiltrating CD4⁺ T cells and in 50%–80% of tumor-infiltrating CD8⁺ T cells (Johnston et al. 2014).

Therefore, TIGIT is a potential target for therapeutic interventions that aim to restore the immune response against the tumor. Agents that inhibit TIGIT interaction with PVR may inhibit an important source of tumor-associated immune suppression, thereby enhancing the activity of other immune-based therapies. Nonclinical studies using genetically deficient mice and blocking antibodies have revealed a key role for TIGIT in regulating T-cell responses in cancer. Taken together, the data support the hypothesis that anti-TIGIT therapy may reactivate anti-tumor immunity and provide clinical benefits to patients with cancer.

A7-2.3 COMBINATION TREATMENT WITH ANTI-PD-L1 AND ANTI-TIGIT AGENTS

Despite robust activity observed with PD-L1/PD-1 pathway inhibitors across diverse malignancies, including NSCLC, durable clinical benefit appears limited to a minority of patients. Host immunosuppression by malignant cells is mediated by multiple pathways; therefore, combination therapy regimens employing two or more targeted CIT agents may be required to fully engage the anti-tumor potential of the host immune system.

Appendix 7: Study Details Specific to Atezo + Tira Arm

Because TIGIT is a novel immune inhibitory receptor and the expression of TIGIT is highly correlated with PD-1 expression on infiltrating T-cells in several human tumors, inhibition of the TIGIT pathway may complement and potentiate the anti-tumor activity of a PD-L1 pathway inhibitor such as atezolizumab (Banta et al. 2022). In preclinical tumor models, TIGIT selectively suppressed the effector function of chronically stimulated CD8⁺ T cells, and co-inhibition of both TIGIT and PD-L1/PD-1 demonstrated superior efficacy over the respective single-agent treatments (Johnston et al. 2014). These studies identify TIGIT as an important immune checkpoint inhibitor that functionally limits chronically activated CD8⁺ T cells and tumor-infiltrating lymphocytes. Notably, co-inhibition of TIGIT and PD-L1 in the syngeneic tumor model was not associated with body weight loss or any other observable adverse responses.

Hence, combination therapy targeting TIGIT and PD-L1 may prove broadly applicable across diverse malignancies, including NSCLC.

A7-2.3.1 Clinical Studies of Tiragolumab as a Single Agent or in Combination with Atezolizumab

Tiragolumab is currently under investigation in patients with solid tumors, *for example*, in the ongoing Phase Ia/Ib study GO30103, the Phase II studies GO40290 (CITYSCAPE) and GO42501 (SKYSCRAPER-05), and the Phase III study GO41854 (SKYSCRAPER-03).

Clinical data for Studies GO30103 and GO40290 are reported below.

A7-2.3.1.1 Study GO30103

Study GO30103 is a first in human Phase Ia/Ib open-label, dose-escalation study of the safety and pharmacokinetics of tiragolumab as a single agent and in combination with atezolizumab in patients with locally advanced or metastatic tumors. As of the clinical cutoff date of 1 October 2021, 42 patients were enrolled in the Phase Ia portion of the study to receive single-agent tiragolumab, and 200 patients were enrolled in the Phase Ib portion of the study to receive tiragolumab in combination with atezolizumab at dose levels of 2–1200 mg tiragolumab and 1200 mg atezolizumab. Of the 42 patients enrolled in the Phase Ia portion of the study, 23 patients crossed over to the Phase Ib portion of the study after disease progression.

Tiragolumab as a single-agent or in combination with atezolizumab was tolerated across all administered dose levels in Study GO30103. The maximum tolerated dose (MTD) was not reached, and the maximum administered dose was 1200 mg. No dose-limiting toxicities (DLTs) or clear dose-related trends in the incidence of adverse events have been observed in the Phase Ia or Phase Ib portions of Study GO30103.

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As of 1 October 2021, in the Phase Ia portion of the study, the most commonly reported Grade 3 or 4 adverse events ($\geq 5\%$ of patients) were anemia (4 patients; 9.5%), and dyspnea (3 patients; 7.1%). Overall, 54.8% of patients reported adverse events considered related to tiragolumab by the investigator. Tiragolumab-related adverse events reported in $\geq 5\%$ of patients were fatigue, pruritus, and infusion-related reaction (IRR) (11.9% each), and rash (9.5%).



In the Phase Ib part of the study, the majority of Grade 3 or 4 adverse events reported occurred in 1 patient each, with anemia (7.5%) as the only Grade 3 or 4 adverse event reported in $\geq 5\%$ of patients.



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[REDACTED]

[REDACTED]

As of 1 October 2021, the anti-tumor activity of tiragolumab as a single-agent and in combination with atezolizumab in patients with advanced solid tumors has been investigated in the Phase Ia/Ib study GO30103. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

A7–2.3.1.2 Study GO40290

Study GO40290 is a Phase II, randomized, blinded, placebo-controlled study to evaluate the safety and efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated, locally advanced unresectable or metastatic PD-L1-selected NSCLC. A total of 135 patients were enrolled in this study

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(last patient was enrolled in March 2019). As of the clinical cutoff date of 16 August 2021, 12 patients were still receiving study treatment in the intent-to-treat (ITT) population.

As of the clinical cutoff date of 16 August 2021, 66 of 67 patients (98.5%) in the tiragolumab plus atezolizumab arm and 66 of 68 patients (97.1%) in the placebo plus atezolizumab arm reported at least one adverse event.

The most common adverse events reported in $\geq 15\%$ of all patients who received tiragolumab plus atezolizumab, regardless of attribution to study treatments included: IRR (31.3%), arthralgia (29.9%), asthenia and pruritus (28.4% each), fatigue (25.4%), rash (23.9%), decreased appetite (22.4%), diarrhea (20.9%), constipation (17.9%), and cough and pneumonia (16.4% each). The most common adverse events in patients who received placebo plus atezolizumab included asthenia (27.9%), dyspnea (25.0%), decreased appetite (23.5%), arthralgia (17.6%), and fatigue, pruritus, and diarrhea (16.2% each).

The adverse events experienced by a higher proportion of patients in the tiragolumab plus atezolizumab arm than the placebo plus atezolizumab arm (preferred term; $\geq 10\%$ difference) were (tiragolumab plus atezolizumab and placebo plus atezolizumab, respectively): IRR (31.3% and 10.3%), arthralgia (29.9% and 17.6%), pruritus (28.4% and 16.2%), and rash (23.9% and 10.3%). The only adverse event experienced more frequently ($\geq 10\%$ difference) in the placebo plus atezolizumab arm was dyspnea (14.9% and 25.0%).

A total of 55 of 67 patients (82.1%) in the tiragolumab plus atezolizumab arm and 48 of 68 patients (70.6%) in the placebo plus atezolizumab arm experienced at least one adverse event that was assessed by the investigator to be related to the study treatments. The most common related adverse events reported in $\geq 10\%$ of patients who received tiragolumab plus atezolizumab and placebo plus atezolizumab, respectively, were IRR (31.3% and 10.3%), pruritus (26.9% and 14.7%), rash (20.9% and 5.9%), asthenia (17.9% and 17.6%), fatigue (17.9% and 7.4%), arthralgia (16.4% and 7.4%), lipase increased (11.9% and 2.9%), hypothyroidism (10.4% and 5.9%), and decreased appetite (9% and 17.6%).

A total of 35 of 67 patients (52.2%) in the tiragolumab plus atezolizumab arm and 27 of 68 patients (39.7%) in the placebo plus atezolizumab arm experienced at least one Grade 3 or 4 adverse event regardless of attribution to study treatments. The Grade 3 or 4 adverse events experienced by a higher proportion of patients in the tiragolumab plus atezolizumab arm than the placebo plus atezolizumab arm ($\geq 2\%$ difference) were pneumonia (11.9% and 5.9%), increased lipase (9.0% and 4.4%), pleural effusion (6.0% and 2.9%), and blood ALP increased, hemoptysis, hepatitis, and

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hypokalemia (3.0% and 0%, each). The Grade 3 or 4 adverse events experienced by a higher proportion of patients in the placebo plus atezolizumab arm than the tiragolumab plus atezolizumab arm ($\geq 2\%$ difference) were (tiragolumab plus atezolizumab and placebo plus atezolizumab, respectively) increased amylase (1.5% and 4.4%) and asthenia (0% and 2.9%).

The data analysis (clinical cutoff date of 16 August 2021) showed that the combination of tiragolumab plus atezolizumab improved objective response rate (ORR) and progression-free survival (PFS) compared with placebo plus atezolizumab in the ITT population. ORR for tiragolumab plus atezolizumab was 38.8% (95% CI: 26.4% to 51.2%) compared with placebo plus atezolizumab, which was 20.6% (95% CI: 10.2% to 30.9%). This was associated with a 38% relative risk reduction in disease worsening or death (median investigator-assessed PFS for tiragolumab plus atezolizumab was 5.6 months (95% CI: 4.2 to 10.4 *months*) compared with placebo plus atezolizumab, which was 3.9 months (95% CI: 2.7 to 4.5 *months*), with a hazard ratio of 0.62 (95% CI: 0.42 to 0.91).

A7-2.4 BENEFIT-RISK ASSESSMENT

The preliminary safety and efficacy data from the ongoing studies of tiragolumab as a single agent or in combination with atezolizumab across different solid tumor indications, support a favorable benefit-risk profile for tiragolumab. Because of the potentially synergistic mechanisms of action of atezolizumab and tiragolumab, as well as their manageable and tolerable safety profiles (see Section A7-2.3), combination treatment with these two treatment modalities appears to have promising therapeutic potential in solid tumors and may reinvigorate and augment the anti-tumor immune response, potentially resulting in improved and more durable clinical benefit for patients with NSCLC.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit-risk assessment, please refer to Section 1.4.

A7-3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+TIRA ARM

A7-3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab (Tecentriq® U.S. *Prescribing Information*).

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The fixed dose of 600 mg IV Q3W was selected on the basis of available clinical pharmacokinetic, efficacy, and safety data from the combined Phase Ia/Ib study GO30103, with single-agent tiragolumab or tiragolumab in combination with atezolizumab. [REDACTED]

Refer to the Tiragolumab Investigator's Brochure for additional details.

A7-4 MATERIALS AND METHODS SPECIFIC TO ATEZO+TIRA ARM

A7-4.1 TREATMENT IN ATEZO+TIRA ARM

A7-4.1.1 Formulation, Packaging, and Handling

A7-4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the atezolizumab formulation, *see* the pharmacy manual and the Atezolizumab Investigator's Brochure.

A7-4.1.1.2 Tiragolumab

The tiragolumab drug product will be supplied by the Sponsor [REDACTED]

For information on the *tiragolumab* formulation, *see* the pharmacy manual and the Tiragolumab Investigator's Brochure.

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A7-4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + Tira arm will receive treatment as outlined in [Table A7-1](#) until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see [Section 3.1.1](#) for details).

Table A7-1 Treatment Regimen for Atezo + Tira Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none">• Atezolizumab 1200 mg IV on Day 1 of each cycle• Tiragolumab 600 mg IV on Day 1 of each cycle

Atez=atezolizumab; Tira=tiragolumab.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in [Section 5.3.5.12](#). No safety data related to overdosing of atezolizumab or tiragolumab are available to date.

A7-4.1.2.1 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#). Atezolizumab infusions will be administered per the instructions outlined in [Table A7-2](#).

Table A7-2 Administration of First and *Subsequent* Atezolizumab Infusions

<ul style="list-style-type: none"> • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] 	<ul style="list-style-type: none"> • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED]

IRR = infusion-related reaction.

Guidelines for medical management of IRRs for atezolizumab are provided in [Table A7-4](#) and [Appendix 6](#).

No dose modification for atezolizumab is allowed. Guidelines for *atezolizumab* treatment interruption or discontinuation because of toxicities are provided in [Section A7-5.1.4.2](#). Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's benefit-risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A7-4.1.2.2 Tiragolumab Administration

Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle with a post-infusion observation period as described in [Table A7-3](#).

Administration of tiragolumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#). Tiragolumab infusions will be administered according to the instructions outlined in [Table A7-3](#).

Table A7-3 Administration of First and Subsequent Tiragolumab Infusions

First Infusion	<i>Subsequent Infusions</i>

Guidelines for medical management of IRRs for tiragolumab are provided in [Table A7-4](#) and [Appendix 6](#).

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section [A7-5.1.4.2](#). Tiragolumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's benefit-risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A7-4.2 CONCOMITANT THERAPY FOR ATEZO + TIRA ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A7-4.2.1 Permitted Therapy for Atezo + Tira Arm

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
[REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

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- *Radiotherapy to the brain as outlined below:*

A horizontal bar chart with a light gray background. The y-axis lists five categories: 'All respondents', 'Men', 'Women', 'High school or less', and 'College or more'. For each category, there are two black bars. The first bar in each pair represents 'U.S. should take action to address climate change' and the second bar represents 'U.S. does not need to take action to address climate change'. The bars for 'U.S. should take action' are significantly longer than the bars for 'U.S. does not need to take action' across all categories. The 'All respondents' bar for 'U.S. should take action' is the longest, followed by 'Men' and 'Women'. The 'High school or less' bar for 'U.S. should take action' is the shortest among the 'should take action' bars. The 'College or more' bar for 'U.S. should take action' is the shortest among the 'does not need to take action' bars.

Category	U.S. should take action to address climate change (%)	U.S. does not need to take action to address climate change (%)
All respondents	88	12
Men	87	13
Women	86	14
High school or less	78	22
College or more	82	18

Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for the second atezolizumab and tiragolumab infusions only, at the discretion of the investigator. [REDACTED]

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 -adrenergic agonists; refer to [Appendix 5](#) for details).

A7-4.2.2 Cautionary Therapy for Atezo+Tira Arm

A7-4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and/or tiragolumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may be administered at the discretion of the investigator.

Appendix 7: Study Details Specific to Atezo+Tira Arm

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab and/or tiragolumab therapy (refer to [Appendix 6](#) for details).

The above list of cautionary medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor is available to advise as needed if questions arise regarding medications not listed above.

A7-4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section [A7-4.2.3](#)) may be used during the study at the discretion of the investigator.

A7-4.2.3 Prohibited Therapy for Atezo+Tira Arm

[REDACTED]:

- **[REDACTED]**
- **[REDACTED]**
- **[REDACTED]**
- **[REDACTED]**

A7-4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + TIRA ARM

Contraception requirements for men and women in the Atezo + Tira arm are outlined below.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the final dose of atezolizumab and for 90 days after the final dose of tiragolumab.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 90 days after the final dose of tiragolumab. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

A7-5 ASSESSMENT OF SAFETY FOR ATEZO+TIRA ARM

A7-5.1 SAFETY PLAN FOR ATEZO+TIRA ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and tiragolumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections [A7-5.1.1](#), [A7-5.1.2](#), and [A7-5.1.3](#)). Guidelines for management of patients who experience specific adverse events are provided in Section [A7-5.1.1](#) and [Appendix 6](#). These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit-risk balance when managing individual cases.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study.

Administration of atezolizumab and tiragolumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections [5.2-5.6](#).

A7-5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A7-5.1.2 Risks Associated with Tiragolumab

IRRs and [REDACTED] are identified risks of tiragolumab. [REDACTED] is a potential risk with tiragolumab. Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events).

Refer to [Appendix 6](#) of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for details on nonclinical and clinical safety assessments.

A7-5.1.2.1 Infusion-Related Reactions

Because tiragolumab is a therapeutic monoclonal antibody and targets immune cells, IRRs associated with hypersensitivity reactions and/or target-mediated cytokine release may occur. Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

IRRs have been reported in patients treated with tiragolumab, with or without atezolizumab. The majority of events were mild to moderate and manageable.

[REDACTED]

All infusions of tiragolumab will be administered in an appropriate medical setting.

Refer to Section [A7-4.1.2](#) for detailed guidance on administration of tiragolumab in this study. Please see [Appendix 5](#) for guidance on anaphylaxis precautions and [Table A7-4](#) and [Appendix 6](#) for guidance on the management of IRRs.

[REDACTED]

[REDACTED]

A7-5.1.2.3 Immune-Mediated Adverse Events

Nonclinical models have suggested a role of TIGIT signaling interruption in autoimmunity. In a knockout model (TIGIT^{-/-}), loss of TIGIT signaling resulted in hyperproliferative T-cell responses and exacerbation of experimental autoimmune encephalitis (EAE). TIGIT^{-/-} and wild-type B6 mice were immunized with myelin oligodendrocyte glycoprotein peptide in an EAE using suboptimal doses. In contrast to the wild-type B6 mice, the majority of the TIGIT^{-/-} mice developed severe EAE (Joller et al. 2011).

Clinical experience with therapeutics intended to enhance anti-tumor T-cell responses has demonstrated that development of autoimmune inflammatory conditions is a general risk and may therefore be considered a potential risk of tiragolumab. Such immune-mediated adverse events have been described for virtually all organ systems and include, but are not limited to, colitis, pneumonitis, endocrinopathies, ocular toxicity,

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pancreatic toxicity, neurologic toxicity, cardiac toxicity, nephritis, myositis, and severe cutaneous adverse reactions.

Patients with a history of autoimmune disease will be excluded from this study. Please see Section 4.1.2 for details.

In this study, immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A7–5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

Suggested management guidelines for individual suspected immune-mediated adverse events are provided in Appendix 6.

[REDACTED]

The IgG1 backbone of tiragolumab with the intact Fc-effector function may lead to antibody-dependent cell-mediated cytotoxicity–mediated reduction in lymphocyte count.

[REDACTED]

[REDACTED] Patients with a lymphocyte count <500 cells/mL will be excluded from the study (Section 4.1.2) and complete blood counts will be monitored regularly during the study.

A7–5.1.2.5 Embryofetal Toxicity

[REDACTED]. Administration of tiragolumab is expected to have adverse effects on pregnancy based on the expression of TIGIT on decidual NK and CD8⁺ T cells (Powell et al. 2017; van der Zwan et al. 2018; Vento-Tormo et al. 2018), and the expected role of these cells in the recognition and response to foreign fetal, placental, and viral antigens at the maternal-fetal interface as well as maintenance of maternal-fetal tolerance. No reproductive or teratogenicity studies in animals have been conducted with tiragolumab. There are no clinical studies of tiragolumab in pregnant women. Tiragolumab should not be administered to pregnant women.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of embryofetal toxicity.

A7–5.1.3 Risks Associated with Combination Use of Atezolizumab and Tiragolumab

Based on results from clinical data with tiragolumab and atezolizumab, there are known and potential overlapping toxicities in patients treated with tiragolumab plus atezolizumab. Because the expected pharmacologic activity of these two molecules is

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to increase adaptive T-cell immune responses, there is the possibility of heightened immune responses.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a list of identified risks associated with tiragolumab in combination with atezolizumab. Based on the mechanism of action of tiragolumab and atezolizumab, additional immune-mediated adverse events are potential overlapping toxicities associated with combination use of tiragolumab plus atezolizumab.

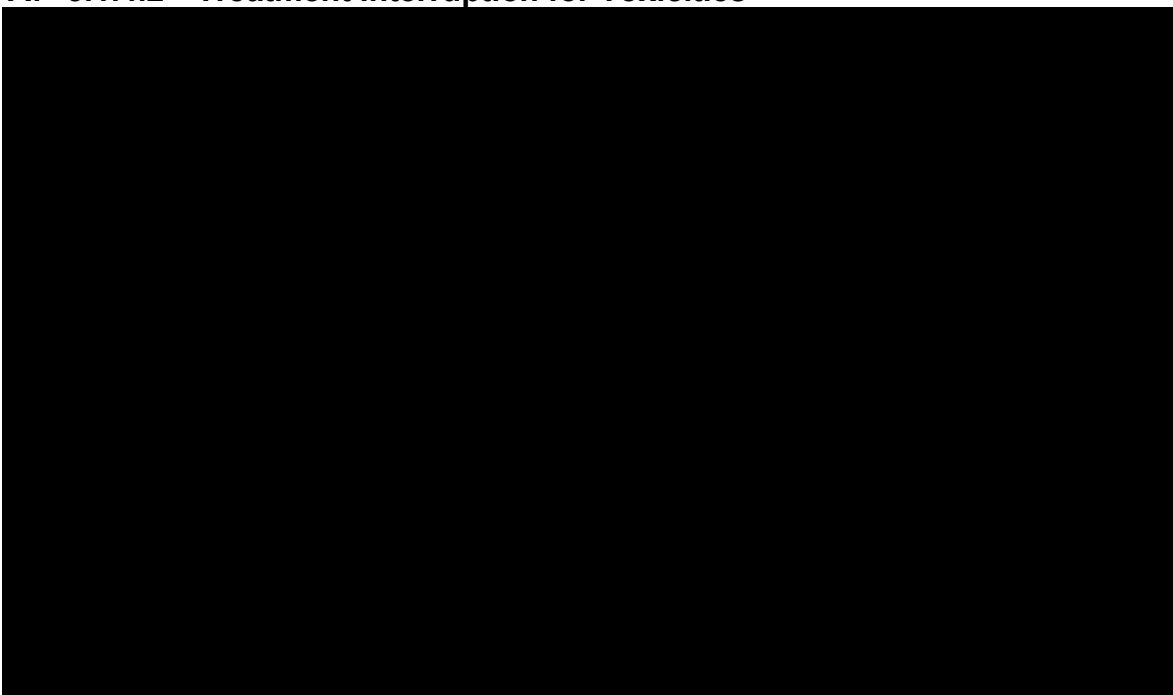
Based on clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with tiragolumab and atezolizumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with immune checkpoint inhibitors to date has been incorporated into the design and safety management plan (see [Appendix 6](#)) in order to reduce the potential risks to participating patients. Patients with a history of autoimmune disease will be excluded from this study (see Section [4.1.2](#)). Patients previously treated with approved or experimental CIT will also be excluded from participation in this study. Owing to the risks of active viral infection and viral reactivation (see Section [4.1.2](#)), patients with active infection [REDACTED] and/or patients with recent severe infections will be excluded from this study (see Section [4.1.2](#)).

A7–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo + Tira Arm

A7–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab or tiragolumab in this study.

A7–5.1.4.2 Treatment Interruption for Toxicities



On the basis of the available characterization of mechanism of action, tiragolumab may cause adverse events similar to, but independent of, atezolizumab. Tiragolumab may also exacerbate the frequency or severity of atezolizumab-related adverse events or may have non-overlapping toxicities with atezolizumab. Because these scenarios may not be distinguishable from each other in the clinical setting, adverse events should generally be attributed to both agents, and dose interruptions or treatment discontinuation in response to adverse events should be applied to both tiragolumab and atezolizumab. If atezolizumab is withheld or discontinued, tiragolumab should also be withheld or discontinued. If tiragolumab is withheld or discontinued, atezolizumab should also be withheld or discontinued.

Refer to [A7–4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A7–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in [Table A7-4](#) and [Appendix 6](#). Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab, as outlined in [Appendix 6](#), are also applicable to tiragolumab.

Appendix 7: Study Details Specific to Atezo + Tira Arm

For cases in which management guidelines are not covered in [Appendix 6](#), patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

[REDACTED]

[REDACTED]

[REDACTED]

A7-5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO+TIRA ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.2.3](#) for reporting instructions). Adverse events of special interest for the Atezo + Tira arm are as follows:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

Appendix 7: Study Details Specific to Atezo + Tira Arm

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

A7-5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+TIRA ARM

A7-5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab or within 90 days after the final dose of tiragolumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A7–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 90 days after the final dose of tiragolumab. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A7–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A7–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.2.2](#)).

A7-6 SCHEDULE OF ACTIVITIES FOR ATEZO+TIRA ARM

Table A7-5 Schedule of Activities for Atezo+Tira Arm

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) ^a		Treatment Discontinuation (see below) ^c	Follow-Up
		Cycles 1 ^b	Cycles ≥ 2		
	Days –28 to –1	Day 1	Day 1 (± 3 days)		Every 3 Months (± 7 days)
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available			
Vital signs ^d		x	x	x	
Weight ^e		x	x	x	
Complete physical examination ^f				x	
Limited physical examination ^{e, g}		x	x		
ECOG Performance Status ^e		x	x	x	
ECG ^{e, h}		Perform as clinically indicated		x	
Hematology ⁱ		x ^{j, k}	x ^j	x	
Chemistry ^l		x ^{j, k}	x ^j	x	
Coagulation (INR and aPTT)		Perform as clinically indicated		x	
TSH, free T3 (or total T3), and free T4 ^m		x ^{j, k, m}		x	
Pregnancy test ⁿ		x ^{j, k}	x ^j	x	x ⁿ
Urinalysis ^o		Perform as clinically indicated ^j			
Serum autoantibody sample ^p		Perform if a patient experiences a suspected immune-mediated adverse event.			
PK samples		Refer to Table A7-6 .			
ADA samples		Refer to Table A7-6 .			

Appendix 7: Study Details Specific to Atezo + Tira Arm

Table A7-5 Schedule of Activities for Atezo + Tira Arm (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) ^a		Treatment Discontinuation (see below) ^c	Follow-Up
		Cycles 1 ^b	Cycles ≥2		Every 3 Months (± 7 days)
	Days –28 to –1	Day 1	Day 1 (± 3 days)		
Biomarker samples	See Appendix 2	Refer to Table A7-6 .			
Blood sample for RBR (optional) ^q		x			
Tumor biopsy ^r		x			
Tumor biopsy (optional) ^s		x			
Tumor response assessments		x ^{t, u}			
Concomitant medications ^v		x	x	x	
Adverse events ^w		x	x	x ^w	x ^w
Atezolizumab administration ^{x, y}		x	x		
Tiragolumab administration ^{y, z}		x	x		
Survival follow-up and anti-cancer treatment					x ^{aa}

ADA=anti-drug antibody; Atezo=atezolizumab; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; PK= pharmacokinetic; RBR=Research Biosample Repository; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; T3=triiodothyronine; T4=thyroxine; *Tira=tiragolumab*; TSH=thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Appendix 7: Study Details Specific to Atezo + Tira Arm

Table A7-5 Schedule of Activities for Atezo + Tira Arm (cont.)

- ^a If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.
- ^b Cohort 2 Stage 1 treatment must begin within 35 days after the patient has experienced disease progression per RECIST v1.1 or unacceptable toxicity in Stage 1. However, it is recommended that patients begin Cohort 2 Stage 1 treatment as soon as possible.
- ^c Patients will return to the clinic for a treatment discontinuation visit not more than 30 days after the *final* dose of study treatment.
- ^d Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (± 5) minutes during and 30 (± 10) minutes after the infusion. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (± 10) minutes after the infusion.
- ^e Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^f *Complete* physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^g Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^h It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.
- ⁱ Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).
- ^j Laboratory tests must be performed within 96 hours prior to dosing on Day 1 of Cycle 1 and within 96 hours prior to specified subsequent visits during the treatment period.
- ^k If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.
- ^l Chemistry panel (serum or plasma) includes bicarbonate or carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included on Day 1 of each treatment cycle.
- ^m TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

Appendix 7: Study Details Specific to Atezo + Tira Arm

Table A7-5 Schedule of Activities for Atezo + Tira Arm (cont.)

- ⁿ All women of childbearing potential will have urine or serum pregnancy tests performed at specified visits during treatment and at 3 months and 6 months after treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^o *Urinalysis* includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted if delivering the requested results.
- ^p Autoantibody testing includes anti-nuclear antibody, anti-double-stranded DNA antibody, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Serum samples collected for the assessment of PK, ADAs, or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.
- ^q Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.
- ^r Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see Section 3.1.2) will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible). See Section 4.5.6 for tissue sample requirements.
- ^s Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation, if deemed clinically feasible and may undergo additional on-treatment biopsies at any other time during the study at the investigator's discretion.
- ^t Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 except in the case of patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.
- ^u All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head CT scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Appendix 7: Study Details Specific to Atezo + Tira Arm

Table A7-5 Schedule of Activities for Atezo + Tira Arm (cont.)

- ^v Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.
- ^w After initiation of study treatment, all adverse events will be reported until [REDACTED] days after the *final* dose of study treatment or until initiation of new [REDACTED], and serious adverse events and adverse events of special interest will continue to be reported until [REDACTED] days after the *final* dose of study treatment [REDACTED]. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.
- ^x Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.
- ^y Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).
- ^z [REDACTED]
- ^{aa} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. The Sponsor may conclude treatment arms in which all patients have discontinued treatment and completed safety follow-up and/or treatment arms in which approximately 80% of patients have discontinued the study (with the remaining ~20% of patients to be discontinued from the study).

Appendix 7: Study Details Specific to Atezo+Tira Arm

[REDACTED]

[REDACTED]

[REDACTED]

Appendix 7: Study Details Specific to Atezo+Tira Arm

[REDACTED]

[REDACTED]

[REDACTED]

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Appendix 8

Study Details Specific to Atezo+Tira+XL092 Arm

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A8–1 BACKGROUND ON ATEZO+TIRA+XL092 ARM

A8–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients *with cancer* and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, myocarditis, and nephritis, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma (in the European Union), non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer (in the European Union), hepatocellular carcinoma, melanoma (in the United States), and alveolar soft part sarcoma (in the United States).

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A8–1.2 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/κ monoclonal antibody that binds to T-cell immunoreceptor with Ig and ITIM domains (TIGIT) and prevents its interaction with CD155 (also known as poliovirus receptor [PVR]). Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of tumor-specific T-cell responses. This may result in improved meaningful anti-tumor activity when tiragolumab is used in combination with other cancer immunotherapies and administered with chemotherapy. The available

Appendix 8: Study Details Specific to Atezo + Tira + XL092 Arm

nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in patients with cancer.

Refer to the Tiragolumab Investigator's Brochure for details on nonclinical *and clinical* studies.

A8-1.3 BACKGROUND ON XL092

XL092 is a new, orally bioavailable, small molecule inhibitor of several receptor tyrosine kinases (RTKs) including MET, vascular endothelial growth factor receptor 2 (VEGFR2), and members of the TAM family (TYRO-AXL and -MER). Inhibition of tumor angiogenesis by blocking the VEGFR-signaling pathway is a therapeutic target for the control of growth, invasion, and metastasis of cancer. MET and AXL play important roles in resistance to anti-angiogenic therapy. TAM family receptors are negative immune regulators and have become a particular focus as targets for CIT. Drugs targeting TAM family kinases are thought to promote an immune-permissive environment which may enhance response to immune checkpoint inhibitors (ICIs). In a preclinical murine MC38 colon carcinoma model, the combination of XL092 with anti-PD1 antibody demonstrated tumor growth inhibition activity when given in combination with an ICI compared with vehicle or either single agent alone. Refer to the XL092 Investigator's Brochure for details on nonclinical *and clinical* studies.

A8-2 RATIONALE FOR ATEZO+TIRA+XL092 ARM

A8-2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses by binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies.

Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma (RCC), melanoma, colorectal cancer (CRC), head and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly ICIs, have had a significant impact on the treatment of patients with *NSCLC* in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active as monotherapy for many patients.

A8–2.2 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin super family (Yu et al. 2009). TIGIT is expressed on the surface of activated T cell and natural killer (NK) cell subsets and interacts with high affinity with CD155 (also known as PVR) (Yu et al. 2009). Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses in nonclinical models of autoimmune and viral infections, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; Johnston et al. 2014). TIGIT expression is elevated in the tumor microenvironment in many human tumors, is concordantly expressed with other checkpoint immune-receptors such as PD-1 on the surface of T cells, and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014; Manieri et al. 2017). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017).

TIGIT is expressed by a wide variety of human tumors, including most solid tumors, such as NSCLC, breast cancer and melanoma, and hematologic tumors, such as multiple myeloma and non-Hodgkin lymphoma. Fluorescence activated cell sorting analysis of T cells isolated from fresh tumor samples revealed that TIGIT and PD-1 are also co-expressed on tumor infiltrating T cells (Johnston et al. 2014; Yadav et al. 2016; Yang 2016; Guillerey et al. 2018). TIGIT expression ranged from 30%–80% and 50%–80% on tumor-infiltrating CD4⁺ and CD8⁺ T cells, respectively (Johnston et al. 2014).

Therefore, TIGIT is a potential target for therapeutic intervention, aimed at restoring the immune response against the tumor. Agents that inhibit TIGIT's interaction with PVR may inhibit an important source of tumor-associated immune suppression and therefore may enhance the activity of other immune-based therapies. Nonclinical studies using genetically deficient mice and blocking antibodies have revealed a key role for TIGIT in regulating T-cell responses in cancer. Together these data support the hypothesis that

anti-TIGIT may reactivate anti-tumor immunity and provide clinical benefits to patients with cancer.

A8–2.3 RECEPTOR TYROSINE KINASES IN CANCER

RTKs play important roles in a number of cellular processes, including cellular proliferation, survival, and migration (Bhullar et al. 2018). Dysregulation leading to elevated kinase expression or constitutive activation is associated with oncogenesis. In addition, several RTKs are known to contribute to the regulation of anti-tumor immunity (Paolino and Penninger 2016).

A8–2.3.1 Role of VEGFR2 in Cancer

The VEGFR2 RTK is prominently expressed on the surface of vascular endothelial cells and on some bone marrow-derived cells and functions as the main mediator of VEGF-induced endothelial proliferation, survival, migration, differentiation, tubular morphogenesis, and sprouting, and is essential for the development of a normal vasculature (Ferrara et al. 2003). Enhanced expression of VEGF by tumor cells is a well-established mechanism for promoting tumor angiogenesis and is induced in response to hypoxia in the tumor microenvironment. However, tumor response to single agent VEGF pathway blockade is limited, and emergence of resistance remains a significant clinical challenge.

A8–2.3.2 Role of MET in Cancer

MET is an RTK that is widely expressed in epithelial and endothelial cells, and is required for normal development of multiple organs and for liver regeneration in adults (Birchmeier et al. 2003). It is activated by a single ligand, hepatocyte growth factor, and activation promotes cell proliferation, survival, and motility. Overexpression of MET has been widely documented as a frequent event in many human tumors including RCC, gastric cancer, hepatocellular carcinoma (HCC), head and neck carcinomas, ovarian carcinomas, lung cancers, and gliomas (Birchmeier et al. 2003; Ma et al. 2003a; Ma et al. 2003b; Yücel et al. 2004). Tumor upregulation and activation of MET is commonly observed in response to multiple therapeutic interventions including chemotherapy, radiotherapy, and treatment with tyrosine kinase inhibitors (TKIs) and confers resistance to treatment and promotes tumor regrowth. In particular, it has been demonstrated in multiple preclinical models that acquired resistance to VEGF pathway inhibition results from upregulation of MET, which promotes increased tumor invasiveness and metastasis (Shojaei et al. 2010; Ebos and Kerbel 2011; Sennino et al. 2012). Combining a MET inhibitor with a VEGFR inhibitor blocked this effect and provided superior tumor control (Sennino et al. 2012), suggesting that this is an attractive target combination for clinical study.

A8–2.3.3 Role of AXL and MER in Cancer

The RTKs, AXL and MER, are two members of the TAM family kinases. Over-expression of AXL and MER has been documented in multiple tumor types including NSCLC, melanoma, RCC, and HCC and is associated with worse prognosis and higher risk of metastasis (Graham et al. 2014). Activation of AXL and MER promotes tumor cell growth, survival, migration, invasion, angiogenesis, and tumor-host interactions by activating downstream phosphoinositide 3-kinase/Akt and/or mitogen-activated protein kinase/extracellular signal-regulated kinase signaling pathways (Schoumacher and Burbridge 2017). There is increasing evidence that AXL/MER over-expression contributes to acquiring resistance to both conventional and targeted therapies in cancers (Vouri and Hafizi 2017). Elevated levels of AXL in RCC cells may be associated with tumor advancement and decreased patient survival (Gustafsson et al. 2009). Expression of AXL has been associated with a worse prognosis for clear-cell RCC patients (Zucca et al. 2018) and its expression was found to increase following VEGFR-TKI therapy (Zhou et al. 2016).

The TAM family kinases are also involved in the regulation of innate and adaptive immunity (Paolino and Penninger 2016). TAM receptors inhibit various types of immune cells including macrophages, dendritic cells, NK cells, NKT cells, and, indirectly, T cells. Therefore inhibition of TAM signaling may promote anti-tumor activity at different levels of immunity. Drugs targeting TAM family kinases are thought to promote an immune-permissive environment which may enhance response to ICIs. Combination therapies of VEGFR-TKIs with ICIs have shown clinical benefits in cancer patients and are now standard of care in advanced RCC (National Comprehensive Cancer Network [NCCN] 2021).

A8–2.4 **COMBINED INHIBITION OF THE PD-L1/PD-1, TIGIT, AND VEGF-, MET-, AXL-, AND MER-PATHWAYS****A8–2.4.1 Combination Treatment with Anti-PD-L1 and Anti-TIGIT Agents**

Durable clinical benefit is limited to a minority of patients treated with single-agent PD-L1/PD-1 inhibitors. Therapies targeting the mechanisms of resistance to anti-PD-L1/PD-1 therapies are needed to improve outcomes in patients with solid cancers. Resistance to PD-L1/PD-1 blockade may result in the expression of multiple co-inhibitory receptors on the surface of effector T cells. Nonclinical tumor models have shown that TIGIT selectively suppressed the effector function of chronically stimulated CD8⁺ T cells, and that inhibiting both TIGIT and PD-L1/PD-1 resulted in superior efficacy compared with single-agent treatments (Johnston et al. 2014). Hence, targeting both TIGIT and PD-L1 with tiragolumab and atezolizumab, respectively, in patients may enhance the efficacy of PD-1/PD-L1 blockade across different cancer types.

A8–2.4.2 Combination of XL092 and PD-(L)1 Checkpoint Inhibitor

[REDACTED]

[REDACTED]

In addition, preclinical studies (Kwilas et al. 2014; Wang et al. 2019) and clinical observations on circulating immune suppressive cells and immune effector cells in cancer patients suggest that VEGFR-TKI targeting TAM kinase inhibitory activity promotes an immune-permissive environment (Apolo et al. 2014). This may lead to synergistic effects from combination treatment with ICIs, independent of PD-L1 expression. Further, combination therapies of VEGFR-TKIs with ICIs have shown clinical benefits in cancer patients and are now standard of care in advanced RCC (NCCN 2019). Based on the mechanism of action and the encouraging findings in the preclinical murine syngeneic CT26 colon carcinoma model, the clinical activity and safety of XL092 in combination with the ICIs atezolizumab and tiragolumab will be evaluated in this Phase I study.

A8–2.4.3 Combination of XL092 and Atezo+Tira

Data related to the triple combination of Atezo+Tira+XL092 is limited. However, each of their mechanisms of action are unique and suggest a promising anti-tumor effect. XL092 increases immune cell activation and promotes an immune-permissive environment, which should synergize with antagonism of multiple immune checkpoints by TIGIT and PD-L1 targeted therapies. TIGIT, similarly to PD-1, is expressed on exhausted CD8⁺ effector T cells, but is also expressed on regulatory T cells at higher levels than PD-1. TIGIT and PVR have been demonstrated to be upregulated in advanced clear cell RCC and are believed to contribute to an immunosuppressive circuit. Co-blockade of TIGIT and PD-1 has resulted in enhanced CD8⁺ T cell infiltration and effector function, a reduction in regulatory T cells, and activation of myeloid cells in preclinical models.

[REDACTED]

A8–2.5 CLINICAL STUDIES OF TIRAGOLUMAB

A8–2.5.1 Clinical Studies of Tiragolumab as a Single Agent or in Combination with Atezolizumab

Tiragolumab is currently under investigation in patients with solid tumors, *for example*, in the ongoing Phase Ia/Ib Study GO30103, the Phase II Studies GO40290 (CITYSCAPE) and GO42501 (SKYSCRAPER-05), and the Phase III Study GO41854 (SKYSCRAPER-03).

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

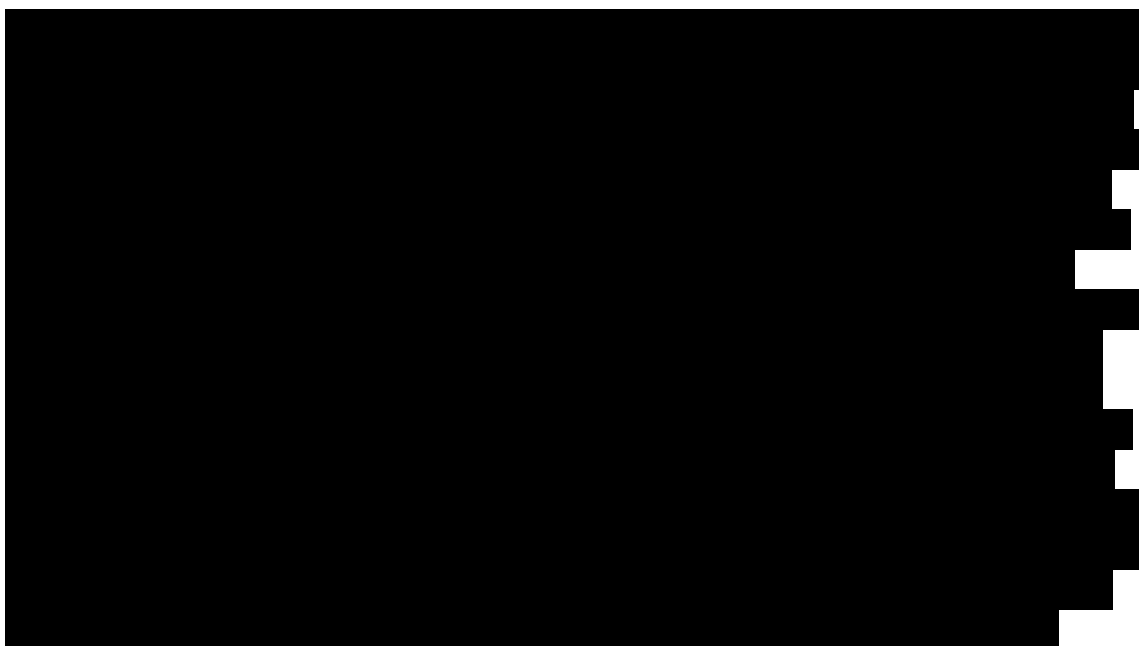
Clinical data for Studies GO30103 and GO40290 are reported below.

A8–2.5.1.1 Study GO30103

Study GO30103 is a first in human Phase Ia/Ib open-label, dose-escalation study of the safety and pharmacokinetics of tiragolumab as a single agent and in combination with atezolizumab in patients with locally advanced or metastatic tumors. As of the clinical cutoff date of 1 October 2021, 42 patients were enrolled in the Phase Ia portion of the study to receive single-agent tiragolumab, and 200 patients were enrolled in the Phase Ib portion of the study to receive tiragolumab in combination with atezolizumab at dose levels of 2–1200 mg tiragolumab and 1200 mg atezolizumab. Of the 42 patients enrolled in the Phase Ia portion of the study, 23 patients crossed over to the Phase Ib portion of the study after disease progression.

Tiragolumab as a single-agent or in combination with atezolizumab was tolerated across all administered dose levels in Study GO30103. The maximum tolerated dose (MTD) was not reached, and the maximum administered dose was 1200 mg. No dose-limiting toxicities (DLTs) or clear dose-related trends in the incidence of adverse events have been observed in the Phase Ia or Phase Ib portions of Study GO30103.

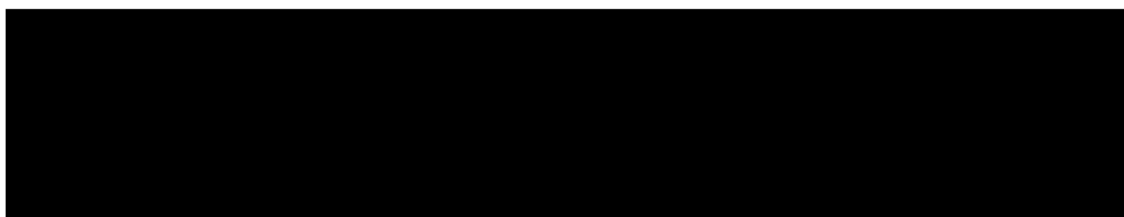
As of 1 October 2021, in the Phase Ia portion of the study, the most commonly reported Grade 3 or 4 adverse events ($\geq 5\%$ of patients) were anemia (4 patients; 9.5%), and dyspnea (3 patients; 7.1%). Overall, 54.8% of patients reported adverse events considered related to tiragolumab by the investigator. Tiragolumab-related adverse events reported in $\geq 5\%$ of patients were fatigue, pruritus, and infusion-related reaction (IRR) (11.9% each), and rash (9.5%).



Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

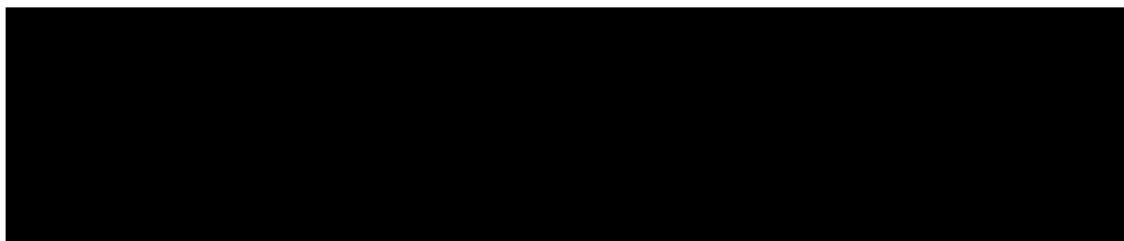
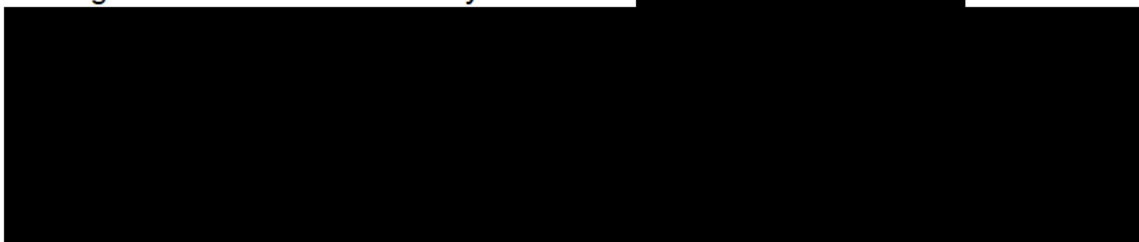


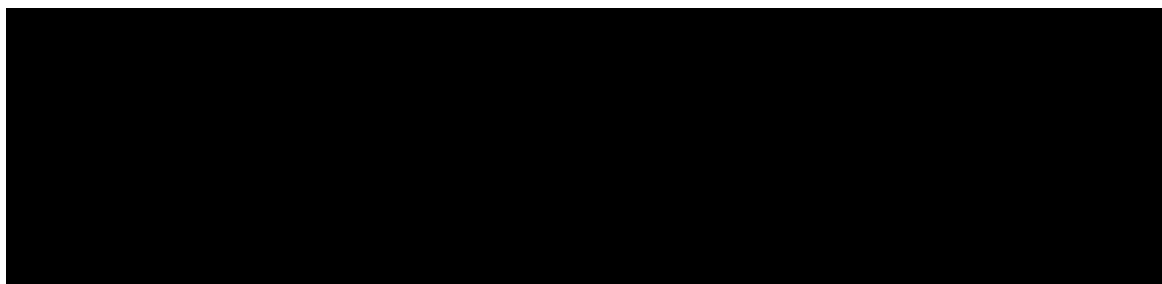
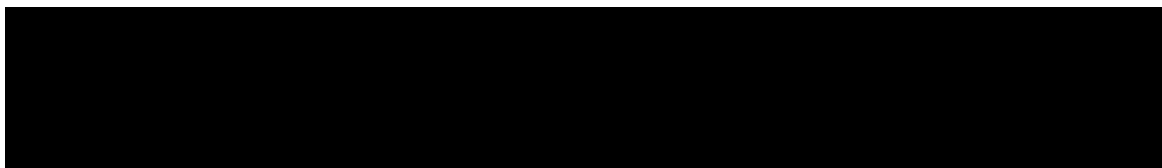
In the Phase Ib part of the study, the majority of Grade 3 or 4 adverse events reported occurred in 1 patient each, with anemia (7.5%) as the only Grade 3 or 4 adverse event reported in $\geq 5\%$ of patients.



In the Phase Ib crossover patients (tiragolumab in combination with atezolizumab) (n=23), Grade 3 or 4 adverse events were reported in 43.5% of crossover patients. Anemia and lipase increased were the most commonly reported Grade 3 or 4 adverse events. No Grade 5 adverse events were reported.

As of 1 October 2021, the anti-tumor activity of tiragolumab as a single-agent and in combination with atezolizumab in patients with advanced solid tumors has been investigated in the Phase Ia/Ib study GO30103.





A8–2.5.1.2 Study GO40290

Study GO40290 is a Phase II, randomized, blinded, placebo-controlled study to evaluate the safety and efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated, locally advanced unresectable or metastatic PD-L1-selected NSCLC. A total of 135 patients were enrolled in this study (last patient was enrolled in March 2019). As of the clinical cutoff date of 16 August 2021, 12 patients were still receiving study treatment in the intent-to-treat (ITT) population.

As of the clinical cutoff date of 16 August 2021, 66 of 67 patients (98.5%) in the tiragolumab plus atezolizumab arm and 66 of 68 patients (97.1%) in the placebo plus atezolizumab arm reported at least one adverse event.

The most common adverse events reported in $\geq 15\%$ of all patients who received tiragolumab plus atezolizumab, regardless of attribution to study treatments included: IRR (31.3%), arthralgia (29.9%), asthenia and pruritus (28.4% each), fatigue (25.4%), rash (23.9%), decreased appetite (22.4%), diarrhea (20.9%), constipation (17.9%), and cough and pneumonia (16.4% each). The most common adverse events in patients who received placebo plus atezolizumab included asthenia (27.9%), dyspnea (25.0%), decreased appetite (23.5%), arthralgia (17.6%), and fatigue, pruritus, and diarrhea (16.2% each).

The adverse events experienced by a higher proportion of patients in the tiragolumab plus atezolizumab arm than the placebo plus atezolizumab arm (preferred term; $\geq 10\%$ difference) were (tiragolumab plus atezolizumab and placebo plus atezolizumab, respectively): IRR (31.3% and 10.3%), arthralgia (29.9% and 17.6%), pruritus (28.4% and 16.2%), and rash (23.9% and 10.3%). The only adverse event experienced more frequently ($\geq 10\%$ difference) in the placebo plus atezolizumab arm was dyspnea (14.9% and 25.0%).

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

A total of 55 of 67 patients (82.1%) in the tiragolumab plus atezolizumab arm and 48 of 68 patients (70.6%) in the placebo plus atezolizumab arm experienced at least one adverse event that was assessed by the investigator to be related to the study treatments. The most common related adverse events reported in $\geq 10\%$ of patients who received tiragolumab plus atezolizumab and placebo plus atezolizumab, respectively, were IRR (31.3% and 10.3%), pruritus (26.9% and 14.7%), rash (20.9% and 5.9%), asthenia (17.9% and 17.6%), fatigue (17.9% and 7.4%), arthralgia (16.4% and 7.4%), lipase increased (11.9% and 2.9%), hypothyroidism (10.4% and 5.9%), and decreased appetite (9% and 17.6%).

A total of 35 of 67 patients (52.2%) in the tiragolumab plus atezolizumab arm and 27 of 68 patients (39.7%) in the placebo plus atezolizumab arm experienced at least one Grade 3 or 4 adverse event regardless of attribution to study treatments. The Grade 3 or 4 adverse events experienced by a higher proportion of patients in the tiragolumab plus atezolizumab arm than the placebo plus atezolizumab arm ($\geq 2\%$ difference) were pneumonia (11.9% and 5.9%), increased lipase (9.0% and 4.4%), pleural effusion (6.0% and 2.9%), and blood ALP increased, hemoptysis, hepatitis, and hypokalemia (3.0% and 0%, each). The Grade 3 or 4 adverse events experienced by a higher proportion of patients in the placebo plus atezolizumab arm than the tiragolumab plus atezolizumab arm ($\geq 2\%$ difference) were (tiragolumab plus atezolizumab and placebo plus atezolizumab, respectively) increased amylase (1.5% and 4.4%) and asthenia (0% and 2.9%).

The data analysis (clinical cutoff date of 16 August 2021) showed that the combination of tiragolumab plus atezolizumab improved objective response rate (ORR) and progression-free survival (PFS) compared with placebo plus atezolizumab in the ITT population. ORR for tiragolumab plus atezolizumab was 38.8% (95% CI: 26.4% to 51.2%) compared with placebo plus atezolizumab, which was 20.6% (95% CI: 10.2% to 30.9%). This was associated with a 38% relative risk reduction in disease worsening or death (median investigator-assessed PFS for tiragolumab plus atezolizumab was 5.6 months (95% CI: 4.2 to 10.4 months) compared with placebo plus atezolizumab, which was 3.9 months (95% CI: 2.7 to 4.5 months), with a hazard ratio of 0.62 (95% CI: 0.42 to 0.91).

A8-2.6 CLINICAL STUDIES OF XL092 AS A SINGLE AGENT OR IN COMBINATION WITH ATEZOLIZUMAB

The ongoing first in human Phase I clinical study XL092-001 (NCT03845166) is currently evaluating the safety and preliminary clinical activity of XL092 as a single-agent and in combination therapy with the PD-L1 ICI atezolizumab in subjects with previously treated advanced solid tumors. [REDACTED]

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

single-agent therapy and 46 subjects received XL092 plus atezolizumab. In the XL092 monotherapy cohorts, XL092 was administered at seven dose levels (DLs): 10 mg (n=3, powder), 20 mg (n=4, powder; n=3, tablet), 40 mg (n=4, tablet), 80 mg (n=3, tablet), 100 mg (n=5, tablet), 120 mg (n=14, tablet), and 140 mg (n=7, tablet). In the XL092 plus atezolizumab cohorts, XL092 was administered in combination with standard dosing of atezolizumab (1200 mg IV every 3 weeks [Q3W]) at four DLs: 40 mg (n=3), 80 mg (n=18), 100 mg (n=18), and 120 mg (n=7).

Among 106 subjects receiving single-agent XL092, 98 subjects (92%) experienced adverse events of any causality with the majority of subjects (n=88; 83%) experiencing adverse events assessed as related to study treatment. The most common all causality adverse events of any grade (incidence $\geq 15\%$) for subjects enrolled in single-agent cohorts across all dose levels were diarrhea (42%), hypertension (37%), nausea (35%), fatigue (25%), decreased appetite (20%), vomiting (19%), and aspartate aminotransferase increased (18%).

Fifty-six patients (53%) experienced adverse events of any causality at Grade 3 severity or higher, with about one-third of subjects (n=33; 31%) experiencing Grade ≥ 3 severity adverse events assessed as related to XL092. The most frequently ($\geq 3\%$ incidence) observed adverse events at Grade ≥ 3 severity were hypertension (14%), fatigue (4.7%), and diarrhea (3.8%); and 13%, 3.8%, and 3.8% were reported as related to XL092, respectively.

A total of 4 subjects (3.8%) experienced Grade 5 adverse events of any causality. In addition to 3 reports of disease progression, 1 event of CRC was reported. Adverse events of Grade 4 severity (large intestine perforation and staphylococcal infection) were reported for 1 subject and were assessed as not related to XL092 treatment.

For subjects who received XL092 in combination with atezolizumab (n=108) or avelumab (n=13) in Study XL092-001, a total of 115 subjects (95%) experienced adverse events of any causality with the majority of subjects (n=105; 87%) experiencing adverse events assessed as related to study treatment. The most common all causality adverse events of any grade for subjects who received XL092 plus atezolizumab combination therapy were diarrhea (56%), fatigue (45%), decreased appetite (40%), nausea (35%), hypertension (28%), vomiting (22%), aspartate aminotransferase increased (21%), alanine aminotransferase increased (19%), hypothyroidism (19%), constipation (17%), headache (17%), weight decreased (17%), and abdominal pain (15%). The majority of reported adverse events were of Grade 1–2 severity. Of the 72 subjects (60%) with Grade 3 or 4 adverse events of any causality, with about one-third of subjects (n=47; 39%) experiencing Grade ≥ 3 adverse events assessed as related to XL092. The most frequent adverse events ($\geq 3\%$ incidence) reported at severity of Grade ≥ 3 were hypertension (12%), fatigue (5.0%), abdominal pain (4.1%),

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

thrombocytopenia (4.1%), diarrhea (3.3%), hyponatremia (3.3%), neutropenia (3.3%), and acute kidney injury (3.3%); of which, hypertension (9.9%), fatigue (5.0%), abdominal pain (0.8%), thrombocytopenia (3.3%), diarrhea (2.5%), hyponatremia (0.8%), neutropenia (2.5%), and acute kidney injury (0.8%) were assessed as related to XL092, respectively. Adverse events of Grade 4 severity were reported for 6 subjects: thrombocytopenia (n = 3; 2.5%), of which 2 events (1.7%) were assessed as related to XL092; and 1 each of hyponatremia, platelet count decreased, lipase increased, and [REDACTED]. Seven Grade 5 events were reported among the combination cohorts, including 3 cases of disease progression, 1 breast cancer, 1 metastases to CNS, 1 death, and 1 sudden death, all of which were unrelated to study treatment.

The adverse events thus far reported indicate that XL092 is well tolerated as single-agent and in combination with ICI therapy. [REDACTED]

[REDACTED] Preliminary data of the ongoing Phase I study also show that XL092 has a promising clinical activity as a single-agent and in combination with ICIs.

A8-2.7 BENEFIT-RISK ASSESSMENT

The preliminary safety and efficacy data from the ongoing studies of tiragolumab as a single agent or in combination with atezolizumab across different solid tumor indications, including treatment naive NSCLC, support a favorable benefit-risk profile for tiragolumab and atezolizumab. Because of the reinvigoration of an anti-tumor immune response by immune-modulating radiotherapy and the potential synergism with ICI treatment, the potentially synergistic mechanisms of action of atezolizumab and tiragolumab, as well as their manageable and tolerable safety profiles, combination treatment with these two treatment modalities appears to have promising therapeutic potential in solid tumors and may reinvigorate and augment the anti-tumor immune response, potentially resulting in improved and more durable clinical benefit for patients with treatment naive NSCLC.

[REDACTED]

The combination of the two ICIs, which target different inhibitory checkpoints and have demonstrated clinical efficacy, with XL092 appears to have promising therapeutic potential in solid tumors and may reinvigorate and augment the anti-tumor immune

Appendix 8: Study Details Specific to Atezo + Tira + XL092 Arm

response, potentially resulting in improved and more durable clinical benefit for patients with NSCLC.

Furthermore, the current study (BO39610) contains all safety measures of an early development study in that it enrolls only a well-defined patient population with good performance status selected on the basis of the known safety profile of the combination partners. In addition, the study implements close safety monitoring, including frequent visits of patients to the site, strict inclusion and exclusion criteria, regular investigator calls, and the implementation of an Internal Monitoring Committee and a Scientific Oversight Committee.

To evaluate potential overlapping toxicities of the experimental treatments, a minimum of 6 patients in the Atezo + Tira + XL092 arm must complete a safety evaluation before additional patients can be enrolled in that arm. In addition, stopping rules will be implemented for this arm to further reduce any potential risk for the patients even further (see Section 3.1.3, and Section A8–5.1 for details).

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.4.

A8–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + TIRA + XL092 ARM

A8–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab (Tecentriq® U.S. *Prescribing Information*).

[REDACTED]

[REDACTED]

[REDACTED]

Appendix 8: Study Details Specific to Atezo + Tira + XL092 Arm

[REDACTED]

Refer to the Tiragolumab Investigator's Brochure for additional details.

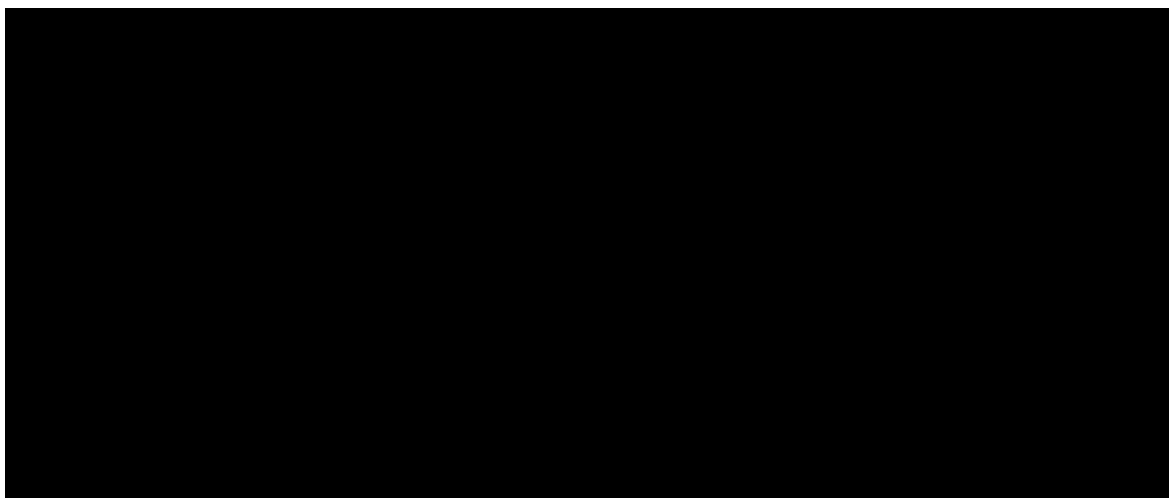
A8–3.3 RATIONALE FOR XL092 DOSE AND SCHEDULE

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



Based on the safety profile of XL092, the combination of XL092 with atezolizumab, and the combination of atezolizumab and tiragolumab, no additional toxicity is expected by the addition of tiragolumab to atezolizumab and XL092. Thus, the recommended Phase II dose for XL092 (100 mg QD) will be used in combination with fixed doses of atezolizumab (1200 mg IV Q3V) and tiragolumab (600 mg IV Q3W).

A8-4 MATERIALS AND METHODS SPECIFIC TO ATEZO+TIRA+XL092 ARM

A8-4.1 TREATMENT IN ATEZO+TIRA+XL092 ARM


A8-4.1.1 Formulation, Packaging, and Handling

A8-4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the atezolizumab formulation, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A8-4.1.1.2 Tiragolumab

The tiragolumab drug product will be supplied by the Sponsor 



Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

For information on the *tiragolumab* formulation, see the pharmacy manual and the Tiragolumab Investigator's Brochure.

A8-4.1.1.3 XL092

For information on the formulation and handling of XL092, see the pharmacy manual and the XL092 Investigator's Brochure.

A8-4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo+Tira+XL092 arm will receive treatment as outlined in [Table A8-1](#) until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see [Section 3.1.1](#) for details).

Table A8-1 Treatment Regimen for Atezo+Tira+XL092 Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none">• Atezolizumab 1200 mg IV on Day 1 of each cycle• Tiragolumab 600 mg IV on Day 1 of each cycle• XL092 100 mg PO QD

Atezo = atezolizumab; PO = by mouth, orally; QD = once a day; Tira = tiragolumab.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in [Section 5.3.5.12](#). No safety data related to overdosing of atezolizumab or tiragolumab are available to date.

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

A8–4.1.2.1 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#). Atezolizumab infusions will be administered per the instructions outlined in [Table A8-2](#).

Table A8-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
<ul style="list-style-type: none">No premedication is permitted prior to the atezolizumab infusion.Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be <i>measured</i> within 60 minutes prior to the infusion.Atezolizumab should be infused over 60 (\pm 15) minutes.If clinically indicated, vital signs should be <i>measured</i> every 15 (\pm 5) minutes during the infusion and at 30 (\pm 10) minutes after the infusion.Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	<ul style="list-style-type: none">If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic <i>medications</i>, and/or analgesics may be administered for subsequent doses at the discretion of the investigator.Vital signs should be <i>measured</i> within 60 minutes prior to the infusion.Atezolizumab should be infused over 30 (\pm 10) minutes if the previous infusion was tolerated without an IRR or 60 (\pm 15) minutes if the patient experienced an IRR with the previous infusion.If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be <i>measured</i> during the infusion and at 30 (\pm 10) minutes after the infusion.

IRR=infusion-related reaction.

Guidelines for medical management of IRRs for atezolizumab are provided in [Appendix 6](#).

No dose modification for atezolizumab is allowed. Guidelines for *atezolizumab* treatment interruption or discontinuation because of toxicities are provided in Section [A8–5.1.6.2](#). Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements

for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A8–4.1.2.2 Tiragolumab Administration

Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle with a post-infusion observation period as described in [Table A8-3](#).

Administration of tiragolumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#). Tiragolumab infusions will be administered *according to* the instructions outlined in [Table A8-3](#).

Table A8-3 Administration of First and Subsequent Tiragolumab Infusions

<ul style="list-style-type: none">	<ul style="list-style-type: none">

Guidelines for medical management of IRRs for tiragolumab are provided in [Appendix 6](#).

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section [A8–5.1.6.2](#). Tiragolumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures).

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A8–4.1.2.3 XL092 Administration

Subjects should be instructed *to fast (with the exception of water)* for at least 2 hours before and at least 1 hour after taking XL092 *to avoid potential food effects*. The subject should take their assigned XL092 dose by mouth with a minimum of 8 ounces (240 mL) of water. On clinic visit days, patients should take their XL092 tablets in the clinic after completion of the atezolizumab and tiragolumab infusions.

The tablets are not to be split or crushed for dissolving in liquid, chewed or administered through other routes including percutaneous endoscopic gastrostomy tubes. XL092 tablets should not be administered to subjects who do not have adequate swallowing capacity and must be stored at room temperature.

There is no human clinical experience with an overdose of XL092. No experiments have been performed to determine whether the effects of overdose can be reversed, and there are no known antidotes.

In the event of overdose, the subject should be monitored, and supportive measures should be undertaken as clinically indicated. Any adverse events that occur as a result of an overdose have to be treated according to clinical standard practice.

Subjects must be instructed to not make up doses missed by more than 12 hours. Subjects who vomit after taking XL092 should not attempt to make up the dose. Subjects should take their tablets in the morning at the same time.

Dosing Diary

To assess patient compliance with self-administration of XL092, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

Guidelines for XL092 treatment interruption or discontinuation because of toxicities are provided in Section [A8–5.1.6.2](#). XL092 treatment may be suspended for reasons other than toxicity (e.g., surgical procedures, please see below). The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Appendix 8: Study Details Specific to Atezo + Tira + XL092 Arm

As general guidance, XL092 must be interrupted for at least 28 days prior to surgical procedures. The decision to resume treatment following surgery will be based on clinical judgment of complete wound healing. Hematologic toxicities (i.e., neutropenia and thrombocytopenia) and associated complications as well as management of stomatitis and mucositis may be managed with dose interruptions and/or dose reductions of XL092 as well.

A8-4.2 CONCOMITANT THERAPY FOR ATEZO+TIRA+XL092 ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from *7 days* prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A8-4.2.1 Permitted Therapy for Atezo+Tira+XL092 Arm

-
- A horizontal bar chart consisting of 15 black bars of varying lengths. The bars are arranged vertically. From top to bottom, the bars have the following approximate relative lengths: 80%, 40%, 100%, 40%, 95%, 60%, 55%, 85%, 70%, 50%, 98%, 98%, 98%, 100%, and 80%. Small markers are present to the left of the first 14 bars: dots for bars 1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 13, and 14; and dashes for bars 4, 5, and 15.

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

- [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
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[REDACTED]
[REDACTED]
- [REDACTED]

Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for the second and subsequent atezolizumab and tiragolumab infusions only, at the discretion of the investigator. [REDACTED]

[REDACTED]
[REDACTED]

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 -adrenergic agonists; refer to [Appendix 5](#) for details).

A8–4.2.2 Cautionary Therapy for Atezo+Tira+XL092 Arm

Concomitant medications with sensitive or moderate sensitive clinical substrates of CYP3A4, 2C9, 2C19, 2C8, 1A2, and 2B6 should be used with caution during treatment with XL092 because XL092 might alter systemic exposures of these substrates. For a list of CYP-sensitive substrates and CYP-moderate sensitive substrates, please refer to the following U.S. Food and Drug Administration website for healthcare professionals:

<https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems>

A8–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and/or tiragolumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab and/or tiragolumab therapy (refer to [Appendix 6](#) for details).

The above list of cautionary medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor is available to advise as needed if questions arise regarding medications not listed above.

A8–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section [A8–4.2.3](#)) may be used during the study at the discretion of the investigator.

A8-4.2.3 Prohibited Therapy for Atezo+Tira+XL092 Arm

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

A8–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + TIRA + XL092 ARM

Contraception requirements for men and women in the Atezo + Tira + XL092 arm are outlined below.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and refrain from donating eggs, as defined below:

Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the final dose of atezolizumab, for 90 days after the final dose of tiragolumab, and for 186 days after the final dose of XL092. *Women must refrain from donating eggs during this same period.*

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Due to potential drug-drug interaction, hormonal contraceptive methods must be supplemented by a barrier method.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 90 days after the final dose of tiragolumab and 96 days after the final dose of XL092. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

A8-5 ASSESSMENT OF SAFETY FOR ATEZO+TIRA+XL092 ARM

A8-5.1 SAFETY PLAN FOR ATEZO+TIRA+XL092 ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab, tiragolumab, and XL092 in completed and ongoing studies.

The anticipated important safety risks are outlined below (see Sections [A8-5.1.1](#), [A8-5.1.2](#), and [A8-5.1.3](#)). Guidelines for management of patients who experience specific adverse events are provided in Section [A8-5.1.6](#) and [Appendix 6](#).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Although the risk for overlapping toxicities of atezolizumab and tiragolumab with XL092 is low, a minimum of 6 patients in the Atezo+Tira+XL092 arm must complete a safety evaluation (see Section [3.1.3](#)) before additional patients can be enrolled in that arm.

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

Administration of atezolizumab and tiragolumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. XL092 will be administered orally as described in [Table A8-1](#) and Section [A8-4.1.2.3](#). Adverse events will be reported as described in Sections [5.2-5.6](#).

A8-5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus,

Appendix 8: Study Details Specific to Atezo + Tira + XL092 Arm

hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A8–5.1.2 Risks Associated with Tiragolumab

IRRs and [REDACTED] are identified risks of tiragolumab. [REDACTED] is a potential risk with tiragolumab. Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events).

Refer to [Appendix 6](#) of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for details on nonclinical and clinical safety assessments.

A8–5.1.2.1 Infusion-Related Reactions

Because tiragolumab is a therapeutic monoclonal antibody and targets immune cells, IRRs associated with hypersensitivity reactions and/or target-mediated cytokine release may occur. Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

IRRs have been reported in patients treated with tiragolumab, with or without atezolizumab. The majority of events were mild to moderate and manageable.

[REDACTED]

[REDACTED] All infusions of tiragolumab will be administered in an appropriate medical setting.

Refer to Section [A8–4.1.2.2](#) for detailed guidance on administration of tiragolumab in this study. Please see [Appendix 5](#) for guidance on anaphylaxis precautions and [Table A8-5](#) and [Appendix 6](#) for guidance on the management of IRRs.

[REDACTED]

A8–5.1.2.3 Immune-Mediated Adverse Events

Nonclinical models have suggested a role of TIGIT signaling interruption in autoimmunity. In a knockout model (TIGIT^{–/–}), loss of TIGIT signaling resulted in hyperproliferative T-cell responses and exacerbation of experimental autoimmune encephalitis (EAE). TIGIT^{–/–} and wild-type B6 mice were immunized with myelin oligodendrocyte glycoprotein peptide in an EAE using suboptimal doses. In contrast to the wild-type B6 mice, the majority of the TIGIT^{–/–} mice developed severe EAE (Joller et al. 2011).

Clinical experience with therapeutics intended to enhance anti-tumor T-cell responses has demonstrated that development of autoimmune inflammatory conditions is a general risk and may therefore be considered a potential risk of tiragolumab. Such immune-mediated adverse events have been described for virtually all organ systems and include, but are not limited to, colitis, pneumonitis, endocrinopathies, ocular toxicity, pancreatic toxicity, neurologic toxicity, cardiac toxicity, nephritis, myositis, and severe cutaneous adverse reactions.

Patients with a history of autoimmune disease will be excluded from this study. Please see Section 4.1.2 for details.

In this study, immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A8–5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

Suggested management guidelines for individual suspected immune-mediated adverse events are provided in Appendix 6.

The IgG1 backbone of tiragolumab with the intact Fc-effector function may lead to antibody-dependent cell-mediated cytotoxicity–mediated reduction in lymphocyte count.

Patients with a lymphocyte count <500 cells/mL will be excluded from the study (Section 4.1.2) and complete blood counts will be monitored regularly during the study.

A8–5.1.2.5 Embryofetal Toxicity

[REDACTED]. Administration of tiragolumab is expected to have adverse effects on pregnancy based on the expression of TIGIT on decidual NK and CD8⁺ T cells (Powell et al. 2017; van der Zwan et al. 2018; Vento-Tormo et al. 2018), and the expected role of these cells in the recognition and response to foreign fetal, placental, and viral antigens at the maternal-fetal interface as well as maintenance of maternal-fetal tolerance. No reproductive or teratogenicity studies in animals have been conducted with tiragolumab. There are no clinical studies of tiragolumab in pregnant women. Tiragolumab should not be administered to pregnant women.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of embryofetal toxicity.

A8–5.1.3 Risks Associated with XL092

A8–5.1.3.1 Hypertension

Subjects treated with XL092 have experienced hypertension, including Grade 3 events.

In alignment with the recommendation from the Angiogenesis Task Force of the National Cancer Institute investigational drug steering committee (Maitland et al. 2010), blood pressures will be monitored closely. Subjects with uncontrolled hypertension at screening will be excluded from receiving XL092 treatment. XL092 should be discontinued in subjects with hypertensive emergency.

As XL092 undergoes hepatic metabolism via the CYP450 system, special attention should be paid to the particular type of hypertensive treatment administered to subjects. For example, subjects should avoid concomitant administration of CYP3A4-inhibiting calcium channel blockers since concomitant use may increase plasma concentrations of XL092. A list of prohibitive medications is available in Section [A8–4.2.3](#).

All study sites should have cardiologists available for consultation when required.

A8–5.1.3.2 Diarrhea

Diarrhea has been observed in subjects treated with XL092. Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Guidance and management of TKI-induced diarrhea is outlined in [Table A8-5](#). Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol. Recurrent or prolonged diarrhea can be associated with anal or perianal skin erosions

which increase the risk for anal abscesses, fistulas, or proctitis. Good personal hygiene should be emphasized. Regular examinations of the perianal region should be performed whenever diarrhea has occurred during treatment with XL092. Infections of the perianal region should be treated per local guidelines.

A8–5.1.3.3 Nausea and Vomiting

Nausea and vomiting have been observed in subjects treated with XL092. Guidance and management of TKI-induced nausea and vomiting are outlined in [Table A8-5](#). Anti-emetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented. Anti-emetic medications should be assessed for potential drug interactions.

A8–5.1.3.4 Proteinuria

Proteinuria has been observed in subjects receiving XL092 and is a common adverse effect from VEGFR targeting agents since VEGF plays an important role in normal renal function (Semeniuk-Wojtas et al. 2016; Launay-Vacher et al. 2011).

Though low-grade proteinuria is typically asymptomatic, high grade (\geq Grade 3) proteinuria may contribute to morbidity. Guidelines for the management of treatment-emergent proteinuria are provided in [Table A8-5](#).

XL092 should be discontinued in subjects who develop nephrotic syndrome.

A8–5.1.3.5 Thyroid Dysfunction

Hypothyroidism has been observed in subjects receiving XL092 and has been associated with a number of VEGFR kinase inhibitors (Ahmadieh and Salti 2013). Based on the risk of developing hypothyroidism, early detection and characterization of thyroid dysfunction is essential. Subjects with pharmacologically uncompensated, symptomatic hypothyroidism will be excluded from this study. Thyroid function tests will be performed at screening and monitored closely. XL092-induced thyroid disorders should be treated per standard clinical practice and additional guidance is available in [Table A8-5](#).

A8–5.1.3.6 Hematologic Toxicities

Subjects must have adequate bone marrow function prior to enrollment. Hematologic toxicities (i.e., neutropenia and thrombocytopenia) and associated complications may be managed with dose interruptions and/or dose reductions of XL092. In addition, blood cell transfusions and granulocyte-colony stimulating factor supplementation should be provided per standard of care. Guidance for the management of hematologic disorders is provided in [Table A8-5](#).

Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

A8–5.1.3.7 Palmar-Plantar Erythrodysesthesia

Palmar-plantar erythrodysesthesia (PPE), also known as hand-foot skin reaction, associated with TKIs has features that differ from chemotherapy-related PPE. Symptoms may occur at pressure points, such as the palms of the hands, elbows or the soles of the feet. Symptoms typically appear within the first 4 weeks of therapy, most often within the first 2 weeks. Patients typically complain of dysesthesia with tingling that develops into burning over a few days. They develop bilateral painful erythema and also large, intense blisters that evolve eventually into hyperkeratosis.

Based on the theoretical risk of PPE for XL092, guidance and management of PPE is provided in [Table A8-5](#).

A8–5.1.3.8 Stomatitis and Mucositis

Though stomatitis and mucositis are generally reversible, the patient's quality of life can be severely impacted. Severe stomatitis and mucositis may not only result in malnutrition, fatigue, and anorexia, but may also increase the risk of local and systemic infection. A high incidence of stomatitis has been reported for TKIs that target VEGFR (Arena et al. 2018). Stomatitis- and mucositis-related symptoms experienced by patients include dysgeusia, ulcers, cheilitis, and substantial pain. Management of stomatitis and mucositis may include XL092 dose interruptions or dose-reductions. It should be noted that the pain experienced by patients may continue after treatment is discontinued. More specific guidance and management of stomatitis and mucositis is provided in [Table A8-5](#).

A8–5.1.3.9 Fatigue

Fatigue has been observed in subjects receiving XL092. Common causes of fatigue, such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, dehydration, sleep disturbance, and hypothyroidism should be ruled out and treated according to standard of care.

A8–5.1.3.10 Weight Loss

Weight loss and anorexia have been observed in subjects receiving XL092 and are also commonly observed in patients with cancer following TKI therapy (Schmidinger 2013).

A8–5.1.3.11 Edema

Edema has been reported for MET antagonists (Ye et al. 2016). Management of subjects with edema should follow accepted clinical practice guidelines.

A8–5.1.3.12 Liver Enzymes

Increased liver enzymes has been observed in subjects receiving XL092 and for multiple TKIs (Shah et al. 2013). Based on this risk, only patients with adequate liver function will be enrolled into this study. Liver enzymes will also be monitored regularly throughout treatment with XL092. Evaluation of subjects with elevated transaminases or bilirubin should be individualized and guided by the presence of specific risk factors such as liver conditions (e.g., liver cirrhosis, thrombosis of portal or hepatic vein, liver cancer and liver metastasis, infectious hepatitis), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes. Guidance for management of hepatobiliary events is provided in [Table A8-5](#).

A8–5.1.3.13 Thromboembolic Events

Venous thromboembolic events, including deep vein thrombosis and pulmonary embolism, have been observed in subjects receiving XL092. Other vascular events associated with VEGFR-TKIs include angina, acute myocardial infarction (AMI), and stroke (Touyz et al. 2018). The risk of AMI and stroke is low for the majority of VEGFR-TKI therapies.

Patients with recent (within 6 months before first dose) history of cardiovascular events (e.g., stroke, myocardial infarction, unstable angina pectoris, serious cardiac arrhythmias, or other ischemic or thromboembolic events) or higher grade cardiac disease according to New York Heart Association classification will be excluded from receiving XL092 treatment. Subjects should be evaluated for preexisting risk factors for arterial thrombotic events such as diabetes mellitus, hyperlipidemia, hypertension, coronary artery disease, history of tobacco use, and cardiac and/or thromboembolic events that occurred prior to initiation of XL092 treatment.

Subjects who develop a venous thromboembolism should have XL092 treatment withheld until therapeutic anticoagulation is established. Subjects who develop an arterial thromboembolism (e.g., acute myocardial infarction, stroke) while receiving XL092 should discontinue treatment.

A8–5.1.3.14 Other Important Side Effects of Protein Kinase Inhibitors QT Interval Prolongation

TKIs have been reported to prolong the QT interval (Kloth et al. 2015). XL092 should be used with caution in subjects with QT prolongation risk, a history of QT interval prolongation, or those who are taking antiarrhythmics or drugs known to prolong the QT interval (see [Appendix 21](#)). All study sites should have cardiologists available for consultation when required.

Wound Healing Complications

As angiogenesis plays a key role during the granulation phase of wound healing, disruption of endothelial-cell response to injury through VEGF inhibition may lead to wound-healing complications (Chapin et al. 2011; Scappaticci et al. 2005). Therefore, complete wound healing following surgery is required for participation in Study BO39610. As general guidance, XL092 must be interrupted for at least 28 days prior to surgical procedures. The decision to resume treatment following surgery will be based on clinical judgment of complete wound healing.

Hemorrhage

Agents targeting the VEGF-signaling pathway can cause bleeding events through alterations of endothelial function and increased vascular fragility. While most bleeding complications are mild, for example increased frequency of nosebleeds (epistaxis), other more serious complications may include bleeding from wound dehiscence, hemoptysis, and organ bleeding due to tumor necrosis. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

- Tumor of the lung with cavitory lesions or tumor lesions which invade or encase major blood vessels. Thus, the anatomic location and characteristics of the tumor and the medical history of the patient should be carefully reviewed in the selection of subjects for treatment.
- Recent or concurrent radiation to the thoracic cavity
- Active peptic ulcer disease, inflammatory GI diseases including Crohn's disease and ulcerative colitis
- Underlying medical conditions which affect normal hemostasis (e.g., deficiencies in clotting factors and/or platelet function, or thrombocytopenia)
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis

In this study, subjects with a history of clinically significant hemoptysis, hematemesis, or hematuria will be excluded. Subjects should be evaluated for potential bleeding risk factors prior to initiating XL092 treatment and should be monitored for bleeding events with serial complete blood counts and physical examination while in the study.

Gastrointestinal Perforations and Fistulas

Perforations of the GI tract have been observed in subjects treated with XL092.

VEGF-targeted therapy has been associated with perforations of the GI tract and fistula formation. Though the reported incidence of GI perforations and fistulas following VEGF-targeting TKI therapy is relatively low, such events can contribute to mortality (Hapani et al. 2009). In this study, subjects who have a high risk of perforation or fistula formation will be excluded. This includes exclusion of subjects with tumors that invade the GI-tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction. Subjects with recent history (within 6 months prior to first dose) of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess will also be excluded. Prior to initiation of treatment, subjects should be carefully evaluated for potential risk factors including (but not limited to) the following:

- Abdominal carcinomatosis
- Inflammatory bowel disease
- Acute diverticulitis
- Bowel obstruction
- History of pelvic or abdominal perforation
- History of bowel resection
- Inflammatory bowel disease
- Peri-anal abscess
- Tumors invading respiratory tracts
- History of radiation therapy to the abdomen
- Prior GI surgery (particularly when associated with delayed or incomplete healing)

After starting XL092, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever, especially if known risk factors for developing GI perforation or fistula are present (Turnage et al. 2008).

Osteonecrosis

Osteonecrosis has been reported in subjects treated with certain TKIs. Additional risk factors include use of bisphosphonates and denosumab, chemotherapy and anti-angiogenic drugs, use of corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.

Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion.

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Persistent pain or slowly healing wounds of the mouth or jaw after dental surgery may also be manifestations of ONJ.

An oral examination should be performed prior to initiation of XL092 and periodically during XL092 treatment. Subjects should be advised regarding oral hygiene practice and to quickly report symptoms to investigator. Caution should be used in subjects receiving bisphosphonates or denosumab.

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment with XL092 should be held until complete wound healing has occurred. Bone healing may often require a protracted time.

If ONJ occurs, XL092 treatment should be held and should not be restarted until the condition has sufficiently healed. The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A8–5.1.4 Risks Associated with Combination Use of Atezolizumab and Tiragolumab

Based on results from clinical data with tiragolumab and atezolizumab, there are known and potential overlapping toxicities in patients treated with tiragolumab plus atezolizumab. Because the expected pharmacologic activity of these two molecules is to increase adaptive T-cell immune responses, there is the possibility of heightened immune responses.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a list of identified risks associated with tiragolumab in combination with atezolizumab. Based on the mechanism of action of tiragolumab and atezolizumab, additional immune-mediated adverse events are potential overlapping toxicities associated with combination use of tiragolumab plus atezolizumab.

Based on clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with tiragolumab and atezolizumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with ICIs to date has been incorporated into the design and safety management plan (see [Appendix 6](#)) in order to reduce the potential risks to participating patients. Patients with a history of autoimmune disease will be excluded from this study (see Section [4.1.2](#)). Patients previously treated with approved or experimental CIT will also be excluded from participation in this study. Owing to the risks of active viral infection and viral reactivation (see Section [4.1.2](#)), patients with active infection (including, but not limited to, HIV, HBV, HCV, EBV, known and/or suspected chronic

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active EBV infection, or tuberculosis) and/or patients with recent severe infections will be excluded from this study (see Section 4.1.2).

A8-5.1.5 Risks Associated with the Combination Use of Atezolizumab, Tiragolumab, and XL092

The following adverse events are potential overlapping toxicities associated with the combination use of atezolizumab, tiragolumab, and XL092: diarrhea, transaminase increases, and thyroid function disorders.

A8-5.1.6 Management of Patients Who Experience Specific Adverse Events in Atezo+Tira+XL092 Arm

A8-5.1.6.1 Dose Modifications

There will be no dose modifications for atezolizumab or tiragolumab in this study. For management of drug related toxicities, the dose of XL092 can be reduced as outlined in Table A8-4.

Table A8-4 Suggested Dose Reductions for XL092

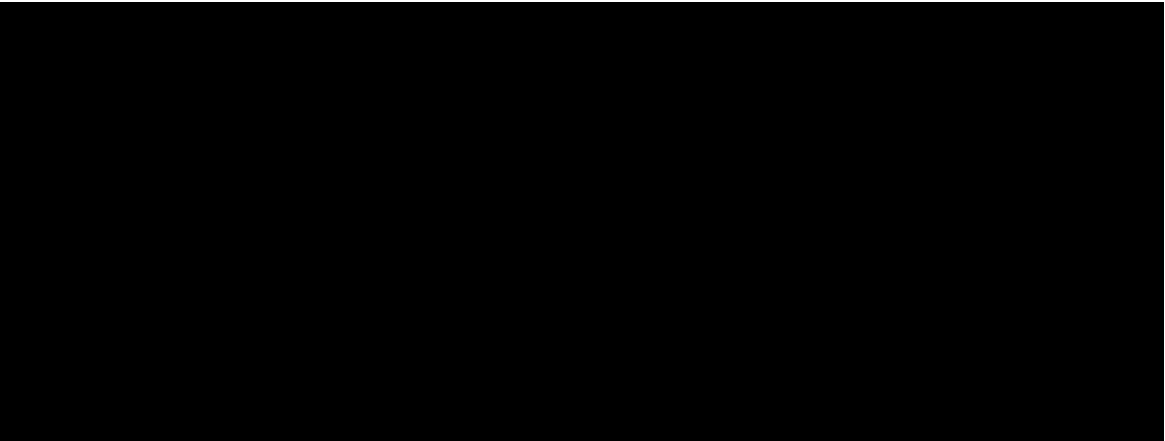
Drug	Initial Dose	First Dose Reduction	Second Dose Reduction
XL092	100 mg QD	60 mg QD	40 mg QD

QD = once a day.

XL092 treatment reductions should be considered to prevent worsening of toxicity if the investigator feels it is in the interest of a patient's safety, and may be required in order to continue with XL092 administration.

A8-5.1.6.2 Treatment Interruption for Toxicities

Atezolizumab and tiragolumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table A8-5).



The acceptable length of treatment interruption must be based on *the investigator's* benefit-risk assessment and

Appendix 8: Study Details Specific to Atezo + Tira + XL092 Arm

in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

On the basis of the available characterization of mechanism of action, tiragolumab may cause adverse events similar to, but independent of, atezolizumab. Tiragolumab may also exacerbate the frequency or severity of atezolizumab-related adverse events or may have non-overlapping toxicities with atezolizumab. Because these scenarios may not be distinguishable from each other in the clinical setting, adverse events should generally be attributed to both agents, and dose interruptions or treatment discontinuation in response to adverse events should be applied to both tiragolumab and atezolizumab. If atezolizumab is withheld or discontinued, tiragolumab should also be withheld or discontinued. If tiragolumab is withheld or discontinued, atezolizumab should also be withheld or discontinued.

XL092 treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If toxicity related to XL092 prevents dose resumption for more than 12 weeks after interrupting treatment, the patient will be discontinued from XL092.

XL092 treatment can be resumed after being withheld for more than 12 weeks if the investigator feels that the patient is likely to derive clinical benefit. If either atezolizumab/tiragolumab or XL092 is discontinued, the other drug(s) can be continued if the patient is likely to derive clinical benefit (i.e., if XL092 is discontinued, treatment with atezolizumab and tiragolumab can be continued and if atezolizumab and tiragolumab are discontinued, treatment with XL092 can be continued).

The decision to re-challenge patients with XL092 or atezolizumab plus tiragolumab should be based on *the* investigator's *benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Refer to [A8–4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A8–5.1.6.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events related to atezolizumab and tiragolumab are provided in [Appendix 6](#). *These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.*

Appendix 8: Study Details Specific to Atezo + Tira + XL092 Arm

For cases in which management guidelines are not covered in [Appendix 6](#), patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Adverse events related to atezolizumab and tiragolumab will be managed according to [Appendix 6](#). Adverse events related to XL092 will be managed as per [Table A8-5](#).

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

Table A8-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Tira+XL092 Arm

Event	Action to Be Taken
[REDACTED]	[REDACTED]
[REDACTED]	<ul style="list-style-type: none"> [REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	<ul style="list-style-type: none"> [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED]	<ul style="list-style-type: none"> [REDACTED] [REDACTED]

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

Table A8-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Tira+XL092 Arm (cont.)

[illegible]

Table A8-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Tira+XL092 Arm (cont.)

Event	Action to Be Taken
[REDACTED]	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]

Table A8-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Tira + XL092 Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events	

Table A8-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Tira+XL092 Arm (cont.)

[illegible]

Table A8-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Tira+XL092 Arm (cont.)

[illegible]

Table A8-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Tira+XL092 Arm (cont.)

Event	Action to Be taken

[illegible]

Table A8-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Tira+XL092 Arm (cont.)

Event	Action to Be Taken
[REDACTED]	<ul style="list-style-type: none">[REDACTED][REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	<ul style="list-style-type: none">[REDACTED][REDACTED][REDACTED][REDACTED]
[REDACTED]	<ul style="list-style-type: none">[REDACTED][REDACTED][REDACTED]

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

Table A8-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Tira+XL092 Arm (cont.)

Event	Action to Be Taken
	<ul style="list-style-type: none">
	<ul style="list-style-type: none">
	<ul style="list-style-type: none">
	<ul style="list-style-type: none">

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

Table A8-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Tira+XL092 Arm (cont.)

Event	Action to Be Taken
[REDACTED]	[REDACTED]
[REDACTED]	<ul style="list-style-type: none"> [REDACTED] [REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED]	<ul style="list-style-type: none"> [REDACTED] [REDACTED]
[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED]	<ul style="list-style-type: none"> [REDACTED]
[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED]	<ul style="list-style-type: none"> [REDACTED]
[REDACTED]	[REDACTED]

Table A8-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Tira+ XL092 Arm (cont.)

Event	Action to Be Taken
[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED]	<ul style="list-style-type: none"> [REDACTED]
[REDACTED] [REDACTED] [REDACTED]	<ul style="list-style-type: none"> [REDACTED]. <p>[REDACTED]</p> <ul style="list-style-type: none"> [REDACTED] [REDACTED] [REDACTED] <p>[REDACTED]</p> <ul style="list-style-type: none"> [REDACTED] [REDACTED] [REDACTED]

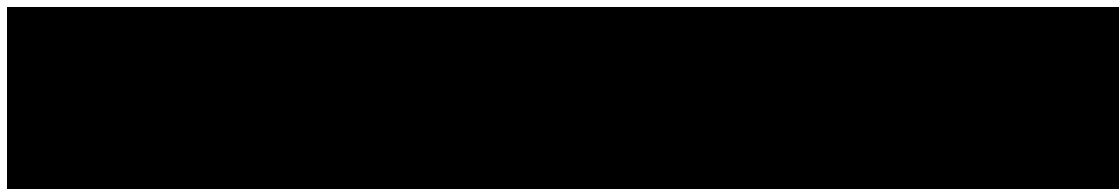
Event	Action to Be Taken
[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] <ul style="list-style-type: none"> [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] <ul style="list-style-type: none"> [REDACTED] [REDACTED] [REDACTED]
[REDACTED]	
a [REDACTED]	

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.2.3 for reporting instructions). Adverse events of special interest for the Atezo+Tira+XL092 arm are as follows:

• [REDACTED]

- [illegible]

-
-
-



A8–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+TIRA+XL092 ARM

A8–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab, within 90 days after the final dose of tiragolumab or within 186 days after the final dose of XL092. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A8–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 90 days after the final dose of tiragolumab or 96 days after the final dose of XL092. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide

information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A8–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A8–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

A8–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+TIRA+XL092 ARM

Table A8-6 Schedule of Activities for Atezo+Tira+ XL092 Arm

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) ^a				Treatment Discontinuation (see below) ^c	Follow-Up
	Days –28 to –1	Cycles 1 ^b			Cycles ≥ 2		Every 3 Months (± 7 days)
		Day 1	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)		
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available					
Vital signs ^d		x	x	x	x	x	
Weight ^e		x	x	x	x	x	
Complete physical examination ^f		x			x	x	
Limited physical examination ^{e, g}			x	x			
ECOG Performance Status ^e		x			x	x	
ECG ^h		x			x		
Hematology ⁱ		x ^{j, k}	x ^j	x ^j	x ^j	x	
Chemistry ^l		x ^{j, k}	x ^j	x ^j	x ^j	x	
Coagulation (INR, aPTT)		x ^{j, k}			x	x	
TSH, free T3 (or total T3), and free T4 ^m		x ^{j, k, m}				x	
Pregnancy test ⁿ		x ^{j, k}			x ^j	x	x ⁿ
Urinalysis ^o		x	x	x	x ^o	x	
UPCR ^p		x	x	x	x		

Appendix 8: Study Details Specific to Atezo + Tira + XL092 Arm

Table A8-6 Schedule of Activities for Atezo + Tira + XL092 Arm (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) ^a				Treatment Discontinuation (see below) ^c	Follow-Up
		Cycles 1 ^b			Cycles ≥2		Every 3 Months (± 7 days)
	Days –28 to –1	Day 1	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)		
Serum autoantibody sample ^q	See Appendix 2	Perform if a patient experiences a suspected immune-mediated adverse event.					
PK samples		Refer to Table A8-7 .					
ADA samples		Refer to Table A8-7 .					
Biomarker samples		Refer to Table A8-7 .					
Blood sample for RBR (optional) ^r		x					
Tumor biopsy ^s		x					
Tumor biopsy (optional) ^t		x					
Tumor response assessments		x ^{u, v}					
Concomitant medications ^w		x	x	x	x	x	
Adverse events ^x		x	x	x	x	x ^x	x ^x
Atezolizumab administration ^{y, z}		x			x		
Tiragolumab administration ^{z, aa}		x			x		
<i>Dispense</i> XL092 ^{bb}		x			x		
Survival follow-up and anti-cancer treatment							x ^{cc}

Appendix 8: Study Details Specific to Atezo + Tira + XL092 Arm

Table A8-6 Schedule of Activities for Atezo + Tira + XL092 Arm (cont.)

ADA=anti-drug antibody; Atezo=atezolizumab; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; MRI=magnetic resonance imaging; PK=pharmacokinetic; PR=beginning of P wave to first part of QRS complex; RBR=Research Biosample Repository; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; T3=triiodothyronine; T4=thyroxine; Tira=tiragolumab; TSH=thyroid-stimulating hormone; UPCR=urine protein/creatinine ratio.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

- ^a If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.
- ^b It is recommended that treatment be initiated no later than 7 days after randomization (Stage 1) or treatment assignment (Stage 2).
- ^c Patients will return to the clinic for a treatment discontinuation visit not more than 30 days after the *final* dose of study treatment.
- ^d Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (\pm 5) minutes during and 30 (\pm 10) minutes after the infusion. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (\pm 10) minutes after the infusion.
- ^e Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^f *Complete physical examination* includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^g Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Appendix 8: Study Details Specific to Atezo + Tira + XL092 Arm

Table A8-6 Schedule of Activities for Atezo + Tira + XL092 Arm (cont.)

- ^h Triplicate 12-lead ECGs will be performed predose (and if indicated, 2 hours [\pm 30 minutes] postdose and at any other timepoints). At the Cycle 1 Day 1 visit, results must be available to, and reviewed by, the investigator prior to any treatment being administered. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording. Additional ECGs should also be performed as clinically indicated throughout the study. At minimum, the following parameters will be collected: QRS, QT (uncorrected and corrected), PR, ventricular rate, and sinus rhythm. Abnormalities in the ECG that lead to a change in subject management (e.g., dose reduction, hold, delay, treatment discontinuation, or requirement for additional medication or monitoring) or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be deemed adverse events. If values meet criteria defining them as serious, they must be reported as serious adverse events. Following re-initiation of XL092 treatment after interruption for QT prolongation, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined timepoints. Baseline is defined as the most recent assessment prior to receiving study drug(s).
- ⁱ Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).
- ^j Laboratory tests must be performed within 96 hours prior to dosing on Day 1 of Cycle 1 and within 96 hours prior to specified subsequent visits during the treatment period.
- ^k If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.
- ^l Chemistry panel (serum or plasma) includes bicarbonate or carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included on Day 1 of each treatment cycle.
- ^m TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).
- ⁿ All women of childbearing potential will have urine or serum pregnancy tests performed at specified visits during treatment and at 3 months and 6 months after treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^o *Urinalysis* includes pH, specific gravity, glucose, protein, ketones, blood, and urine protein/creatinine ratio; dipstick permitted if delivering the requested results. Urinalysis may be performed up to 72 hours prior to Day 1 of each cycle from Cycle 2 onward, as results must be available prior to treatment administration.
- ^p UPCR may be performed up to 72 hours prior to Day 1 of each cycle from Cycle 2 onward, as results must be available prior to treatment administration. 24-hour urine analysis should be performed if clinically indicated (please see [Table A8-5](#)).

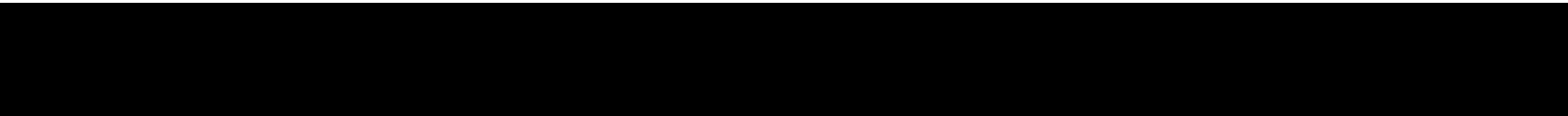
Appendix 8: Study Details Specific to Atezo + Tira + XL092 Arm

Table A8-6 Schedule of Activities for Atezo + Tira + XL092 Arm (cont.)

- ^q Autoantibody testing includes anti-nuclear antibody, anti-double-stranded DNA antibody, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Serum samples collected for the assessment of PK, ADAs, or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment, may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.
- ^r Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.
- ^s Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see Section 3.1.2) will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible). See Section 4.5.6 for tissue sample requirements.
- ^t Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation, if deemed clinically feasible and may undergo additional on-treatment biopsies at any other time during the study at the investigator's discretion.
- ^u Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first *48 weeks* following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 except in the case of patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.
- ^v All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head CT scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).
- ^w Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from *7 days* prior to initiation of study treatment until the treatment discontinuation visit.

Appendix 8: Study Details Specific to Atezo + Tira + XL092 Arm

Table A8-6 Schedule of Activities for Atezo + Tira + XL092 Arm (cont.)

- ^x After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.
- ^y Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.
- ^z Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).
- ^{aa} 
- ^{bb} XL092 tablets should not be crushed or chewed. Subjects should be instructed not to eat for at least 2 hours before, and at least 1 hour after, taking XL092. The subject should take their assigned XL092 dose by mouth with a minimum of 8 ounces (240 mL) of water. The starting XL092 tablet dose will be at 100 mg once a day. To assess patient compliance with self-administration of XL092, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.
- ^{cc} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. The Sponsor may conclude treatment arms in which all patients have discontinued treatment and completed safety follow-up and/or treatment arms in which approximately 80% of patients have discontinued the study (with the remaining ~20% of patients to be discontinued from the study).

Appendix 8: Study Details Specific to Atezo+Tira+XL092 Arm

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A9–1 BACKGROUND ON ATEZO + EVO ARM

A9–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, *myocarditis*, and *nephritis*, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma (in the European Union), non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer (in the European Union), hepatocellular carcinoma, melanoma (in the United States), and alveolar soft part sarcoma (in the United States).

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A9–1.2 BACKGROUND ON EVOLOCUMAB

Proprotein convertase subtilisin/kexin type 9 (PCSK9) was first described in 2003 to play a role in liver regeneration and neuronal differentiation and was later implicated in cholesterol homeostasis (Seidah et al. 2003). In humans, the clinical importance of PCSK9 was highlighted when its gain-of-function mutation was associated with autosomal dominant hypercholesterolemia (Abifadel et al. 2003).

These and multiple subsequent studies led to the development of various strategies to reduce circulating PCSK9 levels—including PCSK9 inhibitors and monoclonal antibodies

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to PCSK9 like evolocumab and alirocumab—demonstrating a large benefit in the field of atherosclerosis and cardiovascular diseases (Liberale et al. 2017, 2018).

PCSK9 is primarily synthesized in the liver and secreted into the blood. It acts as a major regulator of circulating LDL cholesterol (LDL-C) by binding to hepatic cell surface LDL receptors (LDLRs).

Large Phase III trials demonstrated that both monoclonal antibodies evolocumab and alirocumab produce mean reductions in LDL-C of approximately 60% with a good safety profile, both when used alone or when added to standard statin treatment (Robinson et al. 2015; Giugliano et al. 2017).

Evolocumab is a 154-kDa human monoclonal antibody with high binding affinity for PCSK9 and is approved for the treatment of hypercholesterolemia. Evolocumab has been tested in an extensive study program, consisting of five Phase II studies and seven Phase III studies as well as two open-label extension studies and one outcomes study. Evolocumab has been generally very well tolerated and adverse events have mostly been manageable and reversible. An overview on the safety and efficacy data from clinical studies can be found in Section [A9–2.4](#)).

Based on these clinical studies, evolocumab was approved in the European Union in July 2015 for adults with primary hypercholesterolemia (heterozygous familial hypercholesterolemia [HeFH] or nonfamilial hypercholesterolemia) as well as for adults and adolescents ≥ 12 years of age with homozygous familial hypercholesterolemia (HoFH).

In the United States, evolocumab was approved in August 2015 for adult patients with HeFH, clinical atherosclerotic cardiovascular disease, or HoFH (who require supplementary LDL-C-lowering treatment in addition to background LDL-lowering therapies [e.g., statins, ezetimibe, LDL apheresis]).

A9–2 RATIONALE FOR ATEZO+EVO ARM

A9–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses by binding to its

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two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors (CPIs), have *had* a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active *as monotherapy* for many patients.

A9-2.2 PCSK9 SIGNALING IN CANCER

Proprotein convertases (PCs) of the subtilisin and kexin family constitute a group of nine calcium-dependent serine proteases: PC1/3, Furin, PC2, PC4, PC5/6, PC7, PACE4 (Thomas 2002), SKI-1 (Seidah et al. 1999), and PCSK9 (Seidah et al. 2003). PCs were associated with cancer since the early 1990s (Smeekens and Steiner 1990), and their expression was found to be different between normal tissue and tumor cells.

Research by Momtazi-Borojeni et al. (2019) demonstrated that inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) by vaccination with a nanoliposomal anti-PCSK9 vaccine improved breast cancer outcomes while having no harmful effects in tumor-bearing BALB/C mice inoculated with 4T1 breast carcinoma cells. Furthermore, Abdelwahed et al. (2020) demonstrated that inhibition of PCSK9 by pseurotin A suppressed the progression of hormone-dependent BT-474 breast cancer cells in an orthotopic nude mouse xenograft model by reducing PCSK9 expression on the cancer cells as well as the locoregional recurrence after primary tumor surgical excision.

Importantly, Liu and colleagues (2020) recently discovered that PCSK9 is also a protein of interest in modulating response to immunotherapy. Syngeneic inoculation of mice

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with PCSK9-knockout mouse melanoma, mammary cancer, and colon cancer cell lines resulted in substantially reduced tumor growth compared with tumors in mice inoculated with PCSK9–wild-type variants of the same cancer cell lines. Interestingly, this effect was independent of host LDL receptor (LDLR) and cholesterol levels.

Knocking out PCSK9, as well as treatment with either of the two approved PCSK9 antibodies (evolocumab and alirocumab), synergized with anti–PD-1 treatment in all four syngeneic mouse models tested. Strikingly, the anti–PD-1 antibody plus evolocumab combination was efficacious even in anti-PD-1–resistant MC38R colon cancer models. Notably, treatment with evolocumab was effective in this setting either alone or in combination with anti–PD-1 treatment.

Flow cytometric analyses revealed that tumors grown from syngeneically transplanted PCSK9-knockout melanoma cells had substantially increased intratumoral infiltration of CD8⁺ cytotoxic T cells, CD4⁺ helper T cells, $\gamma\delta$ T cells, and natural killer cells.

Additionally, the ratio of CD8⁺ cytotoxic T cells to regulatory T cells was increased in PCSK9-knockout tumors, and interferon (IFN)- γ ⁺ CD8⁺ and GzmB⁺ CD8⁺ cytotoxic T cells were more abundant in PCSK9-knockout tumors. Depletion of CD8⁺ cytotoxic T cells eliminated the tumor growth suppression observed in PCSK9 knockout tumors, demonstrating the importance of tumor-infiltrating CD8⁺ cytotoxic T cells for suppressing tumor growth.

Mechanistically, PCSK9 activity reduced major histocompatibility complex class I (MHC-I) presentation on tumor cell surfaces by physically interacting with this complex and promoting its lysosomal degradation, hence leading to reduced tumor growth upon knockout or inhibition of PCSK9. In summary, the work of Liu et al. (2020) reveals a previously unknown role for PCSK9 independent of its canonical function in the regulation of cholesterol levels and demonstrates the efficacy of combining CPI-treatment with PCSK9 inhibition in CPI-resistant tumor models.

In addition to the data generated by Liu et al. (2020), Yuan et al. (2020) generated supporting evidence for the role of PCSK9 in anti-tumor immune responses by modifying LDLR expression, cholesterol metabolism, and T-cell receptor (TCR) activity in tumor infiltrating lymphocytes. The group demonstrated that intratumoral CD8⁺ T cells have reduced cholesterol levels, resulting from decreased levels of LDLR on the cell surface. As LDL-derived cholesterol is one of the key resources necessary for CD8⁺ T cell proliferation and effector function (Kidani et al. 2013; Yang et al. 2016; Proto et al. 2018) and LDL uptake in activated CD8⁺ T cells is almost completely dependent on LDLR, downregulation of LDLR on the surface of intratumoral CD8⁺ T cells—by PCSK9-driven internalization of LDLR—can significantly attenuate their proliferative activity.

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In addition, the group demonstrated that reduced LDLR expression also affects TCR signaling and the effector functions of CD8⁺ T cells. LDLR interacts with CD3, a subunit of the TCR complex, modulating the TCR signaling pathway. The phosphorylation of CD3ζ was inhibited in *ldlr*^{-/-} CD8⁺ T cells as compared with wild-type CD8⁺ T cells upon stimulation with anti-CD3 and anti-CD28, thus hampering TCR signal transduction. This demonstrates that CD3ζ phosphorylation and subsequent TCR-signal transduction is inhibited by LDLR deficiency. Furthermore, LDLR deficiency appears to inhibit TCR recycling to the plasma membrane.

Together, these experiments indicate that LDLR interacts with the TCR complex and regulates TCR signaling and expression on the cell surface as an immune regulatory membrane protein.

The investigators also demonstrated that PCSK9 was highly expressed in tumors as compared with normal tissue, and PCSK9 levels were negatively correlated with CD3⁺ T-cell infiltration, demonstrating that the tumor derived PCSK9 predominantly inhibits CD8⁺ T cell immune response leading to immune evasion by the tumor. Furthermore, the group also demonstrated that PCSK9 intrinsically inhibits the anti-tumor activity of CD8⁺ T cells by decreasing LDLR expression and ultimately downregulating plasma membrane TCR levels, CD3 phosphorylation, and the effector function.

Inhibiting PCSK9 in the respective syngeneic mouse models effectively inhibited tumor progression, and combination therapy of PCSK9 inhibition and checkpoint inhibition in immunocompetent MC38 tumor burdened C57BL/6 mice resulted in stronger tumor suppressive effect than either monotherapy.

A9-2.3 RATIONALE FOR COMBINING ATEZOLIZUMAB WITH EVOLOCUMAB

Liu et al. (2020) were able to demonstrate that PCSK9 knockout synergized with anti-PD-1 treatment in all four syngeneic mouse models tested, as did treatment with either of the two PCSK9 antibodies (evolocumab or alirocumab) that are currently approved for the treatment of refractory hyperlipidemia (please refer to Sections [A9-2.2](#) and [A9-2.4](#)).

In addition to the enhanced efficacy of both treatments in combination—with long-term survival of some host mice—the group was able to demonstrate efficacy of the anti-PD-1 antibody and evolocumab combination in anti-PD-1-resistant MC38R colon cancer models. Notably, treatment with evolocumab and alirocumab was effective either alone or in combination with anti-PD-1 treatment.

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The synergistic effect of combining checkpoint blockade and inhibition of PCSK9 in attenuating tumor growth was confirmed by Yuan et al. (2020) in the respective syngeneic mouse models tested.

To validate the role of PCSK9 in cancer in CPI-treated patients with NSCLC, the association between PCSK9 gene expression status and the efficacy of atezolizumab in NSCLC in two clinical trials was retrospectively explored: the Phase III second-line NSCLC trial OAK and the Phase III first-line NSCLC trial IMpower 150.

OAK evaluated the efficacy and safety of atezolizumab as a single agent versus docetaxel in patients with locally advanced or metastatic NSCLC that had progressed during or following treatment with a platinum-containing regimen. The study met its co-primary endpoints of overall survival (OS) in all randomized patients (intent-to-treat [ITT] population) and OS in a PD-L1-selected subgroup in the primary analysis population (tumor cell 1/2/3 or immune cell 1/2/3). Retrospective subgroup analysis of the OAK ITT dichotomized by PCSK9 expression as determined by RNA-sequencing (above or below the median), revealed that atezolizumab demonstrated a significant OS benefit versus docetaxel in PCSK9-low expressors, whereas there was no difference in OS between atezolizumab and docetaxel in the PCSK9-high expressor group.

This finding was consistent with the results of the same analysis of IMpower150 where patients with NSCLC who had high PCSK9 tumor expression derived limited benefit from atezolizumab plus carboplatin plus paclitaxel (ACP) or atezolizumab plus bevacizumab plus carboplatin/paclitaxel (ABCP), although bevacizumab may provide some benefit to PCSK9-high patients. Patients with low PCSK9 expression derived significant benefit from both ACP and ABCP but not from the chemotherapy control. Together these results suggest PCSK9 expression may be predictive of clinical efficacy of atezolizumab.

It was also observed that PCSK9 expression is generally anti-correlated with both immune infiltration and PD-L1 expression in OAK, which may partially explain why PCSK9-high patients show limited benefit from atezolizumab.

Taken together, the existing preclinical and clinical data on the role of PCSK9 in anti-tumor immune response suggest that the PCSK9/LDLR axis is a promising target and combined inhibition of PCSK9 and PD-1/PD-L1 could significantly enhance immunotherapy efficacy and re-sensitize patients to CPI treatment.

A9–2.4 CLINICAL STUDIES WITH EVOLOCUMAB

In randomized placebo-controlled clinical studies, evolocumab doses of 140 mg every 2 weeks (Q2W) or 420 mg once monthly (QM) for 12 weeks reduced LDL-C by approximately 55%–75%, compared with placebo, at the mean of Weeks 10 and 12 among patients with primary hyperlipidemia and mixed dyslipidemia who received

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evolocumab either as monotherapy (Koren et al. 2012, 2014) or in combination with a statin (Giugliano et al. 2012; Robinson et al. 2014) and in patients with HeFH who received evolocumab with a statin (Raal et al. 2012, 2015). In randomized active-control studies, these doses of evolocumab for 12–24 weeks reduced LDL-C by approximately 35%–45% compared with ezetimibe in patients with primary hyperlipidemia and mixed dyslipidemia (Koren et al. 2012, 2014), including patients with documented statin intolerance (Sullivan et al. 2012; Stroes et al. 2014; Nissen et al. 2016).

A9–2.4.1 Adverse Reactions in Adults with Primary Hyperlipidemia (including Heterozygous Familial Hypercholesterolemia)

The data described below reflect exposure to evolocumab in eight placebo-controlled trials that included 2651 patients treated with evolocumab, including 557 patients exposed for 6 months and 515 patients exposed for 1 year (median treatment duration of 12 weeks). The mean age of the population was 57 years; 49% of the population were women; 85% White, 6% Black, 8% Asians, and 2% other races.

Safety Profile in a 52-Week Controlled Trial (DESCARTES, NCT01516879)

In this 52-week, double-blind, randomized, placebo-controlled trial, 599 patients received 420 mg of evolocumab subcutaneously QM. The mean age was 56 years (range: 22 to 75 years); 23% were older than 65 years; 52% were women; 80% White, 8% Black, 6% Asian, and 6% identified as Hispanic ethnicity. Adverse reactions reported in at least 3% of evolocumab-treated patients, and more frequently than in placebo-treated patients in DESCARTES, are shown in [Table A9-1](#) below. Adverse reactions led to discontinuation of treatment in 2.2% of evolocumab-treated patients and 1% of placebo-treated patients. The most common adverse reaction that led to evolocumab treatment discontinuation and occurred at a rate greater than placebo was myalgia (0.3% vs. 0% for evolocumab and placebo, respectively).

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Table A9-1 Adverse Reactions Occurring in Greater Than or Equal to 3% of Evolocumab-Treated Patients and More Frequently Than with Placebo in DESCARTES

<i>Adverse Reaction</i>	Placebo (N=302) %	REPATHA (N=302) %
Nasopharyngitis	9.6	10.5
Upper respiratory tract infection	6.3	9.3
Influenza	6.3	7.5
Back pain	5.6	6.2
Injection-site reactions	5.0	5.7
Cough	3.6	4.5
Urinary tract infection	3.6	4.5
Sinusitis	3.0	4.2
Headache	3.6	4.0
Myalgia	3.0	4.0
Dizziness	2.6	3.7
Musculoskeletal pain	3.0	3.3
Hypertension	2.3	3.2
Diarrhea	2.6	3.0
Gastroenteritis	2.0	3.0

Safety Profile in Seven Pooled 12-Week Controlled Trials

In seven pooled 12-week, double-blind, randomized, placebo-controlled trials, 993 patients received 140 mg of evolocumab subcutaneously Q2W and 1059 patients received 420 mg of evolocumab subcutaneously QM. The mean age was 57 years (range: 18 to 80 years); 29% were older than 65 years; 49% were women; 85% White, 5% Black, 9% Asian, and 5% identified as Hispanic ethnicity. Adverse reactions reported in at least 1% of evolocumab-treated patients, and more frequently than in placebo-treated patients, are shown in [Table A9-2](#) below.

Table A9-2 Adverse Reactions Occurring in Greater Than 1% of Evolocumab-Treated Patients and More Frequently Than with Placebo in Pooled 12-Week Trials

<i>Adverse Reaction</i>	Placebo (N=1224) %	REPATHA^a (N=2052) %
Nasopharyngitis	3.9	4.0
Back pain	2.2	2.3
Upper respiratory tract infection	2.0	2.1
Arthralgia	1.6	1.8
Nausea	1.2	1.8
Fatigue	1.0	1.6
Muscle spasms	1.2	1.3
Urinary tract infection	1.2	1.3
Cough	0.7	1.2
Influenza	1.1	1.2
Contusion	0.5	1.0

^a 140 mg every 2 weeks and 420 mg once monthly combined.

Safety Profile in Eight Pooled Controlled Trials (Seven 12-Week Trials and One 52-Week Trial)

The adverse reactions described below are from a pool of the 52-week trial (DESCARTES) and seven 12-week trials. The mean and median exposure durations of evolocumab in this pool of eight trials were 20 weeks and 12 weeks, respectively.

- **Local Injection-Site Reactions:** Injection-site reactions occurred in 3.2% and 3.0% of evolocumab-treated and placebo-treated patients, respectively. The most common injection-site reactions were erythema, pain, and bruising. The proportions of patients who discontinued treatment due to local injection-site reactions in evolocumab-treated patients and placebo-treated patients were 0.1% and 0%, respectively.
- **Allergic reactions:** Allergic reactions occurred in 5.1% and 4.7% of evolocumab-treated and placebo-treated patients, respectively. The most common allergic reactions were rash (1.0% vs. 0.5% for evolocumab and placebo, respectively), eczema (0.4% vs. 0.2%), erythema (0.4% vs. 0.2%), and urticaria (0.4% vs. 0.1%).

A9–2.4.2 Safety Profile in Cardiovascular Outcomes Trial

In a double-blind, randomized, placebo-controlled cardiovascular outcomes trial (evolocumab Cardiovascular Outcomes Trial, FOURIER, NCT01764633), 27525 patients received at least one dose of evolocumab or placebo [see Clinical Studies

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(14.1)]. The mean age was 62.5 years (range: 40 to 86 years); 45% were 65 years or older, 9% were 75 years or older; 25% were women; 85% White, 2% Black, 10% Asian, and 8% identified as Hispanic ethnicity. Patients were exposed to evolocumab or placebo for a median of 24.8 months; 91% of patients were exposed for ≥ 12 months, 54% were exposed for ≥ 24 months, and 5% were exposed for ≥ 36 months. The safety profile of evolocumab in this trial was generally consistent with the safety profile described above in the 12- and 52-week controlled trials involving patients with primary hyperlipidemia (including HeFH). Serious adverse events occurred in 24.8% and 24.7% of evolocumab-treated and placebo-treated patients, respectively. Adverse events led to discontinuation of study treatment in 4.4% of patients assigned to evolocumab and 4.2% assigned to placebo. Common adverse reactions ($>5\%$ of patients treated with evolocumab and occurring more frequently than placebo) included diabetes mellitus (8.8% evolocumab, 8.2% placebo), nasopharyngitis (7.8% evolocumab, 7.4% placebo), and upper respiratory tract infection (5.1% evolocumab, 4.8% placebo).

A9–2.4.3 Safety Profile in Patients with Homozygous Familial Hypercholesterolemia

In a 12-week, double-blind, randomized, placebo-controlled trial of 49 patients with HoFH (TESLA, NCT01588496), 33 patients received 420 mg of evolocumab subcutaneously QM. The mean age was 31 years (range: 13–57 years); 49% were women; 90% White, 4% Asian, and 6% other. The adverse reactions that occurred in at least two (6.1%) evolocumab-treated patients, and more frequently than in placebo-treated patients, included:

- Upper respiratory tract infection (9.1% vs. 6.3%)
- Influenza (9.1% vs. 0%)
- Gastroenteritis (6.1% vs. 0%)
- Nasopharyngitis (6.1% vs. 0%)

A9–2.4.4 Immunogenicity

In clinical studies, 48 of 17,992 patients (0.3%) treated with at least one dose of evolocumab tested positive for binding antibody development. The patients whose sera tested positive for binding antibodies were further evaluated for neutralizing antibodies, and none of the patients tested positive for neutralizing antibodies. The presence of anti-evolocumab binding antibodies did not impact the pharmacokinetic profile, clinical response, or safety of evolocumab.

A9–2.4.5 Drug Interactions

As monoclonal antibodies have a low potential for pharmacokinetic drug interactions, no in vitro and in vivo drug interaction studies have been performed for evolocumab so far. However, the pharmacokinetic interaction between statins and evolocumab was

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evaluated in clinical trials. An approximately 20% increase in the clearance of evolocumab was observed in patients co-administered statins. This increased clearance is in part mediated by statins increasing the concentration of PCSK9, which did not adversely impact the pharmacodynamic effect of evolocumab on lipids. No statin dose adjustments are necessary when used in combination with evolocumab.

Refer to the Evolocumab Summary of Product Characteristics for details on nonclinical and clinical studies.

A9–2.5 BENEFIT–RISK ASSESSMENT

Metastatic NSCLC remains an incurable disease with a high unmet medical need, especially in the CPI-pretreated patient population. Two important mechanisms of resistance to CPI treatment, particularly in this growing population of CPI-experienced patients, is decreased antigen presentation (e.g., by downregulation of MHC-1 on the cell surface via PCSK9) and impaired TCR function. Taking into account the potentially synergistic mechanisms of action of atezolizumab and PCSK9 inhibition by evolocumab that has been well demonstrated in preclinical studies, as well as the known, manageable, and very tolerable safety profile for each of these agents, combination treatment with these two agents appears to have a very promising therapeutic potential for solid tumors such as NSCLC.

Furthermore, the current study (BO39610) contains all safety measures of an early development study in that it enrolls only a well-defined patient population with good performance status selected on the basis of known safety profile of the combination partners. In addition, the study implements close safety monitoring, including frequent visits of patients to the site, strict inclusion and exclusion criteria, regular investigator calls, and the implementation of an Internal Monitoring Committee and a Scientific Oversight Committee.

Given the well-controlled Phase Ib setting and the tolerable safety profile of both drugs, together with the promising preclinical and retrospective clinical data, the benefit–risk ratio for testing the combination of atezolizumab and evolocumab in NSCLC is positive.

For the evaluation of the impact of the *coronavirus disease 2019* (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.4.

A9–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+ EVO ARM

A9–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at the approved fixed dose of 840 mg Q2W (840 mg on Days 1 and 15 of each 28-day cycle). The average concentration following the

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840 mg Q2W dosage is equivalent to that of 1200 mg every 3 weeks (Q3W), *which is an approved dosage for atezolizumab (Tecentriq® U.S. Prescribing Information).*

A9-3.2 RATIONALE FOR EVOLOCUMAB DOSE AND SCHEDULE

Evolocumab will be administered subcutaneously at the approved fixed dose of 140 mg Q2W on Days 1 and 15 of each 28-day cycle.

A9-4 MATERIALS AND METHODS SPECIFIC TO ATEZO + EVO ARM

A9-4.1 TREATMENT IN ATEZO + EVO ARM

A9-4.1.1 Formulation, Packaging, and Handling

A9-4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the atezolizumab formulation, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A9-4.1.1.2 Evolocumab

Evolocumab will be supplied as 140 mg/mL solution in a single-use pre-filled SureClick® autoinjector.

For information on the formulation and handling of evolocumab, see the pharmacy manual and the Evolocumab Summary of Product Characteristics.

A9-4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + Evo arm will receive treatment as outlined in [Table A9-3](#) until unacceptable toxicity or loss of clinical benefit, as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section [3.1.1](#) for details). It is recommended that treatment be initiated no later than 7 days after randomization; *however, the first dose of study treatment should not occur within 3 days after a core biopsy or other surgical procedure.*

Table A9-3 Treatment Regimen for Atezo + Evo Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	<ul style="list-style-type: none">• Atezolizumab 840 mg IV on Days 1 and 15 <i>of each cycle</i>• Evolocumab 140 mg SC on Days 1 and 15 <i>of each cycle</i>

Atezo = atezolizumab; Evo = evolocumab.

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Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

No safety data related to overdosing of atezolizumab or evolocumab are available.

A9–4.1.2.1 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#). Atezolizumab infusions will be administered per the instructions outlined in [Table A9-4](#).

Table A9-4 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
<ul style="list-style-type: none">No premedication is permitted prior to the atezolizumab infusion.Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be <i>measured</i> within 60 minutes prior to the infusion.Atezolizumab should be infused over 60 (\pm 15) minutes.If clinically indicated, vital signs should be <i>measured</i> every 15 (\pm 5) minutes during the infusion and at 30 (\pm 10) minutes after the infusion.Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	<ul style="list-style-type: none">If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for subsequent doses at the discretion of the investigator.Vital signs should be <i>measured</i> within 60 minutes prior to the infusion.Atezolizumab should be infused over 30 (\pm 10) minutes if the previous infusion was tolerated without an IRR or 60 (\pm 15) minutes if the patient experienced an IRR with the previous infusion.If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be <i>measured</i> during the infusion and at 30 (\pm 10) minutes after the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in [Appendix 6](#).

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No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section [A9–5.1.4](#). Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A9–4.1.2.2 Evolocumab Administration

Evolocumab will be administered by SC injection at a fixed dose of 140 mg on Days 1 and 15 of each 28-day cycle.

- Administer evolocumab subcutaneously into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated using a single-use prefilled syringe.
- Do not co-administer evolocumab with other injectable drugs at the same administration site.
- Rotate the site of each SC administration (abdomen, thigh, or upper arm)

If an evolocumab dose is missed, administer evolocumab within 7 days from the missed dose and resume the original schedule. If dose is not administered within 7 days, wait until the next dose on the original schedule.

No dose modification for evolocumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section [A9–5.1.4](#). Evolocumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A9–4.1.3 Stage 2 Treatment

Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section [3.1.1](#)) or unacceptable toxicity related to atezolizumab will be given the option of receiving a different treatment combination during Stage 2, as outlined in [Table A9-5](#), provided they meet the eligibility criteria for Stage 2 (see Section [4.1](#)) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation

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of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A9-5 Stage 2 Treatment Regimens Available for Atezo + Evo Arm

Study Treatment	Appendix
Atezo + Docetaxel	Appendix 16
Atezo + Lina	Appendix 17

Atezo = atezolizumab; Evo = evolocumab; Lina = linagliptin.

Refer to [Appendix 16](#) and [Appendix 17](#) for details specific to the atezolizumab plus docetaxel arm, and atezolizumab plus linagliptin arm, respectively.

A9-4.2 CONCOMITANT THERAPY FOR ATEZO + EVO ARM

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A9-4.2.1 Permitted Therapy for Atezo + Evo Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Inactivated vaccines (such as influenza and COVID-19)
 - Live, attenuated vaccines are not permitted (see [A9-4.2.3](#)).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer

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- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and evolocumab may be continued during palliative radiotherapy *with sufficient monitoring of hematologic parameters in place*.

- Radiotherapy to the brain as outlined below:

Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the criteria listed below are met.

- The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.
- The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

- Anticonvulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections [A9-4.2.2](#) and [A9-4.2.3](#)) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 -adrenergic agonists; see [Appendix 5](#)).

At this time there is no evidence on potential interactions of COVID-19 vaccines with evolocumab. COVID-19 vaccines must be given in accordance with the approved/authorized vaccine label and official immunization guidance. The decision of

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administration of a COVID-19 vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

A9–4.2.2 Cautionary Therapy for Atezo + Evo Arm

A9–4.2.2.1 Corticosteroids and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may be administered at the discretion of the investigator. The Medical Monitor is available to advise as needed.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to [Appendix 6](#) for details).

The above list of cautionary medications is not necessarily comprehensive.

The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment.

In addition, the Medical Monitor is available to advise as needed if questions arise regarding medications not listed above.

A9–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section [A9–4.2.3](#)) may be used during the study at the discretion of the investigator.

A9–4.2.3 Prohibited Therapy for Atezo + Evo Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section [4.1.2](#)), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section [A9–4.2.1](#).
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.

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- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the *final* dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin [IL]-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

A9-4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + EVO ARM

Contraception requirements for women and men in the Atezo + Evo arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of < 1% per year during the treatment period and for 5 months after the final dose of atezolizumab and for 3 months after the final dose of evolocumab.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A9-5 ASSESSMENT OF SAFETY FOR ATEZO + EVO ARM

A9-5.1 SAFETY PLAN FOR ATEZO + EVO ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and evolocumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections [A9-5.1.1](#), [A9-5.1.2](#), and [A9-5.1.3](#)). Guidelines for management of patients who experience specific adverse events are provided in Section [A9-5.1.4](#).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of

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patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections [5.2–5.6](#).

A9–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial palsy, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis. Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A9–5.1.2 Risks Associated with Evolocumab

The most common side effects (in more than 5% of patients in clinical studies) of evolocumab include nasopharyngitis, upper respiratory tract infections, influenza, diabetes mellitus, back pain, injection-site reactions, and allergic reactions.

The most common adverse reactions in clinical trials in primary hyperlipidemia (including HeFH, in more than 5% of patients treated with evolocumab and occurring more frequently than placebo) include nasopharyngitis, upper respiratory tract infection, influenza, back pain, injection-site reactions, and allergic reactions.

The most common adverse reactions in the cardiovascular outcomes trial (in more than 5% of patients treated with evolocumab and occurring more frequently than placebo) include diabetes mellitus, nasopharyngitis, and upper respiratory tract infection.

For more details regarding the safety profile for evolocumab, refer to section [A9–2.4](#) in this appendix as well as the evolocumab prescribing information.

A9–5.1.3 Risks Associated with Combination Use of Atezolizumab and Evolocumab

There are no significant overlapping toxicities associated with combination use of atezolizumab and evolocumab.

A9–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo + Evo Arm

A9–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab or evolocumab in this study.

A9–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see [Table A9-6](#)). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to *the equivalent of* ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.* Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Evolocumab treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If evolocumab has been withheld for > 28 days after event onset because of toxicity, the patient should be discontinued from evolocumab, unless resumption of treatment is approved at the investigator's discretion. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

If atezolizumab is discontinued, evolocumab should also be discontinued. If evolocumab is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section [A9–4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A9–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in [Table A9-6](#). These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Appendix 9: Study Details Specific to Atezo + Evo Arm

Table A9-6 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo + Evo Arm*

Event	Action to Be Taken
Pulmonary events including pneumonitis	
Pulmonary event, Grade 1	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue evolocumab.
Pulmonary event, Grade 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold evolocumab; evolocumab can be resumed once atezolizumab treatment is resumed. ^a
Pulmonary event, Grade 3 or 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Permanently discontinue atezolizumab and evolocumab and contact Medical Monitor. ^b
Endocrine events	
Asymptomatic hypothyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue evolocumab.
Symptomatic hypothyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold evolocumab; evolocumab can be resumed once atezolizumab treatment is resumed. ^a
Asymptomatic hyperthyroidism	<p>TSH ≥ 0.1 mU/L and < 0.5 mU/L:</p> <ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue evolocumab. <p>TSH < 0.1 mU/L:</p> <ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold evolocumab; evolocumab can be resumed once atezolizumab treatment is resumed. ^a
Symptomatic hyperthyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold evolocumab; evolocumab can be resumed once atezolizumab treatment is resumed. ^a

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Table A9-6 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo + Evo Arm* (cont.)

Event	Action to Be Taken
Endocrine events (cont.)	
Symptomatic adrenal insufficiency, Grade 2–4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold evolocumab; evolocumab can be resumed once atezolizumab treatment is resumed. ^a
Hyperglycemia, Grade 1 or 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue evolocumab.
Hyperglycemia, Grade 3 or 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold evolocumab; evolocumab can be resumed once atezolizumab treatment is resumed. ^a
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold evolocumab; evolocumab can be resumed once atezolizumab treatment is resumed. ^a
Hypophysitis (pan-hypopituitarism), Grade 4	<ul style="list-style-type: none"> Permanently discontinue atezolizumab and evolocumab and contact Medical Monitor. ^b
Evolocumab-related events not described above	
Grade 1 or 2	<ul style="list-style-type: none"> Continue evolocumab and atezolizumab.
Grade 3	<ul style="list-style-type: none"> Withhold evolocumab treatment; continue atezolizumab. If event resolves to Grade 2 within 28 days, resume evolocumab. If not, permanently discontinue evolocumab. If event resolves to Grade 1 or better within 28 days, resume evolocumab. If not, permanently discontinue evolocumab.

Appendix 9: Study Details Specific to Atezo + Evo Arm

Table A9-6 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo+Evo Arm* (cont.)

Event	Action to Be Taken
Evolocumab-related events not described above	
Grade 4	<ul style="list-style-type: none"> • Withhold evolocumab and atezolizumab. • If event resolves to Grade 1 or better within 28 days, resume evolocumab. If not, permanently discontinue evolocumab. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab.
Atezolizumab-related events not described above	
Grade 1 or 2	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue evolocumab.
Grade 3	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue evolocumab.
Grade 4	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • If atezolizumab is discontinued, evolocumab should also be discontinued.

Atezo = atezolizumab; *Evo* = evolocumab; TSH = thyroid-stimulating hormone.

- ^a If evolocumab has been withheld for >28 days after event onset because of toxicity, the patient should be discontinued from evolocumab, unless resumption of treatment is approved at the investigator's discretion. The decision to re-challenge patients should be based on investigator's *benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

A9–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + EVO ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Evo arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7).
- Suspected transmission of an infectious agent by the study treatment, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

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- Myelitis
- Facial paresis

A9–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+ EVO ARM

A9–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab and 3 months after the *final* dose of evolocumab. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue atezolizumab and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A9–5.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A9–5.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

Appendix 9: Study Details Specific to Atezo + Evo Arm

A9–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+EVO ARM

Table A9-7 Schedule of Activities for Atezo + Evo Arm

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (28-day cycles) ^a				Stage 2 Screen. (see Appendix 2) ^c or Treat. Discon. ^d (see below)	Follow- Up ^d
	Day –28 to –1	Cycle 1 ^b		Cycles ≥ 2			Every 3 Months (±7 days)
		Day 1	Day 15 (± 3 days)	Day 1 (± 3 days)	Day 15 (± 3 days)		
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available					
Vital signs ^e		x	x	x	x	x	
Weight ^f		x		x		x	
Complete physical examination ^g						x	
Limited physical examination ^{f, h}		x	x	x	x		
ECOG Performance Status ^f		x		x		x	
ECG ^{f, i}		Perform as clinically indicated					
Hematology ^j		x ^k	x	x	x	x	
Chemistry ^l		x ^k	x	x	x	x	
Coagulation (INR and aPTT)		x ^k	x	x	x	x	
Fasting lipid panel ^m		x ^k				x	
TSH, free T3 (or total T3), free T4 ⁿ		x ^k				x	
Pregnancy test ^o		x ^k		x		x	x
Blood sample for blood-based NGS ctDNA test ^p						x	
Urinalysis ^q		Perform as clinically indicated					

Appendix 9: Study Details Specific to Atezo + Evo Arm

Table A9-7 Schedule of Activities for Atezo + Evo Arm (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (28-day cycles) ^a				Stage 2 Screen. (see Appendix 2) ^c or Treat. Discon. ^d (see below)	Follow- Up ^d
	Day –28 to –1	Cycle 1 ^b		Cycles ≥ 2			Every 3 Months (±7 days)
		Day 1	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)		
Serum autoantibody sample ^r	See Appendix 2	Perform if a patient experiences a suspected immune-mediated adverse event					
PK samples		Refer to Table A9-8 .					
ADA samples		Refer to Table A9-8 .					
Biomarker samples		Refer to Table A9-8 .					
Blood sample for RBR (optional) ^s		x					
Tumor biopsy		x ^t					
Tumor biopsy (optional)		x ^u					
Tumor response assessments		x ^{v, w, x}					
Concomitant medications ^y		x	x	x	x	x	
Adverse events ^z		x	x	x	x	x ^z	x ^z
Atezolizumab administration ^{aa, bb}		x	x	x	x		
Evolocumab administration ^{aa, cc}		x	x	x	x		
Survival follow-up and anti-cancer treatment							x ^{dd}

Appendix 9: Study Details Specific to Atezo + Evo Arm

Table A9-7 Schedule of Activities for Atezo + Evo Arm (cont.)

ADA=anti-drug antibody; Atezo=atezolizumab; CT=computed tomography; ctDNA=circulating tumor DNA; Discon.=discontinuation; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; Evo=evolocumab; NGS=next generation sequencing; PK=pharmacokinetic; RBR=Research Biosample Repository; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen.=screening; T3=triiodothyronine; T4=thyroxine; Treat.=treatment; TSH=thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

- ^a If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. The Medical Monitor is available to advise as needed.
- ^b It is recommended that treatment be initiated no later than 7 days after randomization.
- ^c Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) or unacceptable toxicity to evolocumab will be given the option of receiving a different treatment combination in Stage 2 of the study (as outlined in Section 3.1.4) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.
- ^d Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the *final* dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments.
- ^e Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (\pm 5) minutes during and 30 (\pm 10) minutes after the infusion. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (\pm 10) minutes after the infusion.
- ^f Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^g Physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^h Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ⁱ It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

Appendix 9: Study Details Specific to Atezo + Evo Arm

Table A9-7 Schedule of Activities for Atezo + Evo Arm (cont.)

- ^j Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
- ^k If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.
- ^l Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included on Day 1 of each treatment cycle.
- ^m Fasting lipid panel (cholesterol, HDL, LDL, and triglyceride) will be assessed (after ≥ 8 hr of fasting) on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).
- ⁿ TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).
- ^o All women of childbearing potential will have a urine or serum pregnancy test performed at specified visits during treatment and at 3 months and 6 months after the *final* dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^p Blood samples for blood-based NGS ctDNA test will not be collected from Protocol Version 19 *onward*.
- ^q Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ^r Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Serum samples collected for the assessment of PK, ADAs, or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment, may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.
- ^s Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.
- ^t Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see Section 3.1.2) will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible). See Section 4.5.6 for tissue sample requirements.
- ^u Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation, if deemed clinically feasible and may undergo additional on-treatment biopsies at any other time during Stage 1 or Stage 2 at the investigator's discretion.

Appendix 9: Study Details Specific to Atezo + Evo Arm

Table A9-7 Schedule of Activities for Atezo + Evo Arm (cont.)

- ^v Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of atezolizumab-treated patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.
- ^w All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).
- ^x For patients who undergo screening for Stage 2: Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.
- ^y Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 *days* prior to initiation of study treatment until the treatment discontinuation visit.
- ^z After initiation of study treatment, all adverse events will be reported until 30 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.
- ^{aa} Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).

Appendix 9: Study Details Specific to Atezo + Evo Arm

Table A9-7 Schedule of Activities for Atezo + Evo Arm (cont.)

- ^{bb} Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle. The initial dose of atezolizumab will be delivered over 60 (\pm 15) minutes. Subsequent infusions will be delivered over 30 (\pm 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (\pm 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Refer to Section [A9-4.1.1.1](#) for details on atezolizumab infusions (including measurement of vital signs).
- ^{cc} Evolocumab will be administered by SC injection at a fixed dose of 140 mg on Days 1 and 15 of each 28-day cycle. Refer to Section [A9-4.1.2.2](#) for details on evolocumab injections.
- ^{dd} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Appendix 9: Study Details Specific to Atezo + Evo Arm

Table A9-8 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Evo Arm

Visit	Time	Sample
Day 1 of Cycle 1	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Evolocumab PK (serum) • Evolocumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 2	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Evolocumab PK (serum) • Evolocumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Evolocumab PK (serum) • Evolocumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Evolocumab PK (serum) • Evolocumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycle 8	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Evolocumab PK (serum) • Evolocumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Evolocumab PK (serum) • Evolocumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after <i>final</i> dose)	At visit	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)

ADA=anti-drug antibody; Atezo + Evo=atezolizumab plus evolocumab; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

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Appendix 10

Study Details Specific to Docetaxel Arm

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Appendix 10: Study Details Specific to Docetaxel Arm

A10–1 MATERIALS AND METHODS SPECIFIC TO DOCETAXEL ARM

A10–1.1 TREATMENT IN DOCETAXEL ARM

A10–1.1.1 Formulation, Packaging, and Handling

For information on the formulation, packaging, and handling of docetaxel, refer to the local prescribing information.

A10–1.1.2 Dosage, Administration, and Compliance

Patients in the docetaxel arm will receive treatment as outlined in [Table A10-1](#) until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). Treatment must be initiated no later than 7 days after treatment assignment.

Table A10-1 Treatment Regimen for Docetaxel Arm

Cycle Length	Dose, Route, and Regimen
21 days	• Docetaxel 75 mg/m ² IV over 60 minutes on Day 1 of each cycle

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Docetaxel will be administered in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. To reduce the incidence and severity of fluid retention, as well as the severity of hypersensitivity reactions, patients should be premedicated with corticosteroids according to local practice (e.g., 8 mg of oral dexamethasone administered twice daily) for 3 days, starting 1 day prior to docetaxel administration. Anti-emetic medications may be administered prophylactically according to local practice at the investigator's discretion.

Guidelines for docetaxel dose modification and treatment interruption or discontinuation because of toxicities are provided in Section [A10–2.1.2](#). Docetaxel treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section [5.3.5.12](#).

Appendix 10: Study Details Specific to Docetaxel Arm

For information on overdosing of docetaxel, refer to the local prescribing information for each agent.

A10–1.1.3 Stage 2 Treatment

Patients who experience disease progression per RECIST v1.1 or unacceptable toxicity related to docetaxel will be given the option of receiving a different treatment combination during Stage 2, as outlined in [Table A10-2](#), provided they meet eligibility criteria (see Section [4.1](#)) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced disease progression or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of disease progression or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A10-2 Stage 2 Treatment Regimens Available for the Docetaxel Arm

Study Treatment	Appendix
Atezo + Lina	Appendix 17

Atezo = atezolizumab; Lina = linagliptin.

Refer to [Appendix 17](#) for details specific to the atezolizumab plus linagliptin arm.

A10–1.2 CONCOMITANT THERAPY, PROHIBITED FOOD, AND OTHER RESTRICTIONS FOR DOCETAXEL ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

For information on permitted, prohibited, or cautionary therapy, prohibited foods, and other restrictions (as applicable) for docetaxel, refer to the local prescribing information.

A10–1.3 CONTRACEPTION REQUIREMENTS FOR DOCETAXEL ARM

Contraception requirements for women and men in the docetaxel arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 6 months after the *final* dose of docetaxel.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below:

With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for 6 months after the *final* dose of docetaxel. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the *final* dose of docetaxel to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A10–2 ASSESSMENT OF SAFETY FOR DOCETAXEL ARM

A10–2.1 SAFETY PLAN FOR DOCETAXEL ARM

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of docetaxel will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections [5.2–5.6](#).

A10–2.1.1 Risks Associated with Docetaxel

The most common side effects of docetaxel include infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.

For more details regarding the safety profile for docetaxel, refer to the docetaxel prescribing information.

A10–2.1.2 Management of Patients Who Experience Specific Adverse Events in Docetaxel Arm

A10–2.1.2.1 Dose Modifications

The dose of docetaxel can be reduced to 55 mg/m² (e.g., for management of drug-related toxicities). If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose will not be escalated during subsequent administrations.

A10–2.1.2.2 Treatment Interruption for Toxicities

Docetaxel treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment (see [Table A10-3](#)). If docetaxel has been withheld for >63 days because of toxicity, the patient should be discontinued from docetaxel.

Refer to Section [A10–1.1.2](#) for information on dose interruptions for reasons other than toxicity (e.g., surgical procedures).

A10–2.1.2.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in [Table A10-3](#). The investigator may use discretion in adhering to the guidelines described below, taking into account the severity of the event and benefit versus risk for the patient, with the goal of maximizing patient compliance and access to supportive care. Additionally, the prescribing information, as well as local hospital or clinical practice must be followed.

Appendix 10: Study Details Specific to Docetaxel Arm

Table A10-3 Guidelines for Management of Patients Who Experience Adverse Events in Docetaxel Arm

Event	Action to Be Taken
Hematologic events	
Nadir ANC $< 0.5 \times 10^9/L$ (500/ μL) for ≥ 7 days ^a or Febrile neutropenia	First occurrence: <ul style="list-style-type: none"> Withhold docetaxel. If event resolves to ANC $\geq 1.5 \times 10^9/L$ (1500/μL) within 63 days,^b and platelet count is $\geq 100 \times 10^9/L$ (100,000/μL), resume docetaxel with dose reduced to 55 mg/m².^c If not, permanently discontinue docetaxel. Second occurrence: <ul style="list-style-type: none"> Permanently discontinue docetaxel.
Hepatotoxicity	
ALT/AST $> 1.5 \times ULN$ in combination with ALP $> 2.5 \times ULN$	<ul style="list-style-type: none"> Withhold docetaxel. If event resolves to baseline within 63 days,^b resume docetaxel with dose reduced to 55 mg/m².^c If not, permanently discontinue docetaxel.
Bilirubin $> 1 \times ULN$ or ALT/AST $> 3.5 \times ULN$ in combination with ALP $> 6 \times ULN$	<ul style="list-style-type: none"> Permanently discontinue docetaxel.
Neurologic disorders	
Grade 1 or 2	<ul style="list-style-type: none"> Continue docetaxel.
Grade 3	First occurrence: <ul style="list-style-type: none"> Withhold docetaxel. If event resolves to Grade 1 or better within 63 days,^b resume docetaxel with dose reduced to 55 mg/m².^c If not, permanently discontinue docetaxel. Second occurrence: <ul style="list-style-type: none"> Permanently discontinue docetaxel.
Grade 4	Permanently discontinue docetaxel.

Appendix 10: Study Details Specific to Docetaxel Arm

Table A10-3 Guidelines for Management of Patients Who Experience Adverse Events in Docetaxel Arm (cont.)

Event	Action to Be Taken
Hypersensitivity reaction	
Grade 1 or 2	<ul style="list-style-type: none"> Continue docetaxel at the discretion of the investigator.
Grade 3 or 4	<ul style="list-style-type: none"> Immediate discontinuation of the docetaxel infusion and aggressive therapy. Permanently discontinue docetaxel.
Pleural effusion	
Grade 1	<ul style="list-style-type: none"> Continue docetaxel. Monitor patient closely for possible exacerbation.
Grade 2	<ul style="list-style-type: none"> Continue docetaxel. Consider initiation of standard treatment measures (e.g., salt restriction, oral diuretic). Monitor patient closely (e.g., by ultrasound Q2W). Consider thoracentesis if clinically indicated. Consider consultation with thoracic surgeon.
Grade 3	<p>First occurrence:</p> <ul style="list-style-type: none"> Withhold docetaxel treatment until resolution to Grade ≤ 1. Initiate standard treatment measures (e.g., salt restriction, oral diuretic). Consider consultation with thoracic surgeon. If event resolves to Grade ≤ 1 within 63 days, ^b resume docetaxel with dose reduced to 55 mg/m². ^c If not, permanently discontinue docetaxel. <p>Second occurrence:</p> <ul style="list-style-type: none"> Permanently discontinue docetaxel. Consider treatment measures as outlined for first occurrence.
Pleural effusion (cont.)	
Grade 4	<ul style="list-style-type: none"> Permanently discontinue docetaxel. Consider treatment measures as outlined for Grade 3 events.

Appendix 10: Study Details Specific to Docetaxel Arm

Table A10-3 Guidelines for Management of Patients Who Experience Adverse Events in Docetaxel Arm (cont.)

Event	Action to Be Taken
Pericardial effusion	
Grade 2	<ul style="list-style-type: none"> • Continue docetaxel. • Monitor patient closely for possible exacerbation. • Consider initiation of standard treatment measures. • Consider consultation with cardiologist.
Grade 3	<p>First occurrence:</p> <ul style="list-style-type: none"> • Withhold docetaxel until resolution to Grade ≤ 2. • Monitor patient closely (e.g., by ECG and echocardiography weekly). • Initiate standard treatment measures. • Consider consultation with cardiologist. • If event resolves to Grade ≤ 2 within 63 days, ^b resume docetaxel with dose reduced to 55 mg/m². ^c If not, permanently discontinue docetaxel. <p>Second occurrence:</p> <ul style="list-style-type: none"> • Permanently discontinue docetaxel. • Consider treatment measures as outlined for first occurrence.
Grade 4	<ul style="list-style-type: none"> • Permanently discontinue docetaxel. • Consider treatment measures as outlined for Grade 3 events.
Ascites	
Grade 1	<ul style="list-style-type: none"> • Continue docetaxel. • Monitor patient closely for possible exacerbation.
Grade 2	<ul style="list-style-type: none"> • Continue docetaxel. • Consider initiation of standard treatment measures (e.g., salt restriction, oral diuretic). • Monitor patient closely (e.g., by ultrasound Q2W). • Consider paracentesis if clinically indicated.

Appendix 10: Study Details Specific to Docetaxel Arm

Table A10-3 Guidelines for Management of Patients Who Experience Adverse Events in Docetaxel Arm (cont.)

Event	Action to Be Taken
Ascites (cont.)	
Grade 3	<p>First occurrence:</p> <ul style="list-style-type: none"> • Withhold docetaxel treatment until resolution to Grade ≤ 1. • Initiate standard treatment measures (e.g., salt restriction, oral diuretic). • Monitor patient closely (e.g., by ultrasound Q2W). • Consider paracentesis if clinically indicated. • If event resolves to Grade ≤ 1 within 63 days, ^b resume docetaxel with dose reduced to 55 mg/m². ^c If not, permanently discontinue docetaxel. <p>Second occurrence:</p> <ul style="list-style-type: none"> • Permanently discontinue docetaxel. • Consider treatment measures as outlined for first occurrence.
Grade 4	<ul style="list-style-type: none"> • Permanently discontinue docetaxel. • Consider treatment measures as outlined for Grade 3 events.
Fluid retention (other than pleural effusion, pericardial effusion, or ascites)	
Grade 1	<ul style="list-style-type: none"> • Continue docetaxel.
Grade 2	<ul style="list-style-type: none"> • Continue docetaxel. • Monitor patient closely. • Consider initiation of standard treatment measures (e.g., salt restriction, oral diuretic).
Grade 3	<p>First occurrence:</p> <ul style="list-style-type: none"> • Withhold docetaxel. • Initiate standard treatment measures (e.g., salt restriction, oral diuretic). • If event resolves to Grade 1 or better within 63 days, ^b resume docetaxel with dose reduced to 55 mg/m². ^c If not, permanently discontinue docetaxel. <p>Second occurrence:</p> <ul style="list-style-type: none"> • Permanently discontinue docetaxel. • Initiate standard treatment measures (e.g., salt restriction, oral diuretic).

Appendix 10: Study Details Specific to Docetaxel Arm

Table A10-3 Guidelines for Management of Patients Who Experience Adverse Events in Docetaxel Arm (cont.)

Event	Action to Be Taken
Non-hematologic events not described above	
Grade 1 or 2	<ul style="list-style-type: none">• Continue docetaxel.
Grade 3	First occurrence: <ul style="list-style-type: none">• Withhold docetaxel.• If event resolves to Grade 1 or better within 63 days, ^b resume docetaxel with dose reduced to 55 mg/m². ^c If not, permanently discontinue docetaxel. Second occurrence: <ul style="list-style-type: none">• Permanently discontinue docetaxel.
Grade 4	<ul style="list-style-type: none">• Permanently discontinue docetaxel.

Q2W = every 2 weeks; ULN = upper limit of normal.

^a Nadir of prior cycle.

^b If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for > 63 days. The decision to re-challenge patients with docetaxel should be based on *the* investigator's *benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

^c The dose of docetaxel can be reduced to 55 mg/m². If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose will not be escalated during subsequent administrations.

A10–2.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR DOCETAXEL ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the docetaxel arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

A10–2.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN DOCETAXEL ARM

A10–2.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 6 months after the *final* dose of docetaxel. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF.

The investigator should discontinue docetaxel and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A10–2.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the *final* dose of docetaxel. The investigator should report the pregnancy

Appendix 10: Study Details Specific to Docetaxel Arm

on the Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to docetaxel. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A10–2.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A10–2.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

Appendix 10: Study Details Specific to Docetaxel Arm

A10–3 SCHEDULE OF ACTIVITIES FOR DOCETAXEL ARM

Table A10-4 Schedule of Activities for Docetaxel Arm

Assessment/Procedure	Screening	Treatment Cycles (21-Day Cycles) ^a			Stage 2 Screen. (see Appendix 2) ^c or Treat. Discon. ^d (see below)	Follow-Up ^d Every 3 Months (± 7 days)
		Cycle 1 ^b		Cycles ≥ 2		
	Days –28 to –1	Day 1	Day 15 (± 3 days)	Day 1 (± 3 days)		
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available				
Vital signs ^e		x	x	x	x	
Weight ^f		x		x	x	
Complete physical examination ^g					x	
Limited physical examination ^{f, h}		x	x	x		
ECOG Performance Status ^f		x		x	x	
ECG ^{f, i}		Perform as clinically indicated				
Hematology ^j		x ^k	x	x	x	
Chemistry ^l		x ^k	x	x	x	
Pregnancy test ^m		x		x	x	
Blood sample for blood-based NGS ctDNA test ⁿ					x	
Urinalysis ^o		Perform as clinically indicated				
Serum autoantibody sample ^p						
Plasma and serum samples for biomarkers		x ^q		x ^q	x ^q	
PBMC sample for biomarkers		x ^r		x ^r		

Appendix 10: Study Details Specific to Docetaxel Arm

Table A10-4 Schedule of Activities for Docetaxel Arm (cont.)

Assessment/Procedure	Screening	Treatment Cycles (21-Day Cycles) ^a			Stage 2 Screen. (see Appendix 2) ^c or Treat. Discon. ^d (see below)	Follow-Up ^d Every 3 Months (± 7 days)
		Cycle 1 ^b		Cycles ≥ 2		
	Days –28 to –1	Day 1	Day 15 (± 3 days)	Day 1 (± 3 days)		
Blood sample for RBR (optional) ^s	See Appendix 2	x				
Tumor biopsy		x ^t				
Tumor biopsy (optional)		x ^u				
Tumor response assessments		x ^{v, w, x}				
Concomitant medications ^y		x	x	x	x	
Adverse events ^z		x	x	x	x ^z	x
Docetaxel administration ^{aa}		x		x		
Survival follow-up and anti-cancer treatment						x ^{bb}

CT=computed tomography; ctDNA=circulating tumor DNA; Discon.=discontinuation; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; NGS=next-generation sequencing; PBMC=peripheral blood mononuclear cell; RBR=Research Biosample Repository; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen.=screening; T3=triiodothyronine; T4=thyroxine; Treat.=treatment; TSH=thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

- ^a If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. The Medical Monitor is available to advise as needed.
- ^b It is recommended that treatment be initiated no later than 7 days after randomization.
- ^c Patients who experience disease progression per RECIST v1.1, as determined by the investigator (see [Section 3.1.1](#) for details) will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in [Section 3.1.4](#)) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

Appendix 10: Study Details Specific to Docetaxel Arm

Table A10-4 Schedule of Activities for Docetaxel Arm (cont.)

- ^d Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the *final* dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments.
- ^e Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (\pm 5) minutes during and 30 (\pm 10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (\pm 10) minutes after the infusion.
- ^f Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^g Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^h Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ⁱ ECG recordings will be obtained during screening and as clinically indicated at other timepoints. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.
- ^j Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).
- ^k If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.
- ^l Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included on Day 1 of each treatment cycle.
- ^m All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum pregnancy tests will be performed at specified subsequent visits during treatment and at 3 months and 6 months after the *final* dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ⁿ Blood samples for blood-based NGS ctDNA test will not be collected from Protocol Version 19 *onward*.
- ^o Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

Appendix 10: Study Details Specific to Docetaxel Arm

Table A10-4 Schedule of Activities for Docetaxel Arm (cont.)

- ^p Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Serum samples collected for the assessment of PK, ADAs, or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment, may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.
- ^q Plasma and serum samples for biomarker analyses will be collected on Day 1 of Cycle 1, Day 1 of Cycles 2, 3, 4, and 8, and at treatment discontinuation.
- ^r PBMC samples for biomarker analyses will be collected on Day 1 of Cycles 1 and 2.
- ^s Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.
- ^t Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or disease progression per RECIST v1.1 (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or disease progression, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.6 for tissue sample requirements.
- ^u Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.
- ^v Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (± 1 week) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 6 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.
- ^w All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).
- ^x For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of radiographic disease progression according to RECIST v1.1 during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

Appendix 10: Study Details Specific to Docetaxel Arm

Table A10-4 Schedule of Activities for Docetaxel Arm (cont.)

- ^y Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.
- ^z After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.
- ^{aa} Docetaxel will be administered by IV infusion at a dose of 75 mg/m² IV over 60 minutes on Day 1 of each cycle. Treatment will continue until unacceptable toxicity or radiographic disease progression according to RECIST v1.1.
- ^{bb} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Appendix 11

Placeholder for Future Arm

The atezolizumab plus ipatasertib arm has been removed. The content of Appendix 11 (previously entitled "Study Details Specific to Atezo + Ipat Arm") has been deleted. Appendix 11 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 12

Study Details Specific to Atezo+SG Arm

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A12–1 BACKGROUND ON ATEZO + SG ARM

A12–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, myocarditis, and nephritis, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma (in the European Union), non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer (in the European Union), hepatocellular carcinoma, melanoma (in the United States), and alveolar soft part sarcoma (in the United States).

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A12–1.2 BACKGROUND ON SACITUZUMAB GOVITECAN

Sacituzumab govitecan is a trophoblast cell-surface antigen 2 (TROP-2)-directed antibody–drug conjugate (ADC) consisting of three components: 1) a humanized IgG1 κ monoclonal antibody hRS7, which binds to TROP-2; 2) SN-38, a topoisomerase I inhibitor and active metabolite of irinotecan; and 3) a proprietary hydrolyzable linker (CL2A) that couples hRS7 to SN-38.

TROP-2 is a transmembrane calcium signal transducer glycoprotein of the tumor-associated calcium signal transducer gene family that is expressed in many

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tumors. Pharmacology data suggest that sacituzumab govitecan binds to TROP-2–expressing cancer cells and undergoes internalization with the subsequent release of SN-38 via hydrolysis of the linker. Upon release, SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I–induced single-stranded DNA breaks, resulting in DNA damage that leads to apoptosis and cell death. The hydrolyzable linker of sacituzumab govitecan may also permit release of SN-38 in the acidic microenvironment of the tumor without TROP-2 binding.

Sacituzumab govitecan has shown anti-tumor activity in nonclinical and clinical studies and was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult patients with metastatic TNBC who have received at least 2 prior therapies for metastatic disease and fast track designation for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (FDA 2020).

Refer to the Sacituzumab Govitecan Investigator's Brochure for details on nonclinical and clinical studies.

A12–2 RATIONALE FOR ATEZO + SG ARM

A12–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses by binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including

Appendix 12: Study Details Specific to Atezo + SG Arm

NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors (CPIs), have *had* a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active *as monotherapy* for many patients.

A12-2.2 TARGETING TROP-2

TROP-2 is a cell-surface marker of trophoblast cells that is expressed in many solid tumors at higher levels compared with normal tissue. TROP-2 binds several cellular proteins, including insulin-like growth factor-1, claudin-1, claudin-7, cyclin D1, and protein kinase C, and has been implicated in the regulation of tumor growth, invasion, and spread. Through activation of the ERK1/2-mitogen-activated protein kinase (MAPK) pathway, TROP-2 also contributes to cell cycle progression and could play a role in stem-cell biology through deregulation of stem-cell functions via the Notch, Hedgehog, and Wnt pathways.

Overexpression of TROP-2 has been reported in most human epithelial cancers, including oral, head and neck, thyroid, lung, esophageal, gastric, colorectal, pancreatic, breast, renal, uterine, cervical, ovarian, and glioma (Goldenberg et al. 2018).

Therapeutic targeting of TROP-2 may therefore be a promising treatment for patients across a wide spectrum of malignancies. However, the predictive value of TROP-2 expression remains unclear because of the absence of a control arm and the lack of a clear association between tumor TROP-2 expression per immunohistochemistry (IHC) and efficacy in patients with NSCLC (Heist et al. 2017). In addition, the utility of TROP-2 as biomarker for selection of patients with NSCLC for sacituzumab govitecan is not clear because of the high prevalence of TROP-2 expression in NSCLC, ranging from 64% (high expression per IHC, non-squamous NSCLC) and 75% (high expression per IHC, squamous NSCLC) (Inamura et al. 2017) to 80% (high expression per IHC, non-squamous NSCLC) and 100% (high expression per IHC, squamous NSCLC) (Omori et al. 2019).

A12-2.3 BENEFIT-RISK ASSESSMENT

A Phase I study of sacituzumab govitecan in advanced solid cancers, including NSCLC, showed encouraging therapeutic activity (Starodub et al. 2015). Recent data from a single-arm study of sacituzumab govitecan in patients with NSCLC, showed an objective response rate of 19% among the 47 enrolled patients, with a median response duration of 6 months, and a clinical benefit rate (complete response + partial response + stable disease \geq 4 months) of 43%, a median progression-free survival of 5.2 months, and a median overall survival of 9.5 months. Five (36%) of 14 patients who received CPIs

Appendix 12: Study Details Specific to Atezo + SG Arm

showed tumor shrinkage, including two (14%) with partial response (Heist et al. 2017). Combining sacituzumab govitecan, an ADC that can cause tumor-cell death with possible neoantigen release, with atezolizumab, an immune-stimulating agent, could have synergistic effects and have promising therapeutic potential in CPI-experienced NSCLC.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.4.

A12–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + SG ARM

A12–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab (Tecentriq® U.S. *Prescribing Information*).

A12–3.2 RATIONALE FOR SACITUZUMAB GOVITECAN DOSE AND SCHEDULE

Sacituzumab govitecan will be administered at a dose of 10 mg/kg on Days 1 and 8 of each 21-day cycle, which is an approved dosage for sacituzumab govitecan. Additional safety and efficacy information can be found in the Sacituzumab Govitecan Investigator's Brochure.

A12–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + SG ARM

A12–4.1 TREATMENT IN ATEZO + SG ARM

A12–4.1.1 Formulation, Packaging, and Handling

A12–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the atezolizumab formulation, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A12–4.1.1.2 Sacituzumab Govitecan

Sacituzumab govitecan will be supplied by the Sponsor as a sterile, off-white to yellowish lyophilized powder in a single-dose glass vial. The vial contains approximately 200 mg of sacituzumab govitecan for reconstitution.

For information on the formulation and handling of sacituzumab govitecan, see the pharmacy manual.

Appendix 12: Study Details Specific to Atezo + SG Arm

A12–4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + SG arm will receive treatment as outlined in [Table A12-1](#) until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section [3.1.1](#) for details). It is recommended that treatment be initiated no later than 7 days after randomization; *however, the first dose of study treatment should not occur within 3 days after a core biopsy or other surgical procedure.*

Table A12-1 Treatment Regimen for Atezo + SG Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none">• Sacituzumab govitecan 10 mg/kg by IV infusion on Days 1 and 8 of each cycle^a• Atezolizumab 1200 mg by IV infusion on Day 1 of each cycle^b

Atezo + SG = atezolizumab plus sacituzumab govitecan.

^a There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

^b The atezolizumab infusion should be initiated approximately 60 minutes following completion of the sacituzumab govitecan infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section [5.3.5.12](#). No safety data related to overdosing of atezolizumab or sacituzumab govitecan are available.

Sacituzumab govitecan doses in excess of the recommended dose may be associated with exposure-related toxicities, such as neutropenia and diarrhea. These toxicities, frequently associated with chemotherapies, should be managed through supportive care to prevent serious consequences (such as dehydration and infection) and provide symptomatic relief, in accordance with institutional guidelines.

A12–4.1.2.1 Sacituzumab Govitecan Administration

Sacituzumab govitecan will be administered by IV infusion at a dose of 10 mg/kg on Days 1 and 8 of each 21-day cycle.

Administration of sacituzumab govitecan will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#).

Appendix 12: Study Details Specific to Atezo + SG Arm

First infusion: Administer infusion over 3 hours. Observe patients during the infusion and for at least 30 minutes following the initial dose, for signs or symptoms of infusion-related reactions (IRRs).

Subsequent infusions: Administer infusion over 1 to 2 hours if prior infusions were tolerated. Observe patients during the infusion and for at least 30 minutes after infusion. Prior to each dose of sacituzumab govitecan, premedication for prevention of IRRs and prevention of chemotherapy-induced nausea and vomiting is recommended.

Premedicate with antipyretics, H₁, and H₂ blockers prior to infusion; corticosteroids may be used for patients who have had prior IRRs.

Premedicate with a two- or three-drug combination regimen (e.g., dexamethasone with either a 5-HT₃ receptor antagonist or an NK1 receptor antagonist), as well as other drugs as indicated.

Refer to the pharmacy manuals for detailed instructions on drug preparation, storage, and administration.

Guidelines for the medical management of IRRs for sacituzumab govitecan are provided in Section [A12–5.1.4](#).

Guidelines for sacituzumab govitecan treatment interruption or discontinuation because of toxicities are provided in Section [A12–5.1.4](#). Sacituzumab govitecan treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A12–4.1.2.2 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Atezolizumab should be administered approximately 60 minutes after completion of the sacituzumab govitecan infusion.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#). Atezolizumab infusions will be administered per the instructions outlined in [Table A12-2](#).

Table A12-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
<ul style="list-style-type: none"> No premedication is permitted prior to the atezolizumab infusion. Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be <i>measured</i> within 60 minutes prior to the infusion. Atezolizumab should be infused over 60 (\pm 15) minutes. If clinically indicated, vital signs should be <i>measured</i> every 15 (\pm 5) minutes during the infusion and at 30 (\pm 10) minutes after the infusion. Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. 	<ul style="list-style-type: none"> If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic <i>medications</i>, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. Vital signs should be <i>measured</i> within 60 minutes prior to the infusion. Atezolizumab should be infused over 30 (\pm 10) minutes if the previous infusion was tolerated without an IRR or 60 (\pm 15) minutes if the patient experienced an IRR with the previous infusion. If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be <i>measured</i> during the infusion and at 30 (\pm 10) minutes after the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of IRRs for atezolizumab are provided in [Appendix 6](#).

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section [A12–5.1.4](#). Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A12–4.1.3 Stage 2 Treatment

Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section [3.1.1](#)) or unacceptable toxicity related to sacituzumab govitecan will be given the option of receiving a different treatment combination during Stage 2, as outlined in [Table A12-3](#), provided they meet eligibility criteria (see Section [4.1](#)) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible.

Appendix 12: Study Details Specific to Atezo + SG Arm

Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided that the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A12-3 Stage 2 Treatment Regimens Available for Atezo + SG Arm

Study Treatment	Appendix
Atezo + Docetaxel	Appendix 16
Atezo + Lina	Appendix 17

Atezo = atezolizumab; SG = sacituzumab govitecan; Lina = linagliptin.

Refer to [Appendix 16](#) and [Appendix 17](#) for details specific to the atezolizumab plus docetaxel arm and atezolizumab plus linagliptin arm, respectively.

A12-4.2 CONCOMITANT THERAPY FOR ATEZO + SG ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 *days* prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A12-4.2.1 Permitted Therapy for Atezo + SG Arm

Patients are permitted to use the following therapies during the study:

- Colony-stimulating factors (CSFs), such as granulocyte colony-stimulating factors (G-CSFs) and erythropoiesis-stimulating agents (ESAs), which are to be administered per local practice/institutional guidelines or the American Society of Clinical Oncology guidelines for hematopoietic CSFs (Smith et al. 2015) and American Society of Clinical Oncology/American Society of Hematology guidelines for ESAs (Bohlius et al. 2019)
- Oral contraceptives
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- Inactivated vaccines (such as influenza and COVID-19)
Live, attenuated vaccines are not permitted (see [A12-4.2.3](#)).
- Mineralocorticoids (e.g., fludrocortisone)

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- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Bisphosphonates and denosumab for the prevention of skeletal events
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease).

Treatment with atezolizumab and sacituzumab govitecan may be continued during palliative radiotherapy *with sufficient monitoring of hematologic parameters in place*.

- Radiotherapy to the brain as outlined below:

Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

- The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.
- The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

- Anti-convulsant therapy, if required, is administered at a stable dose.

Treatment with atezolizumab may be continued during radiotherapy. Treatment with sacituzumab govitecan should be withheld for 1 week prior to radiotherapy and for 2 weeks after radiotherapy.

Premedication with antihistamines, antipyretic *medications*, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator. *Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.*

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen,

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ibuprofen, diphenhydramine, and/or H₂-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 -adrenergic agonists; see [Appendix 5](#)).

At this time there is no evidence on potential interactions of COVID-19 vaccines with sacituzumab govitecan. Based on the mechanism of action of sacituzumab govitecan, no potential interaction with COVID-19 vaccines is expected. COVID-19 vaccines must be given in accordance with the approved/authorized vaccine label and official immunization guidance. The decision of administration of a COVID-19 vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

A12–4.2.2 Cautionary Therapy for Atezo + SG Arm

A12–4.2.2.1 Corticosteroids and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Section [A12–5.1.4](#) for guidelines for managing specific adverse events).

The above list of cautionary medications is not necessarily comprehensive.

The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment.

In addition, the Medical Monitor is available to advise as needed if questions arise regarding medications not listed above.

A12–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section [A12–4.2.3](#)) may be used during the study at the discretion of the investigator.

A12–4.2.3 Prohibited Therapy for Atezo + SG Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A12–4.2.1.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the *final* dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Strong inhibitors of UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir) should be avoided during study treatment because these agents could potentially increase the risk for neutropenia.
- Strong inducers of UGT1A1 should be avoided during study treatment because these agents could decrease exposure to sacituzumab govitecan.

A12–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + SG ARM

Contraception requirements for women and men in the Atezo + SG arm are outlined below.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:

Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the *final* dose of atezolizumab and for 6 months after the *final* dose of sacituzumab govitecan. *Women must refrain from donating eggs during this same period.*

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A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for 3 months after the *final* dose of sacituzumab govitecan. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 3 months after the *final* dose of sacituzumab govitecan to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A12–5 ASSESSMENT OF SAFETY FOR ATEZO + SG ARM

A12–5.1 SAFETY PLAN FOR ATEZO + SG ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and sacituzumab govitecan in completed and ongoing studies.

The anticipated important safety risks are outlined below (see Sections [A12–5.1.1](#), [A12–5.1.2](#), and [A12–5.1.3](#)). Guidelines for management of patients who experience adverse events are provided in Section [A12–5.1.4](#). These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Because of the potential for overlapping toxicities, a minimum

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of 6 patients in the Atezo + SG arm must complete a safety evaluation before additional patients can be enrolled in that arm. Administration of atezolizumab and sacituzumab govitecan will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections [5.2–5.6](#).

A12–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis. Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A12–5.1.2 Risks Associated with Sacituzumab Govitecan

Sacituzumab govitecan has been associated with risks such as the following: IRRs, gastrointestinal toxicities, infectious toxicities (may involve sepsis, pneumonia), fatigue, and hematologic toxicities. Patients who are homozygous for the UGT1A1*28 allele are potentially at increased risk for neutropenia, febrile neutropenia, diarrhea, and anemia and may be at increased risk for other adverse events following initiation of sacituzumab govitecan treatment. Additional monitoring may be required in those patients. Refer to Section 6 of Sacituzumab Govitecan Investigator's Brochure for a detailed description of anticipated risks for sacituzumab govitecan.

A12–5.1.3 Risks Associated with Combination Use of Atezolizumab and Sacituzumab Govitecan

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and sacituzumab govitecan: gastrointestinal events, dermatologic events, and hepatic events.

A12–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo + SG Arm

A12–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study.

For management of drug-related toxicities, the dose of sacituzumab govitecan can be reduced by 2.5 mg/kg (i.e., one dose level) up to two times, as outlined in [Table A12-4](#).

Table A12-4 Suggested Dose Reductions for Sacituzumab Govitecan

	Initial Dose	First Dose Reduction	Second Dose Reduction
Sacituzumab govitecan	10 mg/kg	7.5 mg/kg	5 mg/kg

If further dose reduction is indicated for sacituzumab govitecan after two dose reductions, sacituzumab govitecan should be discontinued. After dose reduction, the dose of sacituzumab govitecan may not be escalated.

A12–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (*see Table A12-5*). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to *the equivalent of* ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on *the investigator's benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed. *Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Sacituzumab govitecan treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If toxicity related to sacituzumab govitecan prevents dose resumption for more than 3 weeks after interrupting treatment, the patient will be discontinued from sacituzumab govitecan. Sacituzumab govitecan can be resumed after being withheld for more than 3 weeks if the investigator and the patient is likely to derive clinical benefit. If either atezolizumab or sacituzumab govitecan is discontinued, the other drug can be continued if the patient is likely to derive clinical benefit. The decision to re-challenge patients with sacituzumab govitecan or atezolizumab should be based on *the investigator's benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Refer to Section [A12–4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A12–5.1.4.3 Management Guidelines for Adverse Events

Patients are required to have an ANC of $\geq 1.5 \times 10^9/\text{L}$ (1500/ μL) on Day 1 of each cycle and an ANC of $\geq 1.0 \times 10^9/\text{L}$ (1000/ μL) on Day 8 of each cycle to receive treatment with sacituzumab govitecan. Guidelines for management of hematologic toxicities and other toxicities (including guidelines for dose modification and treatment interruption or discontinuation) are provided in [Table A12-5](#). These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm

Event	Action to Be Taken
IRRs, CRS, and anaphylaxis	
General guidelines	<ul style="list-style-type: none"> Guidelines for management of IRRs and CRS for atezolizumab are provided in Appendix 6. Guidelines for management of IRRs for sacituzumab govitecan are provided below. For anaphylaxis precautions, see Appendix 5.
IRR to sacituzumab govitecan, Grade 1	<ul style="list-style-type: none"> Reduce infusion rate to half the rate being given at the time of event onset. After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.

Atezo+SG=atezolizumab plus sacituzumab govitecan; CRS=cytokine release syndrome; G-CSF=granulocyte colony-stimulating factor; IRR=infusion-related reaction; LFT=liver function test; PO=by mouth; ULN=upper limit of normal.

- ^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.
- ^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section [A12–5.1.4.1](#) for details).
- ^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
IRRs, CRS, and anaphylaxis (cont.)	
IRR to sacituzumab govitecan, Grade 2 or 3	<ul style="list-style-type: none"> • Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, administer oral premedication with antihistamine and antipyretic and monitor closely for IRRs. Corticosteroids may be used for patients who have had prior infusion reactions. • For recurrent Grade 2 or Grade 3 IRRs that fail to recover within 6 hours despite optimal management, sacituzumab govitecan should be permanently discontinued.
IRR to sacituzumab govitecan, Grade 4	<ul style="list-style-type: none"> • Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue sacituzumab govitecan and contact Medical Monitor.^a

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit-risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12-5.1.4.1 for details).

^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit-risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
IRRs, CRS, and anaphylaxis (cont.)	
Hemophagocytic lymphohistiocytosis or macrophage activation syndrome	<ul style="list-style-type: none">• Follow guidelines for atezolizumab in Appendix 6.• Withhold sacituzumab govitecan and contact Medical Monitor for guidance.

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

- ^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.
- ^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section [A12–5.1.4.1](#) for details).
- ^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events	
General guidelines	<ul style="list-style-type: none"> General guidance for managing gastrointestinal events of all grades is provided below, followed by grade-specific management guidelines. Because nausea, vomiting, and diarrhea are frequent sacituzumab govitecan–associated toxicities that potentially overlap with atezolizumab-associated toxicities, appropriate treatment, including fluid and electrolyte replacement (as needed), is required to minimize the risk of serious consequences, such as dehydration. <p>Diarrhea:</p> <ul style="list-style-type: none"> Dietary modification should be recommended for the management of diarrhea, including adequate fluid intake to maintain hydration. Administer antibiotics as clinically indicated. For excessive cholinergic responses to study treatment (e.g., abdominal cramping, diarrhea, salivation), administer appropriate premedication (e.g., atropine) for subsequent treatments.

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

- ^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.
- ^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).
- ^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events (cont.)	
General guidelines	<p>Nausea and vomiting:</p> <ul style="list-style-type: none"> Because sacituzumab govitecan is considered to be moderately emetogenic, premedication with a two- or three-drug anti-emetic regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist, as well as other drugs as indicated) should be administered prior to sacituzumab govitecan. If nausea and vomiting are persistent, a three-drug regimen, including a 5-HT3 inhibitor (ondansetron or palonosetron, or other agents according to local practices), an NK1-receptor antagonist (fosaprepitant or aprepitant), and dexamethasone (10 mg PO or IV), may be administered. <p>Anticipatory nausea can be treated with olanzapine.</p>

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

- ^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit-risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.
- ^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12-5.1.4.1 for details).
- ^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit-risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

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Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events (cont.)	
Diarrhea or colitis, Grade 1	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue sacituzumab govitecan. Initiate symptomatic treatment such as the following: <ul style="list-style-type: none"> Loperamide can be administered at the onset of treatment-related diarrhea (after infectious causes are ruled out) at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. If diarrhea is not resolved after 24 hours, consider adding diphenoxylate/atropine and/or opium tincture, as clinically indicated. If diarrhea persists, consider adding octreotide 100–150 µg SC three times per day, or treat as per institutional guidelines.

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

- ^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.
- ^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section [A12–5.1.4.1](#) for details).
- ^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events (cont.)	
Diarrhea or colitis, Grade 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold sacituzumab govitecan. Initiate symptomatic treatment such as the following: <ul style="list-style-type: none"> Loperamide can be administered at the onset of treatment-related diarrhea (after infectious causes are ruled out) at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. If diarrhea is not resolved after 24 hours, consider adding diphenoxylate/atropine and/or opium tincture, as clinically indicated. If diarrhea persists, consider adding octreotide 100–150 µg SC three times per day, or treat as per institutional guidelines. If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan.^b If not, permanently discontinue sacituzumab govitecan and contact Medical Monitor.^a

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section [A12–5.1.4.1](#) for details).

^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events (cont.)	
Diarrhea or colitis, Grade 3 or 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold sacituzumab govitecan. Treat with IV fluids and consider hospitalization. Initiate symptomatic treatment such as the following: <ul style="list-style-type: none"> Loperamide can be administered at the onset of treatment-related diarrhea (after infectious causes are ruled out) at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. If diarrhea is not resolved after 24 hours, consider adding diphenoxylate/atropine and/or opium tincture, as clinically indicated. If diarrhea persists, consider adding octreotide 100–150 µg SC three times per day, or treat as per institutional guidelines.

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

- ^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.
- ^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section [A12–5.1.4.1](#) for details).
- ^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events (cont.)	
Diarrhea or colitis, Grade 3 or 4 (cont.)	<ul style="list-style-type: none"> • <u>First and second occurrence</u>: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan; reduce the dose by one level if event does not resolve within 1 week after interrupting treatment and is not manageable with anti-diarrheal agents. ^{b, c} If not, permanently discontinue sacituzumab govitecan. ^a • <u>Third occurrence</u>: Permanently discontinue sacituzumab govitecan and contact Medical Monitor. ^a

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events (cont.)	
Nausea or vomiting, Grade 1 or 2	<ul style="list-style-type: none"> Refer to general guidelines for managing nausea and vomiting.
Nausea or vomiting, Grade 3	<ul style="list-style-type: none"> Continue atezolizumab. For persistent nausea that does not respond to treatment and for all vomiting events, withhold sacituzumab govitecan. Manage per institutional guidelines. <u>First and second occurrence</u>: If sacituzumab govitecan is withheld and event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan; reduce the dose by one level if event does not resolve within 1 week after interrupting treatment and is not manageable with anti-emetics. ^{b, c} If not, permanently discontinue sacituzumab govitecan. ^a <u>Third occurrence</u>: Permanently discontinue sacituzumab govitecan and contact Medical Monitor. ^a

Atezo+SG=atezolizumab plus sacituzumab govitecan; CRS=cytokine release syndrome; G-CSF=granulocyte colony-stimulating factor; IRR=infusion-related reaction; LFT=liver function test; PO=by mouth; ULN=upper limit of normal.

^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit-risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12-5.1.4.1 for details).

^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit-risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events (cont.)	
Nausea or vomiting, Grade 4	<ul style="list-style-type: none"> • Withhold atezolizumab and sacituzumab govitecan. • Manage per institutional guidelines. • If event resolves to Grade 2 or better within 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab.^a • <u>First and second occurrence</u>: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan; reduce the dose by one level if event does not resolve within 1 week after interrupting treatment and is not manageable with antiemetics.^{b, c} If not, permanently discontinue sacituzumab govitecan.^a • <u>Third occurrence</u>: Permanently discontinue sacituzumab govitecan and contact Medical Monitor.^a

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

- ^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit-risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.
- ^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section [A12-5.1.4.1](#) for details).
- ^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit-risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Neutropenia	
General guidelines	<ul style="list-style-type: none"> General guidance for managing neutropenia of all grades is provided below, followed by grade-specific management guidelines. Sacituzumab govitecan should only be administered if Day 1 ANC $\geq 1.5 \times 10^9/L$ (1500/μL) and Day 8 ANC $\geq 1.0 \times 10^9/L$ (1000/μL). The routine prophylactic use of growth factors is not required; however, prophylactic administration may be considered and should comply with American Society of Clinical Oncology guidelines. Growth factors may be administered to patients who have experienced febrile neutropenia or Grade 3 or Grade 4 neutropenia and to patients at high risk of poor clinical outcomes, including those with prolonged neutropenia, ANC $< 0.1 \times 10^9/L$ (100/μL), febrile neutropenia, or serious infections.

Atezo+SG=atezolizumab plus sacituzumab govitecan; CRS=cytokine release syndrome; G-CSF=granulocyte colony-stimulating factor; IRR=infusion-related reaction; LFT=liver function test; PO=by mouth; ULN=upper limit of normal.

- ^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit-risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.
- ^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section [A12-5.1.4.1](#) for details).
- ^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit-risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Neutropenia (cont.)	
Neutropenia, Grade 3 or 4	<ul style="list-style-type: none"> • Withhold atezolizumab and sacituzumab govitecan. • At first occurrence, initiate G-CSF prophylaxis for subsequent dosing. • If event resolves to Grade 2 or better within 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor. ^a <p>Grade 4 neutropenia lasting ≥7 days, febrile neutropenia, or neutropenia that delayed dosing by 2–3 weeks:</p> <ul style="list-style-type: none"> • <u>First occurrence</u>: If event resolves to Grade 1 or better (Day 1) or to Grade 2 or better (Day 8) within 3 weeks after interrupting treatment, resume sacituzumab govitecan. ^b If not, permanently discontinue sacituzumab govitecan. ^a • <u>Second and third occurrence</u>: If event resolves to Grade 1 or better (Day 1) or to Grade 2 or better (Day 8) within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by one level. ^{b, c} If not, permanently discontinue sacituzumab govitecan. ^a • <u>Fourth occurrence</u>: Permanently discontinue sacituzumab govitecan and contact Medical Monitor. ^a

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section [A12–5.1.4.1](#) for details).

^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Neutropenia (cont.)	
Neutropenia, Grade 3 or 4 (cont.)	<p>All other cases of Grade 3 or 4 neutropenia:</p> <ul style="list-style-type: none"> • If event resolves to Grade 1 or better (Day 1) or to Grade 2 or better (Day 8) within 3 weeks after interrupting treatment, resume sacituzumab govitecan. ^b If not, permanently discontinue sacituzumab govitecan, contact the medical monitor and refer the patient to a hematologist for further investigations.

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

- ^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.
- ^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).
- ^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Dermatologic events	
Dermatologic event, Grade 1 or 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue sacituzumab govitecan.
Dermatologic event, Grade 3	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold sacituzumab govitecan. <p>Event that has delayed treatment by 2–3 weeks or event that persists for ≥ 48 hours despite optimal medical management:</p> <ul style="list-style-type: none"> <u>First and second occurrence</u>: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by one level. ^{b, c} If not, permanently discontinue sacituzumab govitecan. ^a <u>Third occurrence</u>: Permanently discontinue sacituzumab govitecan and contact Medical Monitor. ^a <p>All other Grade 3 events:</p> <ul style="list-style-type: none"> If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan. ^b If not, permanently discontinue sacituzumab govitecan. ^a

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section [A12–5.1.4.1](#) for details).

^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Dermatologic events (cont.)	
Dermatologic event, Grade 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold sacituzumab govitecan. <u>First and second occurrence</u>: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by one level.^{b, c} If not, permanently discontinue sacituzumab govitecan.^a <u>Third occurrence</u>: Permanently discontinue sacituzumab govitecan and contact Medical Monitor.^a
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold sacituzumab govitecan. If event resolves to Grade 1 or better, resume sacituzumab govitecan. Permanently discontinue sacituzumab govitecan if withheld for > 3 weeks or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed.

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section [A12–5.1.4.1](#) for details).

^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin	
AST/ALT > ULN to $\leq 3 \times$ ULN with total bilirubin $\leq 2 \times$ ULN	<ul style="list-style-type: none"> Continue atezolizumab and sacituzumab govitecan.
AST/ALT > $3 \times$ ULN to $5 \times$ ULN with total bilirubin > ULN to $\leq 2 \times$ ULN	<ul style="list-style-type: none"> Continue atezolizumab and sacituzumab govitecan. Monitor LFTs at least weekly. Consider patient referral to a hepatologist and liver biopsy. <p>Suspected immune-mediated events of > 5 days' duration:</p> <ul style="list-style-type: none"> Consider withholding atezolizumab. Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. If atezolizumab is withheld and event resolves to AST/ALT $\leq 3 \times$ ULN with total bilirubin $\leq 2 \times$ ULN within 12 weeks after event onset, resume atezolizumab.^{d, e} If not, permanently discontinue atezolizumab and contact Medical Monitor.^a

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT $> 5 \times$ ULN to $< 10 \times$ ULN with total bilirubin $> \text{ULN}$ to $\leq 2 \times$ ULN	<ul style="list-style-type: none"> Continue atezolizumab. Withhold sacituzumab govitecan. If event resolves to AST/ALT $\leq 3 \times$ ULN within 3 weeks after interrupting treatment, resume sacituzumab govitecan. ^a Monitor LFTs at least weekly. Consider patient referral to hepatologist and liver biopsy.

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

- ^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit-risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.
- ^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12-5.1.4.1 for details).
- ^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit-risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT $> 5 \times$ ULN to $< 10 \times$ ULN with total bilirubin $> \text{ULN}$ to $\leq 2 \times$ ULN (cont.)	Suspected immune-mediated events: <ul style="list-style-type: none"> Withhold atezolizumab and sacituzumab govitecan. Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. If event resolves to AST/ALT $\leq 3 \times$ ULN with total bilirubin $\leq 2 \times$ ULN within 3 weeks after interrupting treatment, resume sacituzumab govitecan. ^b If not, permanently discontinue sacituzumab govitecan and contact Medical Monitor. ^a If event resolves to AST/ALT $\leq 3 \times$ ULN with total bilirubin $\leq 2 \times$ ULN with 12 weeks after event onset, resume atezolizumab. ^{d, e} If not, permanently discontinue atezolizumab and sacituzumab govitecan and contact Medical Monitor. ^a
AST/ALT $> \text{ULN}$ to $\leq 3 \times$ ULN with total bilirubin $> 2 \times$ ULN	<ul style="list-style-type: none"> Investigate causes for elevated bilirubin and initiate treatment as indicated per institutional guidelines. Use best medical judgment when determining whether to continue study treatment.

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT $> 3 \times$ ULN with total bilirubin $> 2 \times$ ULN	<ul style="list-style-type: none"> • Withhold atezolizumab and sacituzumab govitecan. • Monitor LFTs every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist and consider liver biopsy. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT $\leq 3 \times$ ULN with total bilirubin $\leq 2 \times$ ULN while within 3 weeks after interrupting treatment, resume sacituzumab govitecan with dose reduced by one level.^{b, c} If not, permanently discontinue sacituzumab govitecan.^a • If event resolves to AST/ALT $\leq 3 \times$ ULN with total bilirubin $\leq 2 \times$ ULN within 12 weeks after event onset, resume atezolizumab.^{d, e} If not, permanently discontinue atezolizumab and contact Medical Monitor.^a • Permanently discontinue atezolizumab and sacituzumab govitecan for life-threatening hepatic events and contact the Medical Monitor.

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT > 10 × ULN	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^a Withhold sacituzumab govitecan. • Monitor LFTs every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist and consider liver biopsy. • Consider administering 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent or escalating the corticosteroid dose. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN, taper corticosteroids over ≥ 1 month. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 3 weeks after interrupting treatment, resume sacituzumab govitecan with dose reduced by one level. ^{b, c} If not, permanently discontinue sacituzumab govitecan. ^a

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Endocrine events	
Asymptomatic hypothyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue sacituzumab govitecan.
Symptomatic hypothyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold sacituzumab govitecan. When symptoms are controlled and thyroid function is improving, resume sacituzumab govitecan.^b

Atezo+SG=atezolizumab plus sacituzumab govitecan; CRS = *cytokine release syndrome*; G-CSF = granulocyte colony-stimulating factor; IRR=infusion-related reaction; LFT = liver function test; PO=by mouth; ULN = upper limit of normal.

- ^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.
- ^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section [A12–5.1.4.1](#) for details).
- ^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Endocrine events (cont.)	
Asymptomatic hyperthyroidism	<p>TSH ≥ 0.1 mU/L and < 0.5 mU/L:</p> <ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue sacituzumab govitecan. <p>TSH < 0.1 mU/L:</p> <ul style="list-style-type: none"> Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold sacituzumab govitecan. When symptoms are controlled and thyroid function is improving, resume sacituzumab govitecan.^b

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

- ^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.
- ^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section [A12–5.1.4.1](#) for details).
- ^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Sacituzumab govitecan–related <i>events</i> not described above	
Grade 1 or 2	<ul style="list-style-type: none"> Continue atezolizumab and sacituzumab govitecan.
Grade 3	<ul style="list-style-type: none"> Continue atezolizumab. Withhold sacituzumab govitecan. <p>Toxicity that has delayed treatment by 2–3 weeks or non-hematologic toxicity that persists for ≥48 hours despite optimal medical management:</p> <ul style="list-style-type: none"> <u>First and second occurrence</u>: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by one level.^{b, c} If not, permanently discontinue sacituzumab govitecan.^a <u>Third occurrence</u>: Permanently discontinue sacituzumab govitecan and contact Medical Monitor.^a <p>All other Grade 3 toxicities:</p> <ul style="list-style-type: none"> If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan.^b If not, permanently discontinue sacituzumab govitecan.^a

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

- ^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.
- ^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).
- ^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Sacituzumab govitecan–related <i>events</i> not described above (cont.)	
Grade 4	<ul style="list-style-type: none"> Withhold atezolizumab and sacituzumab govitecan. If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. <p>Toxicity that has delayed treatment by 1–3 weeks or non-hematologic toxicity:</p> <ul style="list-style-type: none"> First occurrence: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by one level (e.g., from 10 mg/kg to 7.5 mg/kg).^{b, c} If not, permanently discontinue sacituzumab govitecan.^a Second occurrence: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by two levels (e.g., from 10 mg/kg to 5 mg/kg).^{b, c} If not, permanently discontinue sacituzumab govitecan.^a Third occurrence: Permanently discontinue sacituzumab govitecan and contact Medical Monitor.^a <p>All other Grade 4 toxicities:</p> <ul style="list-style-type: none"> If event resolves to Grade 1 or better while within 3 weeks after interrupting treatment, resume sacituzumab govitecan.^b If not, permanently discontinue sacituzumab govitecan.^a

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Atezolizumab-related events not described above	
Grade 1 or 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue sacituzumab govitecan.
Grade 3 or 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Sacituzumab govitecan may be continued at the discretion of the investigator per medical judgment.

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

- ^a Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^b If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.
- ^c The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section [A12–5.1.4.1](#) for details).
- ^d Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^e If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

A12-5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + SG ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + SG arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

- Myelitis
- Facial paresis

A12–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+SG ARM

A12–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the *final* dose of atezolizumab or within 6 months after the *final* dose of sacituzumab govitecan. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A12–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the *final* dose of sacituzumab govitecan. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A12–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A12–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

Appendix 12: Study Details Specific to Atezo + SG Arm

A12–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + SG ARM

Table A12-6 Schedule of Activities for Patients Treated with Atezo + SG

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-day cycles) ^a				Stage 2 Screen. (see Appendix 2) or Treatment Discontinuation ^d	Follow-Up
	Day –28 to –1	Cycle 1 ^b		Cycles ≥ 2			Every 3 Months
		Day 1	Day 8 ^c	Day 1 ^c	Day 8 ^c		
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available					
Vital signs ^e		x		x		x	
Weight ^f		x		x		x	
Complete physical examination ^g						x	
Limited physical examination ^{f, h}		x	x	x	x		
ECOG Performance Status ^f		x		x		x	
ECG ^{f, i}		Perform as clinically indicated				x	
Hematology ^{j, k}		x	x	x	x	x	
Chemistry ^{k, l}		x	x	x	x	x	
Coagulation (INR and aPTT)		Perform as clinically indicated				x	
TSH, free T3 (or total T3), free T4 ^m		x ^{k, m}				x	
Pregnancy test ^{k, n}		x		x		x	x ⁿ
Blood sample for blood-based NGS ctDNA test ^o						x	
Urinalysis ^p		Perform as clinically indicated					
Serum autoantibody sample ^q		Perform if a patient experiences a suspected immune-mediated adverse event					

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-6 Schedule of Activities for Patients Treated with Atezo + SG (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-day cycles) ^a				Stage 2 Screen. (see Appendix 2) or Treatment Discontinuation ^d	Follow-Up
	Day –28 to –1	Cycle 1 ^b		Cycles ≥ 2			Every 3 Months
		Day 1	Day 8 ^c	Day 1 ^c	Day 8 ^c		
PK sample	See Appendix 2	Refer to Table A12-7 .					
ADA sample		Refer to Table A12-7 .					
Biomarker samples		Refer to Table A12-7 .					
Blood sample for RBR (optional) ^r		x					
Tumor biopsy		x ^s					
Tumor biopsy (optional)		x ^t					
Tumor response assessments		x ^{u, v, w}					
Concomitant medications ^x		x	x	x	x	x	
Adverse events ^y		x	x	x	x	x ^y	x ^y
Sacituzumab govitecan administration ^{z, aa}		x	x	x	x		
Atezolizumab administration ^{z, bb}		x		x			
Survival follow-up and anti-cancer treatment							x ^{cc}

ADA=anti-drug antibody; Atezo + SG=atezolizumab plus sacituzumab govitecan; CT=computed tomography; ctDNA=circulating tumor DNA; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; NGS=next-generation sequencing; PBMC=peripheral blood mononuclear cells; PK=pharmacokinetic; RBR=Research Biosample Repository; RECIST=Response Evaluation Criteria in Solid Tumors; Screen.=screening; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

^a If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. The Medical Monitor is available to advise as needed.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-6 Schedule of Activities for Patients Treated with Atezo + SG (cont.)

- ^b It is recommended that treatment be initiated no later than 7 days after randomization.
- ^c Visits can occur up to 2 days after the scheduled visit day.
- ^d Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the *final* dose of study treatment. The visit at which loss of clinical benefit is confirmed by the investigator (see Section 3.1.1 for details) may be used as the treatment discontinuation visit.
- ^e *Vital signs include* respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion of each drug and, if clinically indicated, every 15 (\pm 5) minutes during and 30 (\pm 10) minutes after the infusion of each drug. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion of each drug and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (\pm 10) minutes after the infusion.
- ^f Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^g *Complete physical examination* includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^h Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ⁱ It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.
- ^j Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
- ^k If screening laboratory assessment are performed within 96 hours before Day 1 of Cycle 1, they do not have to be repeated.
- ^l Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included on Day 1 of each treatment cycle.
- ^m TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).
- ⁿ All women of childbearing potential will have a urine or serum pregnancy test performed at specified visits during treatment and at 3 months and 6 months after the *final* dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^o Blood samples for blood-based NGS ctDNA test will not be collected from Protocol Version 19 *onward*.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-6 Schedule of Activities for Patients Treated with Atezo + SG (cont.)

- ^p *Urinalysis* includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ^q Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Serum samples collected for the assessment of PK, ADAs, or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment, may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.
- ^r Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.
- ^s Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have granted approval for mandatory serial biopsies (see Section 3.1.2) will also undergo tumor biopsy sample collection at Week 4 (± 7 days) (if deemed clinically feasible by the investigator). See Section 4.5.6 for tissue sample requirements.
- ^t Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation, if deemed clinically feasible, and may undergo additional on-treatment biopsies at any other time during the study at the investigator's discretion.
- ^u Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1 with the following exceptions: 1) atezolizumab-treated patients who continue treatment after radiographic disease progression will undergo tumor assessments every 6 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), and 2) patients with bone metastases will have bone scans every 12 weeks (± 1 week for the first 48 weeks, and ± 2 weeks thereafter). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.
- ^v All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the tumor assessment schedule described above (see footnote “s”). Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-6 Schedule of Activities for Patients Treated with Atezo + SG (cont.)

- ^w For patients who undergo screening for Stage 2: Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.
- ^x Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 *days* prior to initiation of study treatment until the treatment discontinuation visit.
- ^y After initiation of study treatment, all adverse events will be reported until 30 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.
- ^z Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).
- ^{aa} Sacituzumab govitecan will be administered by IV infusion at a dose of 10 mg/kg on Day 1 and 8 of each 21-day cycle. Sacituzumab govitecan should be administered prior to the atezolizumab infusion. Sacituzumab govitecan should be infused over approximately 3 hours on first infusion and over 1 hour on subsequent infusions, if the first infusion is well tolerated.
- ^{bb} Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial dose of atezolizumab will be delivered over 60 (\pm 15) minutes. Subsequent infusions will be delivered over 30 (\pm 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (\pm 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Refer to Section A12-4.1.2.2 for details on atezolizumab infusions (including measurement of vital signs).
- ^{cc} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + SG Arm: Preliminary and Expansion Phases

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Sacituzumab govitecan PK ^a (serum) • Sacituzumab govitecan ADA (serum) • Biomarker (plasma, serum, PBMC)
	30 minutes after sacituzumab govitecan infusion	<ul style="list-style-type: none"> • Sacituzumab govitecan PK ^a (serum)
	30 minutes after atezolizumab infusion	<ul style="list-style-type: none"> • Atezolizumab PK (serum)
Day 8 of Cycle 1	Prior to study treatment	<ul style="list-style-type: none"> • Sacituzumab govitecan PK ^a (serum)
Day 1 of Cycle 2	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Sacituzumab govitecan PK ^a (serum) • Sacituzumab govitecan ADA (serum)
	30 minutes after sacituzumab govitecan infusion	<ul style="list-style-type: none"> • Sacituzumab govitecan PK ^a (serum)
Day 8 of Cycle 3	Prior to study treatment	<ul style="list-style-type: none"> • Sacituzumab govitecan PK ^a (serum)
Day 1 of Cycle 4	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycle 5	Prior to study treatment	<ul style="list-style-type: none"> • Sacituzumab govitecan PK ^a (serum) • Sacituzumab govitecan ADA (serum)
	30 minutes after sacituzumab govitecan infusion	<ul style="list-style-type: none"> • Sacituzumab govitecan PK ^a (serum)
Day 1 of Cycle 7	Prior to study treatment	<ul style="list-style-type: none"> • Sacituzumab govitecan PK ^a (serum) • Sacituzumab govitecan ADA (serum)
	30 minutes after sacituzumab govitecan infusion	<ul style="list-style-type: none"> • Sacituzumab govitecan PK ^a (serum)

ADA = anti-drug antibody; Atezo + SG = atezolizumab plus sacituzumab govitecan; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

^a Total antibody, free SN-38, SN-38 glucuronide, and total SN-38 will be tested along with sacituzumab govitecan PK.

Appendix 12: Study Details Specific to Atezo + SG Arm

Table A12-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + SG Arm: Preliminary and Expansion Phases (cont.)

Visit	Time	Sample Type
Day 1 of Cycle 8	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycle 9 Day 1 of Cycle 11 and every third cycle thereafter (e.g., Cycles 14, 17, 20, etc.)	Prior to study treatment	<ul style="list-style-type: none"> • Sacituzumab govitecan PK ^a (serum) • Sacituzumab govitecan ADA (serum)
	30 minutes after sacituzumab govitecan infusion	<ul style="list-style-type: none"> • Sacituzumab govitecan PK ^a (serum)
	Prior to study treatment	<ul style="list-style-type: none"> • Sacituzumab govitecan PK ^a (serum) • Sacituzumab govitecan ADA (serum)
	30 minutes after sacituzumab govitecan infusion	<ul style="list-style-type: none"> • Sacituzumab govitecan PK ^a (serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤30 days after <i>final</i> dose)	At visit	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Sacituzumab govitecan PK ^a (serum) • Sacituzumab govitecan ADA (serum) • Biomarker (plasma, serum)

ADA = anti-drug antibody; Atezo + SG = atezolizumab plus sacituzumab govitecan;

PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

^a Total antibody, free SN-38, SN-38 glucuronide, and total SN-38 will be tested along with sacituzumab govitecan PK.

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Appendix 13

Study Details Specific to Atezo+Camon Arm

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A13–1 BACKGROUND ON ATEZO+CAMON ARM

A13–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, *myocarditis*, and *nephritis*, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma (in the European Union), non-small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer (in the European Union), hepatocellular carcinoma, melanoma (in the United States), and alveolar soft part sarcoma (in the United States).

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A13–1.2 BACKGROUND ON CAMONSERTIB

Camonsertib is a highly potent and selective ATR inhibitor (ATRi) as demonstrated in biochemical and cell-based assays. Camonsertib demonstrates efficacy in several xenograft models of cancer as a single agent. Pharmacokinetic (PK) and pharmacodynamic marker analysis from tumor xenografts demonstrates target engagement and a dose-responsive increase in double-strand DNA breaks leading to tumor cell death in vivo.

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Refer to the Camonsertib Investigator's Brochure for details on nonclinical and clinical studies.

A13–2 RATIONALE FOR ATEZO+CAMON ARM

A13–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).



Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer (CRC), head and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors (CPIs), have *had* a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active *as monotherapy* for many patients.

A13–2.2 DNA DAMAGE RESPONSE IN CANCER

Research in the DNA damage response (DDR) area suggests that tens of thousands of chemical and physical DNA lesions occur in every cell each day (Lindahl *and Barnes* 2000). To thwart the DNA damage threat, cells have evolved into a complex network of proteins, collectively named the DDR. The DDR is responsible for coordinating the early

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detection of DNA damage and signaling this to cell cycle checkpoints and DNA repair pathways, pausing the cell cycle to initiate repair or triggering cell death if damage is too substantial. The DDR is, therefore, key to ensuring overall genome stability and cell viability (Bradbury et al. 2020).

Genomic instability is integral to cancer development. Oncogenic activation causes cells to divide uncontrollably, leading to rapid DNA replication that is prone to mistakes (Halazonetis et al. 2008). At the same time, many cancers harbor defects in certain DDR pathways leading to faulty DNA repair or the dependence of tumor cells to utilize alternative repair mechanisms (Kelley et al. 2014).

Cancer-specific DNA repair defects present an important therapeutic opportunity. One can capitalize on these aberrations either by utilizing a chemical agent causing DNA damage that the tumor is unable to repair or by inhibiting the alternative DNA repair pathways that the cancer cells require for survival. In both cases, normal, healthy cells are less affected by the treatment. This forms the basis of the synthetic lethality concept (Kelley et al. 2014; Yap et al. 2019). Early nonclinical data demonstrated the synthetic lethality between breast cancer (*BRCA*) genetic defects and pharmacologic poly adenosine diphosphate-ribose polymerase (PARP) inhibition, suggesting that there may be monotherapy activity with this class of agents and supporting the early trial testing of this molecularly driven approach. Beyond PARP inhibitors, there is now a large armamentarium of potent and relatively selective inhibitors in clinical trial testing against key targets involved in the DDR, including ATR, ATM, CHK1/2, and WEE1.

A13–2.3 ATR

ATR belongs to a family of PIKKs that also include the ATM and DNA-PK (Blackford *and Jackson* 2017). All three kinases are involved in the DDR; ATR responds primarily to long single-stranded DNA (ssDNA) lesions, while ATM and DNA-PK respond to DNA double-strand breaks.

ATR is recruited to blocked or damaged DNA replication forks as ssDNA is created on the replication fork by uncoupling of the replicative helicase from the stalled DNA polymerase. This ssDNA is first coated by replication protein A, which subsequently recruits ATR and the regulatory partner ATRIP to the ssDNA-double-stranded DNA junction. The ATR/ATRIP complex then interacts with additional regulators, including RAD9, RAD1, and HUS1 (the 9-1-1 complex), and RAD17. Finally, ATR is fully activated upon a conformational change induced by recruitment of activator proteins such as DNA topoisomerase II-binding protein 1 or Ewing tumor-associated antigen 1 (Saldivar et al. 2017).

ATR plays a fundamental role in the cell cycle by protecting against replication stress (e.g., induced by cisplatin and/or other platinating agents). The ATR pathway

counteracts replication stress in at least two ways. First, ATR prevents the breakage or collapse of stalled replication forks. ATR does so by modulating helicases that can remodel the structure of stalled forks to prevent their cleavage, promoting replication fork repair by homologous recombination factors such as BRCA2 and PALB2, controlling replication initiation, and maintaining a sufficient supply of free nucleotides (Lecona *and Fernandez-Capetillo* 2018). At the same time, ATR acts as a cell cycle checkpoint regulator through an activating phosphorylation of the CHK1 on Ser-317 and Ser-345. Once activated, CHK1 phosphorylates and inactivates the cell division cycle 25 (CDC25) phosphatases A, B, and C, leading to their proteasomal degradation. Upon CDC25 degradation, CDK2 activity is decreased and activation of CDK1/cyclin B kinases is abolished, leading to cell cycle arrest in S-phase or at the G2/M boundary (Busino et al. 2004).

A13–2.3.1 Immune-Modulatory Effects of ATR

Recent research has revealed intrinsic links between the ATR-CHK1 pathway and innate immune signaling networks (Gasser et al. 2005). Increased ATR pathway signaling triggered by genotoxic stress and stalled DNA replication upregulates immunosuppressive PD-L1 on tumor cells mediated by signal transducer and activator of transcription (STAT)1– and STAT3–interferon (IFN) regulatory factor 1-related pathways. ATR pathway signaling also upregulates the expression of natural killer (NK) group 2D (NKG2D) cell surface ligands (NKG2DLs) (Gasser et al. 2005), which bind to NKG2D receptors on NK cells and activated CD8⁺ T cells, triggering degranulation and pro-inflammatory cytokine production. In turn, pharmacological inhibition of ATR can suppress NKG2DL upregulation (Gasser et al. 2005). Furthermore, ATR mutations modulate the tumor immune microenvironment in melanoma models. When compared with ATR wild-type tumors, homozygous ATR-mutated melanoma tumors showed reduced numbers of infiltrating CD3⁺ T cells but a significant increase in infiltrating macrophages and B cells compared with ATR wild-type or hemizygous ATR-mutated tumors, as demonstrated on both flow cytometry and immunohistochemistry (IHC) (Chen et al. 2017). This ATR deficient state was associated with increased PD-L1, CD206, and arginase1 expression, along with downregulation of butyrophilin expression, suggesting a T cell–suppressed immune environment (Chen et al. 2017).

ATR has also been shown to mediate robust immunosuppressive effects in the context of *radiotherapy*-driven DNA damage and consequent arrest in the G2/M phase of the cell cycle (Rodriguez-Ruiz et al. 2020). It was demonstrated by Dillon et al. (2019), Feng et al. (2020), and Sheng et al. (2020), that pharmacologic ATR*is* not only boost cGAS-signaling and consequent type I IFN responses (involving CCL5 and CXCL10) driven by *radiotherapy* but also enhance antigen presentation on *major histocompatibility complex* class I molecules, ultimately favoring tumor infiltration by *dendritic cells*, repolarization of the tumor-associated macrophage compartment toward an immunostimulatory profile, and T cell–dependent anti-cancer immunity.

A13–2.4 RATIONALE FOR COMBINING ATEZOLIZUMAB WITH CAMONSERTIB IN CPI-EXPERIENCED PATIENTS WITH NSCLC

ATR inhibition can play a potent immunomodulatory role in the tumor microenvironment through activation of the cyclic GMP-AMP synthase–stimulator of IFN genes (cGAS-STING) pathway, being the primary innate immune sensing pathway for tumor detection (Chatzinikolaou et al. 2014; Barber 2015; Mouw et al. 2017; *Ngoi et al. 2022*). Cytosolic DNA fragments arising through unrepaired DNA damage interact with cGAS-STING, thereby triggering TBK1 and subsequently an IRF3/nuclear factor κ B–dependent transcriptional pathway, leading to increased type I IFN gene transcription (Ablasser et al. 2013; Chen et al. 2016) and PD-L1 upregulation (Mouw et al. 2017). In breast cancer, tumors harboring a 44-gene DDR-deficiency signature associated with loss of S-phase DDR contained increased cytosolic DNA and constitutive PD-L1 expression as a result of cGAS-STING upregulation (Parkes et al. 2017). Increased IFN-related gene expression and CD4⁺/CD8⁺ T cell infiltration were observed in the microenvironment of these tumors (Parkes et al. 2017). In advanced prostate cancer mouse models, features of S-phase DNA damage and cGAS-STING activation were observed in response to ATRi treatment, together with upregulation of CXCL10 and CCL5, which are known transcriptional targets of IRF3, indicating activation of innate immunity (Pilié et al. 2019). Furthermore, in a recent phase I clinical trial of elimusertib in advanced solid cancers, paired tumor samples indicated an upregulation of PD-L1 expression among a subset of patients with PD-L1-positive tumors after treatment with elimusertib (Yap et al. 2020).

In CRC mouse models, the PD-L1 inhibitor avelumab led to improved tumor reduction and survival when added to berzosertib plus cisplatin or carboplatin, in comparison to berzosertib plus platinum chemotherapy alone (Alimzhanov et al. 2019). Importantly, mice who achieved a complete response to avelumab–berzosertib–platinum triple therapy were refractory to attempts at reinoculation with further MC38 CRC cells, suggesting the development of anti-tumor immunogenic memory (Alimzhanov et al. 2019).

Collectively, these data suggest that pharmacologic inhibition of ATR and resultant DNA damage may contribute to cGAS-STING-mediated anti-tumor immunity and may prime and/or re-sensitize tumors for immune checkpoint blockade.

A13–2.4.1 Beyond the cGAS-STING Pathway

A recent study by Chen et al. (2020) has shed light on the presence of additional damage-associated molecular patterns triggered upon ATRi therapy, apart from cGAS-STING activation. Interestingly, loss of cGAS or STING did not completely eliminate inflammatory signaling upon ATRi therapy in cell lines, and the cytosolic RNA sensor retinoic acid-inducible gene I was observed to be an additional component of this inflammatory response (Chen et al. 2020). Furthermore, ATR inhibition may play a

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potential role in increasing the tumor mutational burden (TMB) and neoantigen repertoire. Preclinical studies have explored the role of DDR inhibition as a means of increasing the TMB and therefore the generation of neoantigens (Kakoti et al. 2020), which may, in turn, increase sensitivity to immune checkpoint blockade by increased antigen presentation. An analysis of data from The Cancer Genome Atlas and The Cancer Immunome Atlas showed that samples harboring mutations in DNA damage signaling genes, including ATR, exhibited high neoantigen levels (Kakoti et al. 2020), enhancing the rationale for combining ATRi's with anti-PD-(L)1 immune checkpoint blockade.

The preclinical dataset is corroborated increasingly by clinical and translational evidence. In the HUDSON study (NCT03334617), multiple regimens in biomarker-matched and biomarker-non-matched pretreated patients with locally advanced or metastatic NSCLC were evaluated, among them a combination of the ATRi ceralasertib in combination with the PD-L1 inhibitor durvalumab. Importantly the patients had to be pretreated with platinum-doublet chemotherapy and prior failure of anti-PD-1/PD-L1 immunotherapy. In tumor samples collected from the patients in the ceralasertib plus durvalumab arm collected during a ceralasertib-only period prior to durvalumab treatment showed modified biomarkers of peripheral immunity including significant increases in antigen presentation gene signature and significant decreases in both exhausted T cell and NK cell signatures from bulk whole-blood RNA samples. On treatment samples from patients in the ceralasertib plus durvalumab arm also showed decreased 4 macrophage gene expression signatures. In contrast, similar gene expression profiles were not observed from comparable samples on other non-ceralasertib-containing HUDSON arms (Hernandez et al. 2021). Thus, treatment with an ATRi may indeed re-shape the tumor microenvironment of CPI experienced NSCLC to a more immune-permissive state as suggested by preclinical data. In this analysis no correlation between ATM biomarker status, between TMB or PD-L1 status by IHC and Response Evaluation Criteria in Solid Tumors response was observed.

Importantly, Besse et al. (2022) presented updated efficacy and safety data on the combination of ceralasertib and durvalumab from the HUDSON study (n= 66 patients) at the World Conference on Lung Cancer 2022. The combination demonstrated a promising efficacy signal across biomarker-matched and biomarker-non-matched patients with the highest objective response rate (ORR) (16.7% vs. 0%–4.8%) and disease control rates (12-week: 60.6% vs. 26.7%–36.8%; 24-week: 42.4% vs. 13.3%–17.2%) among the regimens evaluated to date in this study. The median progression-free survival was 6.0 months (80% CI: 4.6 to 7.5 *months*) and median overall survival 15.9 months (80% CI: 14.1 to 20.3 *months*) versus 1.8–2.9 and 7.9–11.0 months, respectively, with the other tested regimens, and the combination had a tolerable safety profile, with no new safety signals reported.

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In support of this clinical data in CPI-experienced patients Kim et al. reported results from a Phase I study evaluating the combination of ceralasertib and paclitaxel that recruited 58 patients with advanced solid tumors; intriguingly, 11 of 33 patients with metastatic melanoma who were previously resistant to PD-1 inhibitors achieved durable responses, resulting in an ORR of 33.3% in this highly pretreated population (Kim et al. 2021; Ngoi et al. 2022).

A13–2.1 CLINICAL STUDIES WITH CAMONSERTIB

Clinical development is ongoing in patients with advanced solid tumors as per eligibility criteria for Phase I/IIa Study RP-3500-01 and Phase Ib/II Study RP-3500-03.

RP-3500-03 is an open-label, Phase Ib/II study to investigate the combination of the ATRi RP-3500 with the PARPi niraparib or olaparib in patients with advanced solid tumors harboring specific deleterious mutations. For safety data from this study, refer to the most recent, effective version of Camonsertib Investigator's Brochure.

A13–2.1.1 Study RP-3500-01

RP-3500-01 (TRESR) is an exploratory modular, Phase I/IIa, first-in-human, multicenter, open-label, non-randomized, dose-escalation, and dose-expansion study of camonsertib administered orally as a single agent or in combination with talazoparib or gemcitabine in patients with advanced solid tumors. Patients are enrolled based on center-specific routine genomic and IHC tests able to detect alterations in genes associated with ATRi sensitivity. A recommended Phase II dose (RP2D) of 160 mg once a day (QD) (3 days on/4 days off schedule) was determined for camonsertib monotherapy.

Study RP-3500-01 currently consists of the following modules:

- Module 1 is the camonsertib monotherapy dose-escalation portion evaluating the safety, tolerability, pharmacokinetics, and food effect of camonsertib administered using two schedules. Module 1 subjects participated in a food-effect evaluation to assess potential differences in camonsertib exposures and absorption following a standard high-fat meal. Enrollment in Module 1 has been completed.
- Module 2 is evaluating the preliminary efficacy of camonsertib in patients with tumors harboring an ATRi sensitizing biomarker. Module 2 enrollment started once the RP2D and recommended dosing schedule for camonsertib monotherapy was determined in Module 1.
- *Other active modules of this study are investigating camonsertib in combination with gemcitabine or PARPi.*

For camonsertib monotherapy, 149 patients have been treated in Module 1+Module 2. For safety data from this study, refer to the most recent, effective version of Camonsertib Investigator's Brochure.

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The safety profile continues to be consistent with other drugs of the class. Refer to the Camonsertib Investigator's Brochure for details.

A13–2.1.2 Drug Interactions

Definitive in vitro drug-drug interaction (DDI) studies have been conducted as per the recommendations of the U.S. Food and Drug Administration (FDA) Guidance for Industry (FDA 2020). In definitive in vitro studies, camonsertib did not appreciably inhibit CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5 (testosterone as substrate), or CYP3A4/5 (midazolam as substrate) with $IC_{50} > 100 \mu M$ and was found to be a weak direct inhibitor of CYP2C8 ($IC_{50}=44 \mu M$) in these same studies. Camonsertib was not a preincubation or time-dependent inhibitor of all CYP isoforms evaluated. Incubations of human hepatocytes with camonsertib showed only minor increases in CYP2B6 and CYP3A4 messenger RNA that did not exceed more than 20% of the associated positive control values. Experiments using cell systems have shown that camonsertib is not an inhibitor of the uptake transporters OATP1B1, OAT1B3, OAT1, OAT3, OCT1, or MATE2-K. Camonsertib is a weak inhibitor of MATE-1 (44% inhibition at $5 \mu M$), MDR1 (40% inhibition at $100 \mu M$), and breast cancer resistant protein (BCRP) ($IC_{50}=17.4 \mu M$). Together the data suggest that camonsertib has a low potential to be a perpetrator of DDIs with co-administered transport substrates; however, depending on the dose, camonsertib may inhibit BCRP in the gastrointestinal tract and increase the absorption of BCRP substrates. Additionally, based on the current data, camonsertib is not expected to be a perpetrator of DDIs at the levels of inhibition or induction of CYP isoforms.



A13–2.2 BENEFIT–RISK ASSESSMENT

Metastatic NSCLC remains an incurable disease with a high unmet medical need, especially in the CPI-pretreated patient population with only few therapeutic options available. Based on the preclinical and translational data, ATR plays an important role in mediating an immune-suppressive environment, potentially attenuating the anti-tumor immune response. Blocking ATR has been shown to effectively reverse this effect, even more pronounced when ATR inhibition is combined with a PD-(L)1 CPI.

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Clinical data available today corroborate these findings, demonstrating anti-tumor efficacy for a platinum/CPI experienced patient population in this hard-to-treat clinical setting.

Taken together, the immune-modulatory effects of blocking ATR and thus potentially re-invigorating the anti-tumor immune response as well as the potential synergism with immune-CPI treatment, as well as the manageable and tolerable safety profile of camonsertib and atezolizumab, treatment with a combination of these two agents appears to have promising therapeutic potential in pretreated patients with NSCLC.

Furthermore, the current study (BO39610) contains all safety measures of an early development study in that it enrolls only a well-defined patient population with good performance status selected on the basis of the known safety profile of the combination partners. In addition, the study implements close safety monitoring, including frequent visits of patients to the site, strict inclusion and exclusion criteria, regular investigator calls, and the implementation of an Internal Monitoring Committee and a Scientific Oversight Committee.

To evaluate potential toxicities of the experimental treatments, a minimum of 6 patients in the *atezolizumab in combination with camonsertib* (Atezo+Camon) arm must complete a safety evaluation before additional patients can be enrolled in that arm (see Section 3.1.3).

In addition, stopping rules have been implemented for this arm to reduce any potential risk for the patients even further (see Section A13–5.1 for details).

Given the well-controlled Phase Ib setting and the tolerable safety profile of both drugs without overlapping mechanisms of toxicity, together with the promising preclinical and retrospective clinical data, the benefit–risk ratio for testing the combination of atezolizumab and camonsertib in NSCLC is positive.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, refer to Section 1.4.

A13–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+CAMON ARM

A13–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab (Tecentriq® U.S. *Prescribing Information*).

A13–3.2 RATIONALE FOR CAMONSERTIB DOSE AND SCHEDULE

[REDACTED]

[REDACTED]

[REDACTED]

Based on emerging data (including, but not limited to, safety, tolerability, PK, and pharmacodynamic data), the Sponsor may modify the study treatment (camonsertib and/or partner agent[s]) dose or schedule (e.g., concomitant vs. sequential dosing or intermittent dosing).

A13–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+CAMON ARM

A13–4.1 TREATMENT IN ATEZO+CAMON ARM

A13–4.1.1 Formulation, Packaging, and Handling

A13–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately ■ mL (1200 mg) of atezolizumab solution.

For information on the atezolizumab formulation, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

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A13–4.1.1.2 Camonsertib

Camonsertib will be supplied by the Sponsor in the form of [REDACTED] mg capsules. The [REDACTED] mg capsule is an immediate-release solid dosage form for oral administration. The drug product contains the camonsertib drug substance blended with common pharmaceutical, compendial excipients and filled-in capsules. Study drug is manufactured, packaged, and labeled in accordance with relevant regional requirements and the principles of Good Manufacturing Practice. For additional information see the pharmacy manual and the Camonsertib Investigator's Brochure.

A13–4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo+ Camon arm will receive treatment as outlined in [Table A13-1](#) until unacceptable toxicity or loss of clinical benefit, as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see [Section 3.1.1](#) for details). It is recommended that treatment be initiated no later than 7 days after randomization; *however, the first dose of study treatment should not occur within 3 days after a core biopsy or other surgical procedure.*

Table A13-1 Treatment Regimen for Atezo+ Camon Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none">Camonsertib [REDACTED] mg PO D1–3, D8–10; Q21 days (<i>recommended starting dose/target dose</i>)Atezolizumab 1200 mg by IV infusion on Day 1 of each cycle

Atezo = atezolizumab; Camon = camonsertib; D = day; PO = by mouth, orally; Q21 = every 21 days.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in [Section 5.3.5.12](#).

No safety data related to overdosing of atezolizumab or camonsertib are available.

A13–4.1.2.1 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to

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manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#). Atezolizumab infusions will be administered per the instructions outlined in [Table A13-2](#).

Table A13-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
<ul style="list-style-type: none">No premedication is permitted prior to the atezolizumab infusion.Vital signs (pulse rate, respiratory rate, <i>pulse oximetry</i>, blood pressure, and temperature) should be <i>measured</i> within 60 minutes prior to the infusion.Atezolizumab should be infused over 60 (\pm 15) minutes.If clinically indicated, vital signs should be <i>measured</i> every 15 (\pm 5) minutes during the infusion and at 30 (\pm 10) minutes after the infusion.Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	<ul style="list-style-type: none">If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic <i>medications</i>, and/or analgesics may be administered for subsequent doses at the discretion of the investigator.Vital signs should be <i>measured</i> within 60 minutes prior to the infusion.Atezolizumab should be infused over 30 (\pm 10) minutes if the previous infusion was tolerated without an IRR or 60 (\pm 15) minutes if the patient experienced an IRR with the previous infusion.If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be <i>measured</i> during the infusion and at 30 (\pm 10) minutes after the infusion.

IRR=infusion-related reaction.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in [Appendix 6](#).

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in [Section A13–5.1.4.2](#). Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A13–4.1.2.2 Camonsertib Administration

Camonsertib will be self-administered by patients orally at home (except on clinic days) at a starting dose of ■ mg. Camonsertib is formulated in ■ mg strength capsules. A treatment cycle consists of 3 weeks and will be given on Days 1–3 and Days 8–10 of every 21-day cycle. The cycle visit Day 1 should remain on schedule as planned starting from actual Day 1 of Cycle 1.

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On clinic visit days, patients should take their capsules in the clinic prior to the atezolizumab infusion, as directed by site personnel.

Day 1 of every cycle is independent of missed doses or dose delays. Camonsertib should be orally self-administered with approximately 240 mL (~8 ounces) of water. Patients will be initially instructed to take their camonsertib dose in the morning at approximately the same time each day. Cycle dosing must start on either Monday, Tuesday, or Wednesday if unable to accommodate weekend visits and should be taken on the same consecutive days each week.

Patients will swallow the study drug whole and will not manipulate or chew the study drug prior to swallowing. On clinic visit days, patients will be instructed to delay self-administration of their treatment dose and to take their study drug at the clinic.

Patients should be instructed that if they forget to take their dose at their usual time, they should take the missed dose as soon as possible on the day it was missed; however, there must be at least 8-hour interval between the missed dose and the next dose. If a dose is missed and the interval to the next dose is less than 8 hours, the missed dose should not be administered. If a patient vomits during or after taking camonsertib, re-dosing is not permitted until the next scheduled dose. To assess patient compliance with self-administration of camonsertib, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

At the end of the study, the Sponsor will provide instructions as to the disposition of any unused study drug.

Refer to the pharmacy manual and/or the *Camonsertib* Investigator's Brochure for information on handling, including preparation and storage, and accountability.

Guidelines for camonsertib dose modification and treatment interruption or discontinuation because of toxicities are provided in Section [A13–5.1.4.2](#). Camonsertib treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A13–4.1.3 Stage 2 Treatment

Patients in Cohort 2, Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section [3.1.1](#)) or unacceptable toxicity related to

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atezolizumab will be given the option of receiving a different treatment combination during Stage 2, as outlined in [Table A13-3](#), provided they meet the eligibility criteria for Stage 2 (see Section 4.1) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A13-3 Stage 2 Treatment Regimens Available for Atezo+Camon Arm

Study Treatment	Appendix
Atezo+Docetaxel	Appendix 16

Atezo = atezolizumab; Camon = camonsertib.

Refer to [Appendix 16](#) for details specific to the Atezo+Docetaxel arm.

A13-4.2 CONCOMITANT THERAPY FOR ATEZO+CAMON ARM

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A13-4.2.1 Permitted Therapy for Atezo+Camon Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of < 1% per year
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Inactivated vaccines (such as influenza and COVID-19)
 - Live, attenuated vaccines are not permitted (see Section [A13-4.2.3](#)).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma

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- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Bisphosphonate use, as recommended according to practice guidelines, as long as prescribed at least 28 days prior to enrollment. Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor use, as recommended according to practice guidelines, as long as prescribed at least 4 months before trial entry.
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy with sufficient monitoring of hematologic parameters in place.

- Radiotherapy to the brain as outlined below:

Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiotherapy) provided that all of the criteria listed below are met.

- The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.
- The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

- Anticonvulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections [A13–4.2.2](#) and [A13–4.2.3](#)) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard

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practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 -adrenergic agonists; see [Appendix 5](#)).

At this time there is no evidence on potential interactions of COVID-19 vaccines with camonsertib. COVID-19 vaccines must be given in accordance with the approved/authorized vaccine label and official immunization guidance. The decision of administration of a COVID-19 vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

A13–4.2.2 Cautionary Therapy for Atezo+Camon Arm

A13–4.2.2.1 Corticosteroids and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may be administered at the discretion of the investigator. The Medical Monitor is available to advise as needed.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to [Appendix 6](#) for details).

The above list of cautionary medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor is available to advise as needed if questions arise regarding medications not listed above.

A13–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential DDIs are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section [A13–4.2.3](#)) and having no impact on CYP3A may be used during the study at the discretion of the investigator.

A13–4.2.3 Prohibited Therapy for Atezo+Camon Arm

Based on in vitro experiments, camonsertib was shown to be a substrate of CYP2C8, CYP4A4, and UGTs (mainly UGT1A4). Camonsertib is a substrate of both multidrug

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resistance transporter (MDR1) and BCRP. The risk of clinically significant DDIs with inducers or inhibitors of CYP2C8, CYP3A4, or UGTs is currently unknown.

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority-approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A13–4.2.1.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the *final* dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, *IFNs* and interleukin [IL]-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Concomitant treatment with any medication that is known to prolong the QT interval and/or cause torsades de pointes is not permitted (see Appendix 21). If a patient requires use of any of these medications during the study, the patient must be removed from study.
- Strong BCRP inhibitors, or strong inhibitors or inducers of *P-gp* and *CYP3A*, including food and herbal sources (see a list of examples in Appendix 22) must be avoided within 28 days (or within five times the elimination half-life, whichever is longer) prior to initiating treatment with camonsertib and during treatment.

A13–4.2.4 Other Study Restrictions

Patients who are blood donors should not donate blood during the study and for 90 days after the *final* dose of study treatment.

Patients should maintain a normal diet unless modifications are required to manage an *adverse event* such as diarrhea, nausea, or vomiting.

Camonsertib may pose a phototoxicity risk based on data from preclinical studies; therefore, patients are advised to take measures, such as use of sunscreen, wearing of hats and long-sleeve garments, and minimizing exposure to ultraviolet light.

A13–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO+CAMON ARM

Contraception requirements for women and men in the Atezo+Camon arm are outlined as follows:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of < 1% per year during the treatment period and for 5 months after the final dose of atezolizumab and for 6 months after the final dose of camonsertib.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Men *must agree to* remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below.

With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 6 months after the *final* dose of camonsertib. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the *final* dose of camonsertib to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A13–5 ASSESSMENT OF SAFETY FOR ATEZO+CAMON ARM

A13–5.1 SAFETY PLAN FOR ATEZO+CAMON ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and *with* camonsertib in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections [A13–5.1.1](#), [A13–5.1.2](#), and [A13–5.1.3](#)). Guidelines for management of patients who experience specific adverse events are provided in Section [A13–5.1.4](#) and [Appendix 6](#).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Although the risk for overlapping toxicities of atezolizumab with camonsertib is low, a minimum of 6 patients in the Atezo+Camon arm must complete a safety evaluation (Section [3.1.3](#)) before additional patients can be enrolled in that arm. To minimize the potential risk for patients, stopping rules will be applied during the 6-patient safety evaluation and at each Internal Monitoring Committee data cut, as described below.

At any timepoint, after thorough review of the totality of safety data, if the Sponsor considers that the recommended starting dose/target dose of [REDACTED] mg of camonsertib is not suitable for this combination with atezolizumab, enrollment may proceed at a lower dose/with schedule change if applicable.

If more than 30% of patients (*with a minimum of 2 patients, e.g., 2 of 2 patients, 2 of 3, ..., 2 of 6, 3 of 7, etc.*) experience one or more of the following events that is *considered* to be related to study treatment, enrollment will be put on hold while the Sponsor evaluates the benefit–risk profile of Atezo+Camon:

- A non-hematologic treatment-related Grade 3 or 4 adverse event that does not improve (with or without corrective treatment) to Grade 1 or better within 2 weeks
- A hematologic treatment-related Grade 3 or 4 adverse event that does not improve to Grade 1 or better within 2 weeks or the event requires transfusion or hematopoietic growth factors
- A treatment-related adverse event that requires permanent discontinuation of study drug
- Death, except those that are incontrovertibly related to disease progression or extraneous causes such as accidents

Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections [5.2–5.6](#).

A13–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis. Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A13–5.1.2 Risks Associated with Camonsertib

Camonsertib has been associated with risks such as the following: hematologic toxicity including anemia, thrombocytopenia, and neutropenia, and non-hematologic toxicities including fatigue, nausea, diarrhea, and vomiting.

Camonsertib is still under clinical development and the safety profile is not yet fully known. Refer to the Camonsertib Investigator's Brochure for a description of anticipated safety risks for camonsertib.

A13–5.1.2.1 Hematologic Toxicities

The most common toxicity for camonsertib are hematologic toxicities, including anemia, neutropenia, and thrombocytopenia, which have been reported as related in > 10% of patients who received camonsertib treatment for solid tumor indications. The most common treatment-related hematologic toxicity for camonsertib is anemia, which tends to appear following completion of the first 21-day cycle of treatment and improves and/or recovers when treatment is interrupted or stopped.

Grade 3 and 4 toxicities include anemia, neutropenia, thrombocytopenia, and white blood cell decrease. Hematologic toxicity has been manageable and reversible with dose interruption in most cases in the ongoing clinical studies.

Routine monitoring of blood counts is required per protocol (with additional testing per clinical judgment) during the entire duration of the study (refer to [Table A13-6](#) for more guidance).

A13–5.1.2.2 Non-Hematologic Toxicities

Fatigue, nausea, diarrhea, and vomiting are the most common treatment-related non-hematologic adverse events.

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In general, most of these toxicities were low grade, manageable, and reversible. Symptomatic participants can be treated with antiemetic and/or antidiarrheal drugs as appropriate per investigator clinical judgment.

A13–5.1.2.3 Potential Teratogenicity/Genotoxicity

Camonsertib has been shown to be genotoxic via an aneugenic mechanism when studied in vitro using a micronucleus test. Additionally, in vivo studies have confirmed that camonsertib is genotoxic inducing micronuclei in peripheral erythrocytes. The positive genotoxic signal with camonsertib does not change the overall benefit–risk profile for the treatment of patients with advanced cancer.

No reproductive or teratogenicity studies in animals have been conducted with camonsertib.

For more details regarding the safety profile for camonsertib, refer to the Camonsertib Investigator's Brochure.

See Section [A13–5.3](#) for information on the reporting requirements for pregnancies in patients receiving atezolizumab and camonsertib.

A13–5.1.2.4 Phototoxicity

Based on data from preclinical studies, camonsertib may pose a phototoxicity risk; therefore, participants are advised to take measures, such as use of sunscreen, wearing of hats and long-sleeve garments, and minimizing exposure to ultraviolet light.

For more details regarding the safety profile for camonsertib, refer to Section [A13–2.5](#) as well as the Camonsertib Investigator's Brochure.

A13–5.1.3 Risks Associated with Combination Use of Atezolizumab and Camonsertib

There are no significant overlapping toxicities expected with combination use of atezolizumab and camonsertib, based on the safety profiles of the individual agents as well as the different mechanisms of toxicity.

A13–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo+Camon Arm

A13–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study.

For management of drug-related toxicities, the dose of camonsertib can be reduced by ■ mg (i.e., one dose level) one time, as outlined in [Table A13-4](#).

Table A13-4 Suggested Dose Adjustment for Camonsertib

Dose Level	Dose
Recommended starting <i>dose/target</i> dose	
First dose adjustment	
Second dose adjustment	

D = days; PO = orally, by mouth; QD = once a day; Q21D = every 21 days.

If further dose adjustment is indicated for camonsertib after two dose adjustments, camonsertib should be discontinued.

A13–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see [Table A13-5](#)). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to *the equivalent of* ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.* Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Dose interruption/modification criteria for camonsertib for hematologic (based on peripheral blood counts) and non-hematologic toxicities possibly related to study drug are outlined in [Table A13-5](#).

Camonsertib treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If camonsertib has been withheld for > 21 days after event onset because of toxicity, the patient should be discontinued from camonsertib, unless resumption of treatment is approved at the investigator's discretion. The decision to re-challenge patients should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

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If atezolizumab is discontinued, camonsertib can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section [A13–4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A13–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in [Table A13-5](#). These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

In case a participant experiences any of the adverse events presented below, which are less likely to be caused by camonsertib based on its mechanism of action, investigators should use their medical judgment to suspend camonsertib dosing or to continue dosing at a reduced dose, and/or implement supportive care as per local guidelines. Thorough monitoring of participants is recommended until the toxicity resolves. The decision to re-challenge participants should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

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Table A13-5 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo+Camon Arm*

Event	Action to Be Taken
Hematologic events (anemia, neutropenia, thrombocytopenia, or leukopenia)	
General guidance	<ul style="list-style-type: none"> • General guidance for managing hematologic events of all grades is provided below, followed by <i>grade-specific</i> management guidelines. <ul style="list-style-type: none"> – Supportive treatment to alleviate hematologic toxicity is permitted per investigator judgment and institutional standards. <i>Transfusions (including RBC and platelet transfusion) and hematopoietic growth factors are permitted to support management of hematologic toxicities at any occurrence per local standard of care and investigator judgment. Prophylactic transfusions and growth factors are not required.</i> – Weekly monitoring of blood counts is required per protocol (with additional testing per clinical judgment) during the first cycle of treatment <i>and</i> with at least two blood counts obtained in subsequent cycles (with additional testing as clinically indicated in the case of hematologic toxicity) up to Cycle 3, then from Cycle 4 at the start of each cycle and per clinical judgment. <i>In case of any hematologic toxicity, (adverse events) weekly monitoring of blood count is required until the adverse event resolves.</i> Protocol dose modification guidance (including interruption, delay, and dose adjustment) is to be followed. – Treatment interruption is advised upon onset of anemia (as per recommendations below), to avoid further deepening of the anemia and the need for <i>transfusions</i>. – Reactive measures implemented to minimize adverse clinical outcome due to neutropenia, taking into account known risk factors for febrile neutropenia per international guidelines, including use of growth factors and prophylactic antibiotics for Grade 3 or 4 neutropenia. – Measures to minimize adverse outcome of thrombocytopenia include platelet transfusion per investigator judgment and institutional standard procedure, and laboratory studies to evaluate any concurrent coagulopathy.

Appendix 13: Study Details Specific to Atezo+Camon Arm

Table A13-5 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo + Camon Arm (cont.)*

Event	Action to Be Taken
Hematologic events (anemia, neutropenia, thrombocytopenia, or leukopenia) (cont.)	
Grade 2	<ul style="list-style-type: none"> • Continue atezolizumab. • Withhold camonsertib and implement supportive care per local guidelines. • Monitor weekly until recovery to at least Grade 1. • If recovered to a Grade ≤ 1 or baseline within 14 days, treatment can resume at the same dose level for the first occurrence of the event. • For a subsequent Grade 2 event or events that did not resolve according to above guidance, dose/schedule of camonsertib should be adjusted (refer to Table A13-4). • Dose interruption caused by any Grade ≥ 2 toxicities lasting longer than 21 days will result in study drug discontinuation.
Grade ≥ 3	<ul style="list-style-type: none"> • Continue atezolizumab. • Withhold camonsertib and implement supportive care per local guidelines. <p>First occurrence:</p> <ul style="list-style-type: none"> • Monitor weekly until recovery to Grade ≤ 1 or baseline. • If recovered to Grade ≤ 1 or baseline, then adjust camonsertib dose/schedule (refer to Table A13-4). <ul style="list-style-type: none"> – If further dose adjustment is not possible, treatment with camonsertib should be discontinued. • Dose interruption caused by any Grade ≥ 3 toxicities lasting longer than 21 days will result in study drug discontinuation. The Medical Monitor is available to advise as needed. <p>Second occurrence (abnormality of the same hematologic parameter):</p> <ul style="list-style-type: none"> • Monitor weekly until recovery to Grade ≤ 1 or baseline. • If recovered to Grade ≤ 1 or baseline, then <i>adjust</i> camonsertib dose/schedule as per Table A13-4. <ul style="list-style-type: none"> – If further dose adjustment change is not possible, treatment with camonsertib should be discontinued.

Appendix 13: Study Details Specific to Atezo + Camon Arm

Table A13-5 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo + Camon Arm (cont.)*

Event	Action to Be Taken
Hematologic events (anemia, neutropenia, thrombocytopenia, or leukopenia) (cont.)	
Grade ≥ 3 (cont.)	<ul style="list-style-type: none"> If not recovered to Grade ≤ 1 or baseline within 21 days treatment with camonsertib should be discontinued. The Medical Monitor is available to advise as needed. <p>Third occurrence (abnormality of the same hematologic parameter):</p> <ul style="list-style-type: none"> Discontinue treatment with camonsertib and implement supportive care per local guidelines.
Nausea, vomiting, and diarrhea	
General guidance	<ul style="list-style-type: none"> No routine prophylactic antiemetics or premedications are required; however, these medications may be administered for symptoms when they occur and may be given prophylactically if needed.
Nausea, vomiting, and diarrhea, Grade 1	<ul style="list-style-type: none"> <i>Continue atezolizumab.</i> Continue camonsertib. Implement supportive care per local guidelines.
Nausea, vomiting, and diarrhea, Grade 2	<ul style="list-style-type: none"> <i>Continue atezolizumab.</i> Continue camonsertib as per investigator's discretion. Implement supportive care per local guidelines.
Nausea, vomiting, and diarrhea, Grade 3	<ul style="list-style-type: none"> <i>Continue atezolizumab.</i> Withhold camonsertib until toxicity resolves to Grade ≤ 1 (or baseline). Implement supportive care per local guidelines. If toxicity persists at Grade 3 for ≤ 3 days or resolves to Grade ≤ 1 (or baseline) within a week, resume camonsertib at the same dose level and recheck toxicity level within a week of resuming treatment. If toxicity persists at Grade 3 for > 3 days after maximal prophylactic and supportive care or resolves to Grade ≤ 1 (or baseline) in > 7 days, with or without treatment, adjust camonsertib dose/schedule (refer to Table A13-4).

Appendix 13: Study Details Specific to Atezo + Camon Arm

Table A13-5 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo + Camon Arm (cont.)*

Event	Action to Be Taken
Nausea, vomiting, and diarrhea (cont.)	
Nausea, vomiting, and diarrhea, Grade 3 (cont.)	<ul style="list-style-type: none"> If further dose adjustment is not possible, treatment with camonsertib should be discontinued.
Nausea, vomiting, and diarrhea, Grade 4	<ul style="list-style-type: none"> Continue atezolizumab. Withhold camonsertib until toxicity resolves to Grade ≤ 1 (or baseline). Implement supportive care per local guidelines. Adjust camonsertib dose/schedule upon resumption of treatment irrespective of the duration of event (<i>refer to Table A13-4</i>). If further dose adjustment is not possible, treatment with camonsertib should be discontinued.
QT/QTc interval prolongation	
General guidance	<ul style="list-style-type: none"> Camonsertib should be discontinued in participants who develop any of the following, unless there is a clear alternative cause for the changes: <ul style="list-style-type: none"> Sustained (at least two ECG measurements >30 minutes apart) QTcF that is >500 ms and >60 ms longer than the baseline value Sustained absolute QTcF that is >515 ms An episode of torsades de pointes or a new ECG finding of clinical concern
Management guidelines for other adverse events while receiving camonsertib	
Grade 1 or 2	<ul style="list-style-type: none"> Continue atezolizumab and camonsertib.
Grade 3	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold camonsertib until toxicity resolves to Grade ≤ 1 (or baseline). Implement supportive care per local guidelines.

Appendix 13: Study Details Specific to Atezo + Camon Arm

Table A13-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Camon Arm (cont.)

Event	Action to Be Taken
<i>Management guidelines for other adverse events while receiving camonsertib (cont.)</i>	
Grade 3 (cont.)	<p>First occurrence:</p> <ul style="list-style-type: none"> • If toxicity resolves to Grade ≤ 1 (or baseline) within a week, resume camonsertib at the same dose level and recheck toxicity level within a week. • If toxicity does not resolve to Grade ≤ 1 (or baseline) within a week, adjust camonsertib dose/schedule (refer to Table A13-4). Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed. <ul style="list-style-type: none"> – If further dose adjustment is not possible, treatment with camonsertib should be discontinued. <p>Second occurrence:</p> <ul style="list-style-type: none"> • If toxicity resolves to Grade ≤ 1 (or baseline), adjust camonsertib dose/schedule (refer to Table A13-4). Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed. <ul style="list-style-type: none"> – If further dose adjustment is not possible, treatment with camonsertib should be discontinued. • If toxicity does not resolve to Grade ≤ 1 (or baseline) within 21 days, treatment with camonsertib should be discontinued.
Grade 4	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Withhold camonsertib until toxicity resolves to Grade ≤ 1 (or baseline). • Implement supportive care per local guidelines. • If toxicity resolves to Grade ≤ 1 (or baseline), adjust camonsertib dose/schedule (refer to Table A13-4). Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed. <ul style="list-style-type: none"> – If further dose adjustment is not possible, treatment with camonsertib should be discontinued. • If toxicity does not resolve to Grade ≤ 1 (or baseline) within 21 days treatment with camonsertib should be discontinued.

Appendix 13: Study Details Specific to Atezo + Camon Arm

Table A13-5 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo + Camon Arm (cont.)*

Event	Action to Be Taken
Pulmonary events including pneumonitis	
<i>General guidance</i>	<ul style="list-style-type: none"> • All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.
Pulmonary event, Grade 1	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue camonsertib as per investigator's discretion.
Pulmonary event, Grade 2	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue camonsertib as per investigator's discretion.
Pulmonary event, Grade 3 or 4	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Hepatic events	
<i>Hepatic event, Grade 1</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue camonsertib as per investigator's discretion. • Implement supportive care as per investigator's discretion.
<i>Hepatic event, Grade 2</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue camonsertib as per investigator's discretion. • Implement supportive care as per investigator's discretion.

Appendix 13: Study Details Specific to Atezo + Camon Arm

Table A13-5 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo + Camon Arm (cont.)*

Event	Action to Be Taken
Hepatic events (cont.)	
<i>Hepatic event, Grade 3 or 4</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • For camonsertib, interrupt camonsertib until toxicity resolves to Grade ≤ 1 (or baseline). If toxicity resolves to Grade ≤ 1 (or baseline), treatment can be resumed at lower dose (refer to Table A13-4). If further dose adjustment is not possible, treatment with camonsertib should be discontinued. If toxicity persists at Grade 3 for > 7 days and does not resolve to Grade ≤ 1 or baseline within 21 days, discontinue treatment with camonsertib. • Patients with an elevation of AST/ALT $\geq 3 \times$ ULN in conjunction with a bilirubin $\geq 2 \times$ ULN may remain in the study only if a correctable, nondrug-related cause of the liver test evaluations can be documented; otherwise, the patient must be discontinued from the study.
Gastrointestinal events	
<i>Colitis, Grade 1</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue camonsertib as per investigator's discretion.
<i>Colitis, Grade 2</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue camonsertib as per investigator's discretion.
<i>Colitis, Grade 3</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Appendix 13: Study Details Specific to Atezo+Camon Arm

Table A13-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in *Atezo+Camon Arm (cont.)*

Event	Action to Be Taken
Gastrointestinal events (cont.)	
<i>Colitis, Grade 4</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Endocrine events	
Asymptomatic hypothyroidism	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue camonsertib as per investigator's discretion.
Symptomatic hypothyroidism	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue camonsertib as per investigator's discretion.
Asymptomatic hyperthyroidism	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue camonsertib as per investigator's discretion.
Symptomatic hyperthyroidism	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue camonsertib as per investigator's discretion.
Symptomatic adrenal insufficiency, Grade 2	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue camonsertib as per investigator's discretion.

Appendix 13: Study Details Specific to Atezo + Camon Arm

Table A13-5 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo + Camon Arm (cont.)*

Event	Action to Be Taken
Endocrine events (cont.)	
Symptomatic adrenal insufficiency, Grade 3 or 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Hyperglycemia, Grade 1 or 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue camonsertib as per investigator's discretion.
Hyperglycemia, Grade 3 or 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Hypophysitis (pan-hypopituitarism), Grade 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue camonsertib as per investigator's discretion.
Hypophysitis (pan-hypopituitarism), Grade 3	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Appendix 13: Study Details Specific to Atezo + Camon Arm

Table A13-5 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo + Camon Arm (cont.)*

Event	Action to Be Taken
Endocrine events (cont.)	
Hypophysitis (pan-hypopituitarism), Grade 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Ocular events	
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 1	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in in Appendix 6. • Continue camonsertib as per investigator's discretion.
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 2	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in in Appendix 6. • Continue camonsertib as per investigator's discretion.
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 3 or 4	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in in Appendix 6. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Cardiac events	
Immune-mediated cardiac events	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in in Appendix 6. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Appendix 13: Study Details Specific to Atezo + Camon Arm

Table A13-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Camon Arm (cont.)

Event	Action to Be Taken
<i>IRRs, CRS, anaphylaxis, and hypersensitivity reaction</i>	
<i>General guidance</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue atezolizumab. • Continue camonsertib as per investigator's discretion.
<i>Pancreatic events</i>	
<i>Amylase and/or lipase elevation, Grade 3 or 4</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Pancreatitis, Grade 2–4</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • For Grade 2 events, camonsertib may be continued as per investigator's discretion. • For Grade ≥ 3 events, for camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Dermatologic events</i>	
<i>General guidance</i>	<ul style="list-style-type: none"> • A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.
<i>Dermatologic event, Grade 1 or 2</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue camonsertib as per investigator's discretion.

Appendix 13: Study Details Specific to Atezo + Camon Arm

Table A13-5 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo + Camon Arm (cont.)*

Event	Action to Be Taken
<i>Dermatologic events (cont.)</i>	
<i>Dermatologic event, Grade 3</i>	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Dermatologic event, Grade 4</i>	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Stevens-Johnson syndrome or toxic epidermal necrolysis, any grade</i>	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Atezolizumab-related events not described above	
Grade 1 or 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue camonsertib at investigator's discretion.
Grade 3	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Appendix 13: Study Details Specific to Atezo+ Camon Arm

Table A13-5 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo + Camon Arm (cont.)*

Event	Action to Be Taken
Atezolizumab-related <i>events</i> not described above (cont.)	
Grade 4	<ul style="list-style-type: none">• Follow guidelines for atezolizumab in Appendix 6.• For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above.• Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Atezo = atezolizumab; Camon = camonsertib; CRS = cytokine release syndrome; IRR = infusion related reaction; QTcF = QT interval corrected through use of Fridericia's formula; ULN = upper limit of normal.

**A13–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR
ATEZO+CAMON ARM (IMMEDIATELY REPORTABLE
TO THE SPONSOR)**

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo+Camon arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7).
- Suspected transmission of an infectious agent by the study treatment, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 × upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

Appendix 13: Study Details Specific to Atezo+ Camon Arm

- Leukemias
- Myelodysplastic syndrome (MDS)
- Grade ≥ 3 hematologic toxicities
- Any grade febrile neutropenia or neutropenic sepsis
- Grade ≥ 3 dyspnea
- Myelitis
- Facial paresis

A13–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+CAMON ARM

A13–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab and 6 months after the final dose of camonsertib. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue atezolizumab and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A13–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the *final* dose of camonsertib. The investigator should report the pregnancy on the Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to docetaxel. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant

partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A13–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A13–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

Appendix 13: Study Details Specific to Atezo+Camon Arm

A13-6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+CAMON ARM

Table A13-6 Schedule of Activities for Atezo+Camon Arm

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-day cycles) ^a						Stage 2 Screen. (see Appendix 2) ^c or Treat. Discon. ^d (see below)	Follow- Up ^d Every 3 Months (± 7 days)
		Cycle 1 ^b			Cycles 2–3		Cycles ≥4		
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available							
Vital signs ^e		x	x	x	x	x	x	x	
Weight ^f		x			x		x	x	
Complete physical examination ^g								x	
Limited physical examination ^{f, h}		x	x	x	x	x	x		
ECOG Performance Status ^f		x			x		x	x	
ECG ^{f, i}		x			x ⁱ				
Hematology ^j		x ^k	x	x	x	x	x	x	
Chemistry ^l		x ^k			x		x	x	
Coagulation (INR and aPTT)		x ^k			x		x	x	
TSH, free T3 (or total T3), free T4 ^m		x ^k						x	
Pregnancy test ⁿ		x ^k			x		x	x	x
Urinalysis ^o		Perform as clinically indicated							

Appendix 13: Study Details Specific to Atezo+Camon Arm

Table A13-6 Schedule of Activities for Atezo+Camon Arm (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-day cycles) ^a					Stage 2 Screen. (see Appendix 2) ^c or Treat. Discon. ^d (see below)	Follow- Up ^d Every 3 Months (± 7 days)
		Cycle 1 ^b	Cycles 2–3		Cycles ≥ 4			
Serum autoantibody sample ^p	See Appendix 2	Perform if a patient experiences a suspected immune-mediated adverse event						
PK samples		Refer to Table A13-7 .						
ADA samples		Refer to Table A13-7 .						
Biomarker samples		Refer to Table A13-7 .						
Blood sample for RBR (optional) ^q		x						
Tumor biopsy		x ^r						
Tumor biopsy (optional)		x ^s						
Tumor response assessments		x ^{t, u, v}						
Concomitant medications ^w		x	x	x	x	x	x	
Adverse events ^x		x	x	x	x	x	x ^x	x ^x
Atezolizumab administration ^{y, z}		x			x		x	
Dispense camonsertib ^{y, aa}		x			x		x	
Survival follow-up and anti-cancer treatment								x ^{bb}

Appendix 13: Study Details Specific to Atezo+Camon Arm

Table A13-6 Schedule of Activities for Atezo+Camon Arm (cont.)

ADA=anti-drug antibody; Atezo=atezolizumab; CT=computed tomography; Discon. = discontinuation; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; NGS=next generation sequencing; PK=pharmacokinetic; QTcF=QT interval corrected through use of Fridericia's formula; RBR=Research Biosample Repository; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen. = screening; T3=triiodothyronine; T4=thyroxine; Treat. = treatment; TSH=thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

- ^a If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. The Medical Monitor is available to advise as needed.
- ^b It is recommended that treatment be initiated no later than 7 days after randomization.
- ^c Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) or unacceptable toxicity to camonsertib will be given the option of receiving a different treatment combination in Stage 2 of the study (as outlined in Section 3.1.4) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.
- ^d Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the *final* dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments.
- ^e Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (\pm 5) minutes during and 30 (\pm 10) minutes after the infusion. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (\pm 10) minutes after the infusion.
- ^f Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^g Physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^h Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Appendix 13: Study Details Specific to Atezo+Camon Arm

Table A13-6 Schedule of Activities for Atezo+Camon Arm (cont.)

- ⁱ *Triplicate ECG should be performed at baseline prior to receiving study treatment on Day 1 of Cycle 1. Subsequently, single ECGs should be performed on Day 1 of odd-numbered cycles for the first 15 cycles of treatment (i.e., Cycles 3, 5, 7, 9, 11, 13 and 15). Subsequently, ECGs can be performed every 3 months. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording. If at a particular timepoint (if applicable) the mean QTcF is > 500 ms and/or > 60 ms longer than the baseline value, another ECG must be recorded more than 30 minutes apart to confirm the QTcF prolongation, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard of care treatment may be instituted per the discretion of the investigator. Additional unscheduled ECGs (triplicate or single) should be performed if clinically indicated.*
- ^j Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, reticulocytes, other cells). If clinically indicated, *a more frequent hematological testing may be required beyond Cycle 1.*
- ^k If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.
- ^l Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, direct bilirubin, ALP, ALT, and AST. Amylase and lipase will be included on Day 1 of each treatment cycle.
- ^m TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).
- ⁿ All women of childbearing potential will have a urine or serum pregnancy test performed at specified visits during treatment and at 3 months and 6 months after the *final* dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^o Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ^p Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Serum samples collected for the assessment of PK, ADAs, or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment, may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.
- ^q Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

Appendix 13: Study Details Specific to Atezo+Camon Arm

Table A13-6 Schedule of Activities for Atezo+Camon Arm (cont.)

- ^r Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see Section 3.1.2) will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible). See Section 4.5.6 for tissue sample requirements.
- ^s Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation, if deemed clinically feasible and may undergo additional on-treatment biopsies at any other time during Stage 1 or Stage 2 at the investigator's discretion.
- ^t Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of atezolizumab-treated patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.
- ^u All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).
- ^v For patients who undergo screening for Stage 2: Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.
- ^w Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

Appendix 13: Study Details Specific to Atezo+Camon Arm

Table A13-6 Schedule of Activities for Atezo+Camon Arm (cont.)

- ^x After initiation of study treatment, all adverse events will be reported until 30 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.
- ^y Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).
- ^z Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial dose of atezolizumab will be delivered over 60 (\pm 15) minutes. Subsequent infusions will be delivered over 30 (\pm 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (\pm 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Refer to Section A13–4.1.2.1 for details on atezolizumab infusions (including measurement of vital signs).
- ^{aa} Camonsertib will be self-administered by patients orally at home (except on clinic days) at a dose of [REDACTED] mg daily (QD; four [REDACTED] mg capsules per day) for [REDACTED] consecutive days per week followed by [REDACTED] off-treatment days of each 21-day treatment cycle (Days 1–3 and Days 8–10). The cycle visit Day 1 should remain on schedule as planned starting from actual Day 1 of Cycle 1. Day 1 of every cycle is independent of missed doses or dose delays. Camonsertib should be taken in the morning at approximately the same time each day. Cycle dosing must start on either Monday, Tuesday, or Wednesday if unable to accommodate weekend visits and should be taken on the same consecutive days each week. On clinic visit days, patients should take their tablets in the clinic. To assess patient compliance with self-administration of camonsertib, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.
- ^{bb} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Appendix 13: Study Details Specific to Atezo + Camon Arm

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Appendix 13: Study Details Specific to Atezo + Camon Arm

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Appendix 14

Study Details Specific to Atezo+Bev+Camon Arm

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A14-1 BACKGROUND ON ATEZO+BEV+CAMON ARM

A14-1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, myocarditis, and nephritis, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma (in the European Union), non-small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer (in the European Union), hepatocellular carcinoma (HCC), melanoma (in the United States), and alveolar soft part sarcoma (in the United States).

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A14-1.2 BACKGROUND ON CAMONSERTIB

Camonsertib is a highly potent and selective ATR inhibitor (ATRi) as demonstrated in biochemical and cell-based assays. Camonsertib demonstrates efficacy in several xenograft models of cancer as a single agent. Pharmacokinetic (PK) and pharmacodynamic marker analysis from tumor xenografts demonstrates target engagement and a dose-responsive increase in double-strand DNA breaks leading to tumor cell death in vivo.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Refer to the Camonsertib Investigator's Brochure for details on nonclinical and clinical studies.

A14-1.3 BACKGROUND ON BEVACIZUMAB

Bevacizumab is a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF) that recognizes all isoforms of VEGF. It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor environment. Additional anti-tumor activity may be on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).

Bevacizumab has been tested in Phase II and III studies in a variety of solid tumors in combination with chemotherapy. Bevacizumab is registered in over 40 countries worldwide for the first-line treatment of metastatic colorectal cancer (CRC) in combination with chemotherapy, as second-line CRC treatment, and first-line treatment of advanced NSCLC, metastatic breast cancer, advanced renal cell carcinoma (RCC), ovarian cancer, and glioblastoma (Reck and Crinò 2009).

In NSCLC, the Phase II/III Study E4599 showed that the addition of bevacizumab (15 mg/kg every 3 weeks [Q3W]) to the paclitaxel and carboplatin regimen led to a clinically relevant and statistically significant prolongation of overall survival ([OS] primary endpoint) compared with patients who were treated with paclitaxel and carboplatin alone (hazard ratio [HR]=0.80; 95% CI: 0.69 to 0.93; $p=0.003$; Kaplan-Meier [KM]-estimated median: 12.3 vs. 10.3 months). The OS benefit was supported by the results of progression-free survival (PFS) (HR=0.65; 95% CI: 0.56 to 0.76; KM-estimated median: 6.4 vs. 4.8 months) and response rate (29.0% vs. 12.9%).

In addition, data from the protocol-defined final PFS (primary efficacy parameter) analysis of Study BO17704 (AVAIL; Roche Report No. 1023798) showed that the addition of bevacizumab (7.5 or 15 mg/kg Q3W) to cisplatin/gemcitabine chemotherapy resulted in a clinically relevant and statistically significant improvement in PFS (bevacizumab 7.5 mg/kg: HR=0.75; 95% CI: 0.62 to 0.91; $p=0.0026$; KM-estimated median PFS: 6.7 vs. 8.1 months) (bevacizumab 15 mg/kg: HR=0.82; 95% CI: 0.68 to 0.98; $p=0.0301$; KM-estimated median PFS: 6.5 vs. 6.1 months). Objective response rate (ORR) was also significantly increased in both bevacizumab-containing arms (7.5 mg/kg: 34.1% vs. 20.1%; bevacizumab 15 mg/kg: 30.4% vs. 20.1%).

Bevacizumab is currently being tested in combination with atezolizumab across different indications in Phase I, II, and III clinical studies. Atezolizumab plus bevacizumab has been approved as the first-line standard of care for patients with metastatic HCC.

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Refer to the Bevacizumab Investigator's Brochure for details on nonclinical and clinical studies.

A14-2 RATIONALE FOR ATEZO+BEV+CAMON ARM

A14-2.1 THE PD-L1 PATHWAY

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

A14-2.2 DNA DAMAGE RESPONSE IN CANCER

Research in the DNA damage response (DDR) area suggests that tens of thousands of chemical and physical DNA lesions occur in every cell each day (Lindahl and Barnes 2000). To thwart the DNA damage threat, cells have evolved into a complex network of proteins, collectively named the DDR. The DDR is responsible for coordinating the

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

early detection of DNA damage and signaling this to cell cycle checkpoints and DNA repair pathways, pausing the cell cycle to initiate repair or triggering cell death if damage is too substantial. The DDR is, therefore, key to ensuring overall genome stability and cell viability (Bradbury et al. 2020).

Genomic instability is integral to cancer development. Oncogenic activation causes cells to divide uncontrollably, leading to rapid DNA replication that is prone to mistakes (Halazonetis et al. 2008). At the same time, many cancers harbor defects in certain DDR pathways leading to faulty DNA repair or the dependence of tumor cells to utilize alternative repair mechanisms (Kelley et al. 2014).

Cancer-specific DNA repair defects present an important therapeutic opportunity. One can capitalize on these aberrations either by utilizing a chemical agent causing DNA damage that the tumor is unable to repair or by inhibiting the alternative DNA repair pathways that the cancer cells require for survival. In both cases, normal, healthy cells are less affected by the treatment. This forms the basis of the synthetic lethality concept (Kelley et al. 2014; Yap et al. 2019). Early nonclinical data demonstrated the synthetic lethality between breast cancer (BRCA) genetic defects and pharmacologic poly adenosine diphosphate-ribose polymerase (PARP) inhibition, suggesting that there may be monotherapy activity with this class of agents and supporting the early trial testing of this molecularly driven approach. Beyond PARP inhibitors, there is now a large armamentarium of potent and relatively selective inhibitors in clinical trial testing against key targets involved in the DDR, including ATR, ATM, CHK1), and WEE1.

A14-2.3 ATR

ATR belongs to a family of PIKKs that also include the ATM and DNA-PK (Blackford and Jackson 2017). All three kinases are involved in the DDR; ATR responds primarily to long single-stranded DNA (ssDNA) lesions, while ATM and DNA-PK respond to DNA double-strand breaks.

ATR is recruited to blocked or damaged DNA replication forks as ssDNA is created on the replication fork by uncoupling of the replicative helicase from the stalled DNA polymerase. This ssDNA is first coated by replication protein A, which subsequently recruits ATR and the regulatory partner ATRIP to the ssDNA-double-stranded DNA (dsDNA) junction. The ATR/ATRIP complex then interacts with additional regulators, including RAD9, RAD1, and HUS1 (the 9-1-1 complex), and RAD17. Finally, ATR is fully activated upon a conformational change induced by recruitment of activator proteins such as DNA topoisomerase II-binding protein 1 or Ewing tumor-associated antigen 1 (Saldivar et al. 2017).

ATR plays a fundamental role in the cell cycle by protecting against replication stress (e.g., induced by cisplatin and/or other platinating agents). The ATR pathway counteracts replication stress in at least two ways. First, ATR prevents the breakage or collapse of stalled replication forks. ATR does so by modulating helicases that can remodel the structure of stalled forks to prevent their cleavage, promoting replication fork repair by homologous recombination factors such as BRCA2 and PALB2, controlling replication initiation, and maintaining a sufficient supply of free nucleotides (Lecona and Fernandez-Capetillo 2018). At the same time, ATR acts as a cell cycle checkpoint regulator through an activating phosphorylation of the CHK1 on Ser-317 and Ser-345. Once activated, CHK1 phosphorylates and inactivates the cell division cycle 25 (CDC25) phosphatases A, B, and C, leading to their proteasomal degradation. Upon CDC25 degradation, CDK2 activity is decreased and activation of CDK1/cyclin B kinases is abolished, leading to cell cycle arrest in S-phase or at the G2/M boundary (Busino et al. 2004).

A14-2.3.1 Immune-Modulatory Effects of ATR

Recent research has revealed intrinsic links between the ATR-CHK1 pathway and innate immune signaling networks (Gasser et al. 2005). Increased ATR pathway signaling triggered by genotoxic stress and stalled DNA replication upregulates immunosuppressive PD-L1 on tumor cells mediated by signal transducer and activator of transcription (STAT)1- and STAT3-interferon (IFN) regulatory factor 1-related pathways. ATR pathway signaling also upregulates the expression of natural killer (NK) group 2D (NKG2D) cell surface ligands (NKG2DLs) (Gasser et al. 2005), which bind to NKG2D receptors on NK cells and activated CD8⁺ T cells, triggering degranulation and pro-inflammatory cytokine production. In turn, pharmacological inhibition of ATR can suppress NKG2DL upregulation (Gasser et al. 2005).

Furthermore, ATR mutations modulate the tumor immune microenvironment in melanoma models. When compared with ATR wild-type tumors, homozygous ATR-mutated melanoma tumors showed reduced numbers of infiltrating CD3⁺ T cells but a significant increase in infiltrating macrophages and B cells compared with ATR wild-type or hemizygous ATR-mutated tumors, as demonstrated on both flow cytometry and immunohistochemistry (IHC) (Chen et al. 2017). This ATR deficient state was associated with increased PD-L1, CD206, and arginase1 expression, along with downregulation of butyrophilin expression, suggesting a T cell-suppressed immune environment (Chen et al. 2017).

ATR has also been shown to mediate robust immunosuppressive effects in the context of radiation therapy (RT)-driven DNA damage and consequent arrest in the G2/M phase of the cell cycle (Rodriguez-Ruiz et al. 2020). It was demonstrated by Dillon et al., Feng et al., and Sheng et al., that pharmacologic ATRi's not only boost cGAS-signaling and consequent type I IFN responses (involving CCL5 and CXCL10) driven by RT (Dillon et al. 2019; Feng et al. 2020) but also enhance antigen presentation on major

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histocompatibility complex class I (MHC-I) molecules, ultimately favoring tumor infiltration by dendritic cells (DCs), repolarization of the tumor-associated macrophage (TAM) compartment toward an immunostimulatory profile, and T cell-dependent anti-cancer immunity (Dillon et al. 2019; Sheng et al. 2020).

A14-2.4 ANTI-VEGF CANCER TREATMENT

In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggested that VEGF may reduce lymphocyte adhesion to vessel walls in the tumor microenvironment, thus contributing to decreased immune cell recruitment to the tumor site (Bouzin et al. 2007). Mice exposed to pathophysiologic levels of VEGF exhibited impaired DC function, which could be restored by blockade of VEGF receptor 2 (Huang et al. 2007). In addition, VEGF recruits macrophages into the tumor microenvironment that have an M2 polarization state, which is typically involved in wound healing. These M2 TAMs ultimately help establish and maintain an immunosuppressive microenvironment (Chen and Mellman 2013). In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). Synergistic effects have also been observed in a clinical study combining an immune-modulatory antibody (anti-cytotoxic T lymphocyte-associated protein 4; ipilimumab) and bevacizumab: Hodi et al. (2010) described increased T-cell trafficking in post-treatment biopsies, as well as marked increases in central memory cells in peripheral blood in the majority of patients.

A14-2.5 RATIONALE FOR COMBINING ATEZOLIZUMAB WITH BEVACIZUMAB AND CAMONSERTIB IN CPI-EXPERIENCED PATIENTS WITH NSCLC



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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

A14-2.6 CLINICAL STUDIES WITH CAMONSERTIB

Clinical development is ongoing in patients with advanced solid tumors as per eligibility criteria for Phase I/IIa Study RP-3500-01 and Phase Ib/II Study RP-3500-03. RP-3500-03 is an open-label, Phase Ib/II study to investigate the combination of the ATRi RP-3500 with the PARPi niraparib or olaparib in patients with advanced solid tumors harboring specific deleterious mutations. For safety data from this study, refer to the most recent, effective version of Camonsertib Investigator's Brochure.

A14-2.6.1 Study RP-3500-01

RP-3500-01 (TRESR) is an exploratory modular, Phase I/IIa, first-in-human, multicenter, open-label, non-randomized, dose-escalation, and dose-expansion study of camonsertib administered orally as a single agent or in combination with talazoparib or gemcitabine in patients with advanced solid tumors. Patients are enrolled based on center-specific routine genomic and IHC tests able to detect alterations in genes associated with ATRi sensitivity. A recommended Phase II dose (RP2D) of 160 mg once a day (QD) (3 days on/4 days off schedule) was determined for camonsertib monotherapy.

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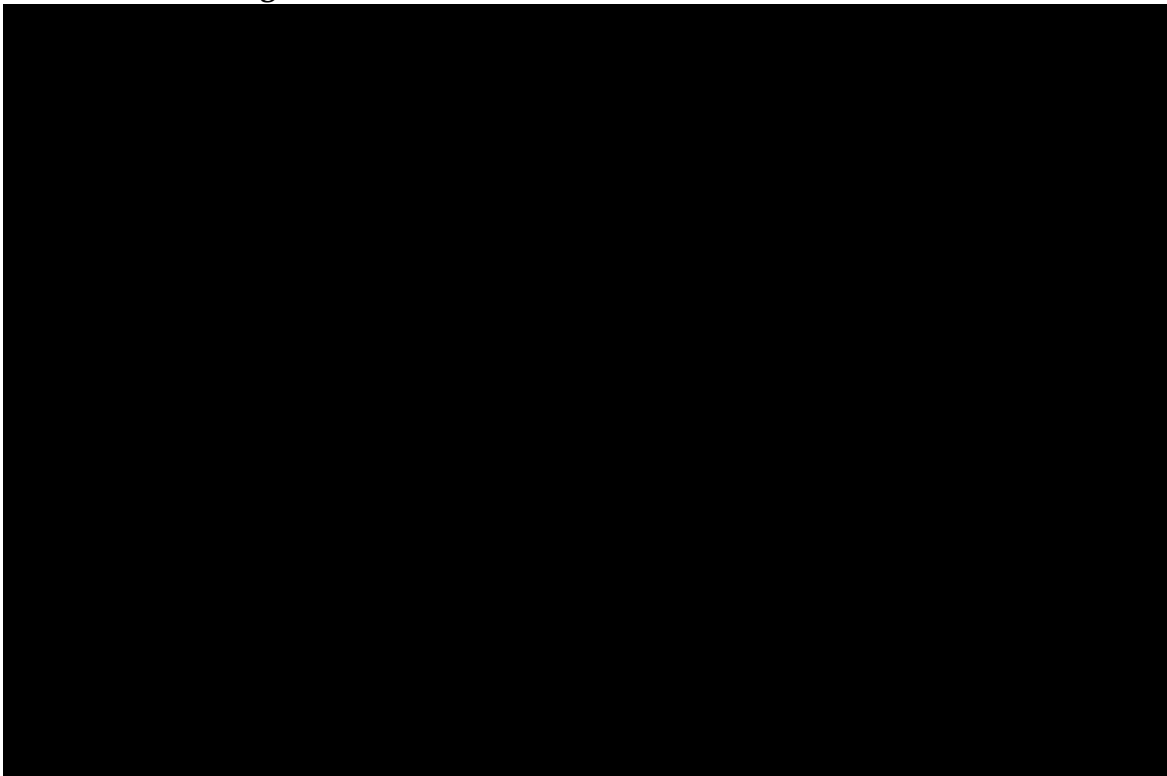
Study RP-3500-01 currently consists of the following modules:

- *Module 1 is the camonsertib monotherapy dose-escalation portion evaluating the safety, tolerability, pharmacokinetics, and food effect of camonsertib administered using two schedules. Module 1 subjects participated in a food-effect evaluation to assess potential differences in camonsertib exposures and absorption following a standard high-fat meal. Enrollment in Module 1 has been completed.*
- *Module 2 is evaluating the preliminary efficacy of camonsertib in patients with tumors harboring an ATRi sensitizing biomarker. Module 2 enrollment started once the RP2D and recommended dosing schedule for camonsertib monotherapy was determined in Module 1.*
- *Other active modules of this study are investigating camonsertib in combination with gemcitabine or PARPi.*

For camonsertib monotherapy, 149 patients have been treated in Module 1+Module 2. For safety data from this study, refer to the most recent, effective version of Camonsertib Investigator's Brochure.

The safety profile continues to be consistent with other drugs of the class. Refer to the Camonsertib Investigator's Brochure for details.

A14-2.6.2 Drug Interactions





A14-2.7 CLINICAL STUDIES OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB

Study GP28328 is an ongoing, Phase Ib, open-label, multicenter study combining atezolizumab (1200 mg Q3W) with bevacizumab (15 mg/kg Q3W) in patients with advanced solid tumors, with expansion arms for patients with RCC, metastatic CRC, gastric cancer, and ovarian cancer. Safety findings have been consistent with the known single-agent safety profiles for each drug; no new safety signals have been identified. The regimen has been well tolerated, and adverse events have been manageable. Another Phase Ib, open-label, multicenter study (GO30140) is investigating a similar dose of atezolizumab combined with bevacizumab in patients with HCC. In addition, this combination is being tested in a Phase II randomized study (WO29074) in which atezolizumab is administered as monotherapy or in combination with bevacizumab, compared with sunitinib, in patients with untreated advanced RCC.

In chemotherapy-naïve patients with Stage IV NSCLC, results from Phase III Study GO29436 (Impower150) have shown that atezolizumab in combination with carboplatin+paclitaxel and bevacizumab results in significantly longer OS compared with carboplatin+paclitaxel and bevacizumab alone (Socinski et al. 2018). For inoperable, locally advanced, or metastatic RCC, Phase III Study WO29637 (Immotion151) demonstrated improved PFS after treatment with the combination of atezolizumab plus bevacizumab compared with sunitinib treatment in treatment-naïve patients (Motzer et al. 2018). Phase Ib Study GO30140 in HCC first-line treatment found an ORR of 65% in 23 evaluable patients, across etiology, geography, baseline α -fetoprotein levels, and extrahepatic spread. The combination is currently being explored in a randomized Phase III study YO40245 (Imbrave150) versus sorafenib in first-line treatment for HCC (Stein et al. 2018). These are examples of clear synergy between atezolizumab and bevacizumab in different tumor types, which support further exploration of the combination in NSCLC.

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Detailed clinical study results for atezolizumab and bevacizumab can be found in the Atezolizumab Investigator's Brochure and the Bevacizumab Investigator's Brochure, respectively.

A14-2.8 BENEFIT-RISK ASSESSMENT

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The triplet combination of atezolizumab, camonsertib, and bevacizumab has not been investigated in the clinic, and although the risk of overlapping toxicities is low, a safety run-in period using a camonsertib dose of [REDACTED] mg will initially be investigated (see Sections [A14-3.2](#) and [A14-5.1.1](#) for details). Dosing at other dose levels/schedules will only proceed if camonsertib [REDACTED] mg is determined to be safe and well tolerated as described in Section [A14-3.2](#). Safety evaluations are planned at defined timepoints and throughout the treatment duration of this study arm in order to ensure patient safety.

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In summary, based on the available safety and efficacy data and the stringent exclusion criteria implemented in this study, the benefit-risk assessment is considered to be favorable with the applied risk-mitigation measures in place.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, refer to Section 1.4.

A14-3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+BEV+CAMON ARM

A14-3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab (Tecentriq® U.S. Prescribing Information).

A14-3.2 RATIONALE FOR CAMONSERTIB DOSE AND SCHEDULE

Non-clinical data indicated that maximizing the daily target coverage above the in vivo pCHK1 IC₈₀ using intermittent schedules of either [REDACTED] should lead to similar anti-tumor efficacy in human tumors. Based on correlation of circulating tumor DNA reductions at IC₈₀ coverage, the predictions from a preliminary population-PK model suggested a similar target coverage with QD or BID administration, and therefore QD dosing was selected. Preliminary clinical data suggested that doses above [REDACTED] mg daily were pharmacologically active, and [REDACTED]-mg doses were determined to be more appropriate to achieve better initial target coverage.

Based on the totality of the data, including manageable adverse events, a [REDACTED]-mg dose is considered to be the target dose in adults in order to reach relevant initial target coverage, while also considered tolerable from an adverse event profile perspective. The dose of [REDACTED] mg on Days 1–3 and Days 8–10 of a 21-day cycle was chosen over continuous dosing due to early data from the TRESR study indicating less events of Grade 3 hematologic toxicity while still maintaining similar levels of efficacy response.

In order to evaluate safety of the Atezo+Bev+Camon combination, an initial safety run-in period with a minimum of 6 patients will be implemented with an initial dose of camonsertib of [REDACTED] mg (D1–3 and D8–10 per 21-day cycle) prior to the target dose of [REDACTED] mg (refer to Section A14-5.1.1 for details). Only if the safety run-in period is completed and the camonsertib [REDACTED]-mg dose has been assessed as safe, the camonsertib dose will be increased to the target dose of [REDACTED] mg (D1–3 and D8–10 per 21-day cycle) to be investigated further.

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A further review of safety data will be conducted after a minimum of 6 patients treated with camonsertib [REDACTED] mg (D1–3, D8–10; Q21D) in combination with atezolizumab 1200 mg Q3W and bevacizumab 15 mg/kg Q3W have completed a safety evaluation, before additional patients can be enrolled in that arm (see Section A14-5.1.1). Stopping rules have been implemented for this arm to reduce any potential risk for the patients even further (see Section A14-5 for details).

After thorough review of the totality of safety data reported from the initial safety run-in period or beyond (see Section A14-5.2 for details), at any timepoint throughout the duration of treatment in this arm, if the Sponsor considers that the target dose of camonsertib is not suitable for this combination experimental arm, enrollment will proceed at the initial dose of [REDACTED] mg or at a lower dose/schedule change if applicable.

Camonsertib food effect has been evaluated at [REDACTED]-mg, [REDACTED]-mg, and [REDACTED]-mg doses. Despite a negative food effect on the pharmacokinetics, the camonsertib exposure difference between fed and fasted states is unlikely to impact the benefit–risk ratio of camonsertib; therefore, camonsertib can be given irrespective of food intake.

Based on emerging data (including, but not limited to, safety, tolerability, PK, and pharmacodynamic data), the Sponsor may modify the study treatment (camonsertib and/or partner agent[s]) dose or schedule (e.g., concomitant vs. sequential dosing or intermittent dosing).

A14-3.3 RATIONALE FOR BEVACIZUMAB DOSE AND SCHEDULE

Bevacizumab will be administered by infusion at a fixed dose of 15 mg/kg Q3W (15 mg/kg on Day 1 of each 21-day cycle), which is an approved dosage for bevacizumab (Avastin® U.S. Prescribing Information).

A14-4 MATERIALS AND METHODS SPECIFIC TO ATEZO+BEV+CAMON ARM

A14-4.1 TREATMENT IN ATEZO+BEV+CAMON ARM

A14-4.1.1 Formulation, Packaging, and Handling

A14-4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately [REDACTED] mL (1200 mg) of atezolizumab solution.

For information on the atezolizumab formulation, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

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A14-4.1.1.2 Camonsertib

The camonsertib drug product will be supplied by the Sponsor in the form of ■-mg capsules. The ■-mg capsule is an immediate-release solid dosage form for oral administration. The drug product contains the camonsertib drug substance blended with common pharmaceutical, compendial excipients and filled-in capsules. Study drug is manufactured, packaged, and labeled in accordance with relevant regional requirements and the principles of Good Manufacturing Practice. For additional information see the pharmacy manual and the Camonsertib Investigator's Brochure.

A14-4.1.1.3 Bevacizumab

The bevacizumab drug product will be supplied by the Sponsor as a sterile solution in a single-use, 4-mL or 16-mL, preservative-free glass vial. The 4-mL vial contains ■ mg of bevacizumab (■ mg/mL), and the 16-mL vial contains ■ mg of bevacizumab (■ mg/mL).

For information on the bevacizumab formulation, see the pharmacy manual and the Bevacizumab Investigator's Brochure.

A14-4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo+Bev+Camon arm will receive treatment as outlined in [Table A14-1](#) until unacceptable toxicity or loss of clinical benefit, as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details). It is recommended that treatment be initiated no later than 7 days after randomization; however, the first dose of study treatment should not occur within 3 days after a core biopsy or other surgical procedure.

Table A14-1 Treatment Regimen for Atezo+Bev+Camon Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none">Camonsertib ■ mg PO D1–3, D8–10; Q21D for patients enrolled for the safety run-in periodCamonsertib ■ mg PO D1–3, D8–10; Q21D for patients enrolled after the safety run-in periodAtezolizumab 1200 mg by IV infusion on Day 1 of each cycleBevacizumab 15 mg/kg by IV infusion on Day 1 of each cycle

Atezo = atezolizumab; Bev = bevacizumab; Camon = camonsertib; D = day; PO = by mouth, orally; Q21D = every 21 days.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

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Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12. No safety data related to overdosing of atezolizumab or camonsertib are available.

A14-4.1.2.1 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5. Atezolizumab infusions will be administered per the instructions outlined in Table A14-2.

Table A14-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
<ul style="list-style-type: none">No premedication is permitted prior to the atezolizumab infusion.Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion.Atezolizumab should be infused over 60 (\pm15) minutes.If clinically indicated, vital signs should be measured every 15 (\pm5) minutes during the infusion and at 30 (\pm10) minutes after the infusion.Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	<ul style="list-style-type: none">If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for subsequent doses at the discretion of the investigator.Vital signs should be measured within 60 minutes prior to the infusion.Atezolizumab should be infused over 30 (\pm10) minutes if the previous infusion was tolerated without an IRR or 60 (\pm15) minutes if the patient experienced an IRR with the previous infusion.If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (\pm10) minutes after the infusion.

IRR=infusion-related reaction.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A14-5.2.5.2. Atezolizumab treatment may be suspended for reasons other than

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toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A14–4.1.2.2 Camonsertib Administration

Camonsertib will be self-administered by patients orally at home (except on clinic days) at a target dose of [REDACTED] mg after the safety run-in period (for details about safety run-in, please see Section A14–5.1.1). Camonsertib is formulated in [REDACTED]-mg strength capsules. A treatment cycle consists of 3 weeks and will be given on Days 1–3 and Days 8–10 of every 21-day cycle. The cycle visit Day 1 should remain on schedule as planned starting from actual Day 1 of Cycle 1.

On clinic visit days, patients should take their capsules in the clinic prior to the atezolizumab infusion, as directed by site personnel.

Day 1 of every cycle is independent of missed doses or dose delays. Camonsertib should be orally self-administered with approximately 240 mL (8 ounces) of water. Patients will be initially instructed to take their camonsertib dose in the morning at approximately the same time each day. Cycle dosing must start on either Monday, Tuesday, or Wednesday if unable to accommodate weekend visits and should be taken on the same consecutive days each week.

Patients will swallow the study drug whole and will not manipulate or chew the study drug prior to swallowing. On clinic visit days, patients will be instructed to delay self-administration of their treatment dose and to take their study drug at the clinic.

Patients should be instructed that if they forget to take their dose at their usual time, they should take the missed dose as soon as possible on the day it was missed; however, there must be at least 8-hour interval between the missed dose and the next dose. If a dose is missed and the interval to the next dose is less than 8 hours, the missed dose should not be administered. If a patient vomits during or after taking camonsertib, re-dosing is not permitted until the next scheduled dose. To assess patient compliance with self-administration of camonsertib, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

At the end of the study, the Sponsor will provide instructions as to the disposition of any unused study drug.

Refer to the pharmacy manual and/or the Camonsertib Investigator's Brochure for information on handling, including preparation and storage, and accountability.

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Guidelines for camonsertib dose modification and treatment interruption or discontinuation because of toxicities are provided in Section [A14-5.2.5.2](#).

Camonsertib treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A14-4.1.2.3 Bevacizumab Administration

Bevacizumab will be administered by IV infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle. On Day 1 of each cycle, bevacizumab will be administered at least 5 minutes after completion of the atezolizumab infusion.

Administration of bevacizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#).

Bevacizumab infusions will be administered per the instructions outlined in [Table A14-3](#).

Table A14-3 Administration of First and Subsequent Bevacizumab Infusions

First Infusion	Subsequent Infusions
<ul style="list-style-type: none">• No premedication is permitted prior to the bevacizumab infusion.• Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) should be measured within 60 minutes prior to the infusion.• Bevacizumab should be infused over 90 (\pm 15) minutes.• Vital signs should be measured at the end of infusion and 2 (\pm 1) hours after the infusion.• Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	<ul style="list-style-type: none">• If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for subsequent doses at the discretion of the investigator.• Vital signs should be recorded within 60 minutes prior to the infusion.• Bevacizumab should be infused over 60 (\pm 10) minutes if the previous 90-minute infusion was tolerated without an IRR, or 90 (\pm 15) minutes if the patient experienced an IRR with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (\pm 5) minutes thereafter.• Vital signs should be measured within 30 minutes after completion of the infusion.

IRR=infusion-related reaction.

Guidelines for medical management of IRRs for bevacizumab are provided in Section [A14-5.2.5](#).

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No dose modification for bevacizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section [A14-5.2.5.2](#). Bevacizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A14-4.1.3 Stage 2 Treatment

Patients in Cohort 2, Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section [3.1.1](#)) or unacceptable toxicity related to atezolizumab will be given the option of receiving a different treatment combination during Stage 2, as outlined in [Table A14-4](#), provided they meet the eligibility criteria for Stage 2 (see Section [4.1](#)) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

**Table A14-4 Stage 2 Treatment Regimens Available for
Atezo+Bev+Camon Arm**

<i>Study Treatment</i>	<i>Appendix</i>
Atezo + Docetaxel	Appendix 16

Atezo = atezolizumab; Bev = bevacizumab; Camon = camonsertib.

Refer to [Appendix 16](#) for details specific to the atezolizumab plus docetaxel arm.

A14-4.2 CONCOMITANT THERAPY FOR ATEZO+BEV+ CAMON ARM

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

A14-4.2.1 Permitted Therapy for Atezo+Bev+Camon Arm

Patients are permitted to use the following therapies during the study:

- *Oral contraceptives with a failure rate of <1% per year*
- *Hormone-replacement therapy*
- *Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)*
- *Prophylactic antibiotic or anti-viral treatment administered according to institutional standards*
- *Inactivated vaccines (such as influenza and COVID-19)*
 - Live, attenuated vaccines are not permitted (see Section [A14-4.2.3](#)).*
- *Megestrol acetate administered as an appetite stimulant*
- *Mineralocorticoids (e.g., fludrocortisone)*
- *Corticosteroids administered for chronic obstructive pulmonary disease or asthma*
- *Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency*
- *Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer*
- *Bisphosphonate use, as recommended according to practice guidelines, as long as prescribed at least 28 days prior to enrollment. Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor use, as recommended according to practice guidelines, as long as prescribed at least 4 months before trial entry.*
- *Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:*

Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy with sufficient monitoring of hematologic parameters in place.

- *Radiotherapy to the brain as outlined below:*

Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain RT) provided that all of the criteria listed below are met.

- *The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.*
- *The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.*

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

- *Anticonvulsant therapy, if required, is administered at a stable dose.*

Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for the second and subsequent atezolizumab and bevacizumab infusions only, at the discretion of the investigator. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections [A14-4.2.2](#) and [A14-4.2.3](#)) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 -adrenergic agonists; see [Appendix 5](#)).

At this time there is no evidence on potential interactions of COVID-19 vaccines with camonsertib and/or bevacizumab. COVID-19 vaccines must be given in accordance with the approved/authorized vaccine label and official immunization guidance. The decision of administration of a COVID-19 vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

A14-4.2.2 Cautionary Therapy for Atezo+Bev+Camon Arm

A14-4.2.2.1 Corticosteroids and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may be administered at the discretion of the investigator. The Medical Monitor is available to advise as needed.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to [Appendix 6](#) for details).

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The above list of cautionary medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor is available to advise as needed if questions arise regarding medications not listed above.

A14-4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential DDIs are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A14-4.2.3), and having no impact on CYP3A may be used during the study at the discretion of the investigator.

A14-4.2.2.3 Bisphosphonates

Osteonecrosis of the jaw has been reported in patients receiving bevacizumab, mainly in combination with bisphosphonates. Thus, caution must be exercised in using bevacizumab in patients receiving concomitant bisphosphonates.

A14-4.2.3 Prohibited Therapy for Atezo+Bev+Camon Arm

Based on in vitro experiments, camonsertib was shown to be a substrate of CYP2C8, CYP4A4, and UGTs (mainly UGT1A4). Camonsertib is a substrate of both multidrug resistance transporter (MDR1) and BCRP. The risk of clinically significant DDIs with inducers or inhibitors of CYP2C8, CYP3A4, or UGTs is currently unknown. Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority-approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A14-4.2.1.*
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.*
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the final dose of atezolizumab.*

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- Systemic immunostimulatory agents (including, but not limited to, IFNs and interleukin [IL]-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Antithrombotic treatment with aspirin (>325 mg/day) or clopidogrel (>75 mg/day) or equivalent is prohibited.
- Concomitant treatment with any medication that is known to prolong the QT interval and/or cause torsades de pointes is not permitted (see [Appendix 21](#)). If a patient requires use of any of these medications during the study, the patient must be removed from study.
- Strong BCRP inhibitors, or strong inhibitors or inducers of P-gp and CYP3A, including food and herbal sources (see a list of examples in [Appendix 22](#)) must be avoided within 28 days (or within five times the elimination half-life, whichever is longer) prior to initiating treatment with camonsertib and during treatment.

A14-4.2.4 Other Study Restrictions

Patients who are blood donors should not donate blood during the study and for 90 days after the final dose of study treatment.

Patients should maintain a normal diet unless modifications are required to manage an adverse event, such as diarrhea, nausea, or vomiting.

Camonsertib may pose a phototoxicity risk based on data from preclinical studies; therefore, patients are advised to take measures, such as use of sunscreen, wearing of hats and long-sleeve garments, and minimizing exposure to ultraviolet light.

A14-4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO+BEV+CAMON ARM

Contraception requirements for women and men in the Atezo+Bev+Camon arm are outlined below.

- Women of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraception, and refrain from donating eggs, as defined below:

Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 5 months after the final dose of atezolizumab and for 6 months after the final dose of camonsertib and bevacizumab. Women must refrain from donating eggs during this same period.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

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Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

Hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- *Men must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below:*

With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for 6 months after the final dose of camonsertib and bevacizumab. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of camonsertib and bevacizumab to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A14-5 ASSESSMENT OF SAFETY FOR ATEZO + BEV + CAMON ARM

A14-5.1 SAFETY PLAN FOR ATEZO+BEV+CAMON ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab, bevacizumab, and camonsertib in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections [A14-5.2.1](#), [A14-5.2.2](#), [A14-5.2.3](#), and [A14-5.2.4](#)). Guidelines for management of patients who experience specific adverse events are provided in Section [A14-5.2.5](#) and [Appendix 6](#).

Measures will be taken to ensure the safety of patients participating in this study, including an initial safety run-in period user a lower dose of camonsertib (for details see Section [A14-5.1.1](#)), a safety evaluation period once the initial safety run-in is completed, use of stringent inclusion and exclusion criteria, and close monitoring of patients during the study.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

A14-5.1.1 Initial Safety Run-In Period

To minimize the potential risk for patients and to evaluate safety of the Atezo+Bev+Camon combination, an initial safety run-in period with a minimum of 6 patients will be implemented with an initial dose of camonsertib of [REDACTED] mg (D1–3 and D8–10 per 21-day cycle) prior to escalating to the target dose of [REDACTED] mg. These patients enrolled for the safety run-in period must receive at least one dose of the assigned treatment (i.e., one dose of each agent for a given combination) and must complete at least one treatment cycle of safety follow-up (see Section 3.1.3).

Only if the safety run-in period is completed as described above and the camonsertib [REDACTED]-mg dose has been assessed as safe, in combination with atezolizumab and bevacizumab, then the camonsertib dose will be increased to the target dose of [REDACTED] mg (D1–3 and D8–10 per 21-day cycle) to be investigated further.

The Sponsor may also increase the initial [REDACTED]-mg dose of camonsertib in the first 6 patients who were enrolled in the initial safety run-in to the target dose of camonsertib as deemed appropriate. A further review of safety data will be conducted after a minimum of 6 patients treated with camonsertib target dose ([REDACTED] mg D1–3, D8–10; Q21D) in combination with atezolizumab and bevacizumab have completed a safety evaluation, before additional patients can be enrolled in that arm.

At any timepoint, after thorough review of the totality of safety data reported from the safety run-in period or beyond (see Sections A14-2.8, A14-3.2, and A14-5.2 for details), if the Sponsor considers that the target dose of camonsertib is not suitable for this combination with atezolizumab and bevacizumab, enrollment will proceed at the initial camonsertib dose of [REDACTED] mg or at a lower dose/schedule change if applicable.

A14-5.2 STOPPING RULES FOR ATEZO+BEV+CAMON ARM

To further minimize any potential risk for patients, stopping rules will be applied during the initial safety run-in period (minimum of 6 patients, camonsertib [REDACTED] mg QD PO D1–3, D8–10; Q21D), during the subsequent 6-patient safety evaluation for the target camonsertib dose ([REDACTED] mg QD PO D1–3, D8–10; Q21D), and at each Internal Monitoring Committee data cut, as described below.

If more than 30% of patients (with a minimum of 2 patients at a given camonsertib dose level, e.g., 2 of 2 patients, 2 of 3, ..., 2 of 6, 3 of 7, etc.) experience one or more of the following events that is considered to be related to study treatment, enrollment will be put on hold while the Sponsor evaluates the benefit–risk profile of Atezo+Bev+Camon:

- A non-hematologic treatment-related Grade 3 or 4 adverse event that does not improve (with or without corrective treatment) to Grade 1 or better within 2 weeks

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- *A hematologic treatment-related Grade 3 or 4 adverse event that does not improve to Grade 1 or better within 2 weeks or the event requires transfusion or hematopoietic growth factors*
- *A treatment-related adverse event that requires permanent discontinuation of study drug*
- *Death, except those that are incontrovertibly related to disease progression or extraneous causes such as accidents*

A14-5.2.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis. Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A14-5.2.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: GI perforations, hemorrhage, arterial thromboembolic events, fistulae, wound-healing complications, hypertension, venous thromboembolism, proteinuria, congestive heart failure, and posterior reversible encephalopathy syndrome.

Refer to Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for bevacizumab.

A14-5.2.3 Risks Associated with Camonsertib

Camonsertib has been associated with risks such as the following: hematologic toxicity including anemia, thrombocytopenia, and neutropenia, and non-hematologic toxicities including fatigue, nausea, diarrhea, and vomiting.

Camonsertib is still under clinical development and the safety profile is not yet fully known. Refer to the Camonsertib Investigator's Brochure for a description of anticipated safety risks for camonsertib.

A14-5.2.3.1 Hematologic Toxicities

The most common toxicity for camonsertib are hematologic toxicities, including anemia, neutropenia, and thrombocytopenia, which have been reported as related in >10% of patients who received camonsertib treatment for solid tumor indications. The most common treatment-related hematologic toxicity for camonsertib is anemia, which tends

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to appear following completion of the first 21-day cycle of treatment and improves and/or recovers when treatment is interrupted or stopped.

Grade 3 and 4 toxicities include anemia, neutropenia, thrombocytopenia. Hematologic toxicity has been manageable and reversible with dose interruption in most cases in the ongoing clinical studies.

Routine monitoring of blood counts is required per protocol (with additional testing per clinical judgment) during the entire duration of the study (refer to [Table A14-7](#) for more guidance).

A14-5.2.3.2 Non-Hematologic Toxicities

Fatigue, nausea, diarrhea, and vomiting are the most common treatment-related non-hematologic adverse events.

In general, most of these toxicities were low grade, manageable, and reversible. Symptomatic participants can be treated with antiemetic and/or antidiarrheal drugs as appropriate per investigator clinical judgment.

A14-5.2.3.3 Potential Teratogenicity/Genotoxicity

Camonsertib has been shown to be genotoxic via an aneugenic mechanism when studied in vitro using a micronucleus test. Additionally, in vivo studies have confirmed that camonsertib is genotoxic inducing micronuclei in peripheral erythrocytes. The positive genotoxic signal with camonsertib does not change the overall benefit–risk profile for the treatment of patients with advanced cancer.

No reproductive or teratogenicity studies in animals have been conducted with camonsertib.

For more details regarding the safety profile for camonsertib, refer to the Camonsertib Investigator’s Brochure.

See Section [A14-5.4](#) for information on the reporting requirements for pregnancies in patients receiving atezolizumab, camonsertib, and bevacizumab.

A14-5.2.3.4 Phototoxicity

Based on data from preclinical studies, camonsertib may pose a phototoxicity risk; therefore, participants are advised to take measures, such as use of sunscreen, wearing of hats and long-sleeve garments, and minimizing exposure to ultraviolet light.

For more details regarding the safety profile for camonsertib, refer to Section [A14-2.6](#) as well as the Camonsertib Investigator’s Brochure.

A14-5.2.4 Risks Associated with Combination Use of Atezolizumab, Camonsertib, and Bevacizumab

On the basis of the frequency of adverse events associated with either atezolizumab or bevacizumab, the following adverse events associated with cardiovascular, GI, renal, and pulmonary organ systems are potential overlapping toxicities associated with combination use of atezolizumab and bevacizumab. In addition, camonsertib is associated with hematologic toxicity (including anemia, neutropenia, thrombocytopenia) and non-hematologic toxicities of fatigue and GI toxicity (nausea, vomiting, diarrhea), which could impact the toxicities known to be associated with atezolizumab or bevacizumab.


It has been observed that bevacizumab in combination with chemotherapy and radiotherapy has been associated with increased incidence of thrombocytopenia. Bevacizumab in combination with myelotoxic chemotherapy has been associated with increased rates of severe neutropenia and febrile neutropenia. However, it is unknown if concurrent administration of bevacizumab and non-chemotherapeutic drug camonsertib will result in increased incidence of these toxicities due to the hematologic toxicities already known to be associated with camonsertib.

Atezolizumab, camonsertib, and bevacizumab have the potential to cause fetal harm.

A14-5.2.5 Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm

A14-5.2.5.1 Dose Modifications

There will be no dose modifications for atezolizumab or bevacizumab in this study.

For management of drug-related toxicities, the dose of camonsertib can be reduced by  mg (i.e., one dose level) one time, as outlined in [Table A14-5](#).

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm**Table A14-5 Suggested Dose Adjustment for Camonsertib**

Dose Level	Dose
Safety Run-In Period	
Initial Dose	
First dose adjustment	
Second dose adjustment	
Recommended target dose	
First dose adjustment	
Second dose adjustment	

D = days; PO = orally, by mouth; QD = once a day; Q21D = every 21 days.

Based on emerging data, the Sponsor may modify the study treatment (camonsertib and/or partner agent [s]) dose or schedule.

If further dose adjustment is indicated for camonsertib after two dose adjustments (where applicable), camonsertib should be discontinued.

Patients enrolled for the safety run-in period, receiving ■ mg of camonsertib QD PO D1–3, D8–10; Q21D, can also have their dose adjusted as per [Table A14-5](#) or interrupted to manage specific adverse events as applicable.

A14-5.2.5.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see [Table A14-6](#)).

If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

For camonsertib, dose interruption/modification criteria for hematologic (based on peripheral blood counts) and non-hematologic toxicities possibly related to study drug are outlined in [Table A14-6](#).

Camonsertib treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If camonsertib has been withheld for >21 days after event onset because of toxicity, the patient should be discontinued from camonsertib, unless resumption of treatment is approved at the investigator's discretion. The decision to re-challenge patients should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 non-serious adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤1, bevacizumab may be restarted at the same dose level. If bevacizumab is delayed due to toxicity for >42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab. Bevacizumab can be resumed after being withheld for >42 days if the patient is likely to derive clinical benefit. The decision to re-challenge patients with bevacizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

If one of the study drugs is discontinued, the other study drugs can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section [A14-4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A14-5.2.5.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in [Table A14-6](#). These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

In case a participant experiences any of the adverse events presented below, which is less likely to be caused by camonsertib based on its mechanism of action, investigators should use their medical judgment in consultation with the Sponsor to suspend camonsertib dosing or to continue dosing at a reduced dose, and/or implement supportive care as per local guidelines as deemed necessary. Thorough monitoring of participants is recommended until the toxicity resolves. The decision to re-challenge participants should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm

Event	Action to Be Taken
Hematologic events (anemia, neutropenia, thrombocytopenia, or leukopenia)	
General guidance	<ul style="list-style-type: none"> • General guidance for managing hematologic events of all grades is provided below, followed by grade-specific management guidelines. <ul style="list-style-type: none"> – Supportive treatment to alleviate hematologic toxicity is permitted per investigator judgment and institutional standards. Transfusions (including RBC and platelet transfusion) and hematopoietic growth factors are permitted to support management of hematologic toxicities at any occurrence per local standard of care and investigator judgment. Prophylactic transfusions and growth factors are not required. – Weekly monitoring of blood counts is required per protocol (with additional testing per clinical judgment) during the first cycle of treatment and with at least two blood counts obtained in subsequent cycles (with additional testing as clinically indicated in the case of hematologic toxicity) up to Cycle 3, then from Cycle 4 at the start of each cycle and per clinical judgment. In case of any hematologic toxicity (adverse events), weekly monitoring of blood count is required until the adverse event resolves. Protocol dose modification guidance (including interruption, delay, and dose adjustment) is to be followed. – Treatment interruption is advised upon onset of anemia (as per recommendations below), to avoid further deepening of the anemia and the need for transfusions. – Reactive measures implemented to minimize adverse clinical outcome due to neutropenia, taking into account known risk factors for febrile neutropenia per international guidelines, including use of growth factors and prophylactic antibiotics for Grade 3 or 4 neutropenia. – Measures to minimize adverse outcome of thrombocytopenia include platelet transfusion per investigator judgment and institutional standard procedure, and laboratory studies to evaluate any concurrent coagulopathy.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
Hematologic events (anemia, neutropenia, thrombocytopenia, or leukopenia) (cont.)	
Grade 2	<ul style="list-style-type: none"> • Continue atezolizumab and bevacizumab. • Withhold camonsertib and implement supportive care per local guidelines. • Monitor weekly until recovery to at least Grade 1. • If recovered to a Grade ≤ 1 or baseline within 14 days, treatment can resume at the same dose level for the first occurrence of the event. • For a subsequent Grade 2 event or events that did not resolve according to above guidance, dose/schedule of camonsertib should be adjusted (refer to Table A14-5). • Dose interruption caused by any Grade ≥ 2 toxicities lasting longer than 21 days will result in study drug discontinuation.
Grade ≥ 3	<ul style="list-style-type: none"> • Continue atezolizumab and bevacizumab. • Withhold camonsertib and implement supportive care per local guidelines. <p>First occurrence:</p> <ul style="list-style-type: none"> • Monitor weekly until recovery to Grade ≤ 1 or baseline. • If recovered to Grade ≤ 1 or baseline, then adjust camonsertib dose/schedule (refer to Table A14-5). <ul style="list-style-type: none"> – If further dose adjustment is not possible, treatment with camonsertib should be discontinued. • Dose interruption caused by any Grade ≥ 3 toxicities lasting longer than 21 days will result in study drug discontinuation. The Medical Monitor is available to advise as needed. <p>Second occurrence (abnormality of the same hematologic parameter):</p> <ul style="list-style-type: none"> • Monitor weekly until recovery to Grade ≤ 1 or baseline. • If recovered to Grade ≤ 1 or baseline, then adjust camonsertib dose/schedule (refer Table A14-5). • If further dose adjustment change is not possible, treatment with camonsertib should be discontinued. <p>Third occurrence (abnormality of the same hematologic parameter):</p> <ul style="list-style-type: none"> • Discontinue treatment with camonsertib and implement supportive care per local guidelines.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm**Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)**

<i>Event</i>	<i>Action to Be Taken</i>
<i>Nausea, vomiting, and diarrhea</i>	
<i>General guidance</i>	<ul style="list-style-type: none">• No routine prophylactic antiemetics or premedications are required; however, these medications may be administered for symptoms when they occur and may be given prophylactically if needed.
<i>Nausea, vomiting, and diarrhea, Grade 1</i>	<ul style="list-style-type: none">• Continue atezolizumab and bevacizumab.• Continue camonsertib as per investigator's discretion.• Implement supportive care per local guidelines.
<i>Nausea, vomiting, and diarrhea, Grade 2</i>	<ul style="list-style-type: none">• Continue atezolizumab and bevacizumab.• Continue camonsertib as per investigator's discretion.• Implement supportive care per local guidelines.
<i>Nausea, vomiting, and diarrhea, Grade 3</i>	<ul style="list-style-type: none">• Continue atezolizumab.• Bevacizumab may continue at the discretion of the investigator per medical judgment.^a• Withhold camonsertib until toxicity resolves to Grade ≤1 (or baseline).• Implement supportive care per local guidelines.• If toxicity persists at Grade 3 for ≤3 days or resolves to Grade ≤1 (or baseline) within a week, resume camonsertib at the same dose level and recheck toxicity level within a week of resuming treatment.• If toxicity persists at Grade 3 for >3 days after maximal prophylactic and supportive care or resolves to Grade ≤1 (or baseline) in >7 days, with or without treatment, adjust camonsertib dose/schedule (refer to Table A14-5).• If further dose adjustment is not possible, treatment with camonsertib should be discontinued.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
<i>Nausea, vomiting, and diarrhea (cont.)</i>	
<i>Nausea, vomiting, and diarrhea, Grade 4</i>	<ul style="list-style-type: none"> • Continue atezolizumab. • Bevacizumab may continue at the discretion of the investigator per medical judgment.^a • Withhold camonsertib until toxicity resolves to Grade ≤ 1 (or baseline). • Implement supportive care per local guidelines. • Adjust camonsertib dose/schedule upon resumption of treatment irrespective of the duration of event (refer to Table A14-5). • If further dose adjustment is not possible, treatment with camonsertib should be discontinued.
<i>QT/QTc interval prolongation</i>	
<i>General guidance</i>	<ul style="list-style-type: none"> • Follow guidelines for cardiac events for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment.^a • Camonsertib should be discontinued in participants who develop any of the following, unless there is a clear alternative cause for the changes: <ul style="list-style-type: none"> – Sustained (at least two ECG measurements >30 minutes apart) QTcF that is >500 ms and >60 ms longer than the baseline value – Sustained absolute QTcF that is >515 ms • An episode of torsades de pointes or a new ECG finding of clinical concern
<i>Management guidelines for other adverse events while receiving camonsertib</i>	
<i>Grade 1 or 2</i>	<ul style="list-style-type: none"> • Continue atezolizumab, bevacizumab and camonsertib.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
Management guidelines for other adverse events while receiving camonsertib (cont.)	
Grade 3	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold bevacizumab. If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. Withhold camonsertib until toxicity resolves to Grade ≤ 1 (or baseline). Implement supportive care per local guidelines. <p>First occurrence:</p> <ul style="list-style-type: none"> If toxicity resolves to Grade ≤ 1 (or baseline) within a week, resume camonsertib at the same dose level and recheck toxicity level within a week. If toxicity does not resolve to Grade ≤ 1 (or baseline) within a week, adjust camonsertib dose/schedule (refer to Table A14-5). Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed. <ul style="list-style-type: none"> If further dose adjustment is not possible, treatment with camonsertib should be discontinued. <p>Second occurrence:</p> <ul style="list-style-type: none"> If toxicity resolves to Grade ≤ 1 (or baseline), adjust camonsertib dose/schedule (refer to Table A14-5). Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed. <ul style="list-style-type: none"> If further dose adjustment is not possible, treatment with camonsertib should be discontinued. If toxicity does not resolve to Grade ≤ 1 (or baseline) within 21 days, treatment with camonsertib should be discontinued.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
Management guidelines for other adverse events while receiving camonsertib (cont.)	
Grade 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold bevacizumab. If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. Withhold camonsertib until toxicity resolves to Grade ≤ 1 (or baseline). Implement supportive care per local guidelines. If toxicity resolves to Grade ≤ 1 (or baseline), adjust camonsertib dose/schedule (refer to Table A14-5). Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed. <ul style="list-style-type: none"> If further dose adjustment is not possible, treatment with camonsertib should be discontinued. If toxicity does not resolve to Grade ≤ 1 (or baseline) within a 21 days treatment with camonsertib should be discontinued.
Pulmonary events including pneumonitis	
General guidance	<ul style="list-style-type: none"> All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.
Pulmonary event, Grade 1	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab, and monitor closely. Continue camonsertib as per investigator's discretion.
Pulmonary event, Grade 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a Continue camonsertib as per investigator's discretion.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm**Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)**

Event	Action to Be Taken
<i>Pulmonary events including pneumonitis (cont.)</i>	
<i>Pulmonary event, Grade 3 or 4</i>	<ul style="list-style-type: none">• Follow guidelines for atezolizumab in Appendix 6.• Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a• For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above.• Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Hepatic events</i>	
<i>Hepatic event, Grade 1</i>	<ul style="list-style-type: none">• Follow guidelines for atezolizumab in Appendix 6.• Continue bevacizumab.• Continue camonsertib as per investigator's discretion.• Implement supportive care as per investigator's discretion.
<i>Hepatic event, Grade 2</i>	<ul style="list-style-type: none">• Follow guidelines for atezolizumab in Appendix 6.• Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a• Continue camonsertib as per investigator's discretion.• Implement supportive care as per investigator's discretion.
<i>Hepatic event, Grade 3 or 4</i>	<ul style="list-style-type: none">• Follow guidelines for atezolizumab in Appendix 6.• Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
Hepatic events (cont.)	
Hepatic event, Grade 3 or 4 (cont.)	<ul style="list-style-type: none"> For camonsertib, interrupt camonsertib until toxicity resolves to Grade ≤ 1 (or baseline). If toxicity resolves to Grade ≤ 1 (or baseline), treatment can be resumed at lower dose (refer to Table A13-4). If further dose adjustment is not possible, treatment with camonsertib should be discontinued. If toxicity persists at Grade 3 for >7 days and does not resolve to Grade ≤ 1 or baseline within 21 days, discontinue treatment with camonsertib. Patients with an elevation of AST/ALT $\geq 3 \times \text{ULN}$ in conjunction with a bilirubin $\geq 2 \times \text{ULN}$ may remain in the study only if a correctable, nondrug-related cause of the liver test evaluations can be documented; otherwise, the patient must be discontinued from the study.
Gastrointestinal events	
Colitis, Grade 1	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab. Continue camonsertib as per investigator's discretion.
Colitis, Grade 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment.^a Continue camonsertib as per investigator's discretion.
Colitis, Grade 3	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment.^a For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events (cont.)	
Colitis, Grade 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Gastrointestinal perforation, any grade	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Discontinue bevacizumab. For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above.
Bowel obstruction, Grade 2	<ul style="list-style-type: none"> Atezolizumab and camonsertib may continue without interruption at the discretion of the investigator per medical judgment. Withhold bevacizumab for partial obstruction requiring medical intervention. Bevacizumab may be restarted upon complete resolution of event. ^a
Bowel obstruction, Grade 3 or 4	<ul style="list-style-type: none"> Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. Withhold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery and at investigator's discretion. ^a For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
Endocrine events	
Asymptomatic hypothyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab. Continue camonsertib as per investigator's discretion.
Symptomatic hypothyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab. Continue camonsertib as per investigator's discretion.
Asymptomatic hyperthyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab. Continue camonsertib as per investigator's discretion.
Symptomatic hyperthyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a Continue camonsertib as per investigator's discretion.
Symptomatic adrenal insufficiency, Grade 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a Continue camonsertib as per investigator's discretion.
Symptomatic adrenal insufficiency, Grade 3 or 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
Endocrine events (cont.)	
Hyperglycemia, Grade 1 or 2	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue bevacizumab. • Continue camonsertib as per investigator's discretion.
Hyperglycemia, Grade 3 or 4	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue bevacizumab. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Hypophysitis (pan-hypopituitarism), Grade 2	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a • Continue camonsertib as per investigator's discretion.
Hypophysitis (pan-hypopituitarism), Grade 3	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
Endocrine events (cont.)	
Hypophysitis (pan-hypopituitarism), Grade 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Ocular events	
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 1	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab. Continue camonsertib as per investigator's discretion.
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab. Continue camonsertib as per investigator's discretion.
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 3 or 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Cardiac events	
<i>Immune-mediated cardiac events</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Congestive heart failure, Grade 3 or 4</i>	<ul style="list-style-type: none"> • Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
IRRs, CRS, anaphylaxis, and hypersensitivity reaction	
<i>General guidance</i>	<ul style="list-style-type: none"> • Guidelines for management of IRRs and CRS for atezolizumab are provided in Appendix 6. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue atezolizumab and bevacizumab. • Continue camonsertib as per investigator's discretion.
<i>IRR to bevacizumab, Grade 1</i>	<ul style="list-style-type: none"> • Continue bevacizumab. • System intervention is not indicated.
<i>IRR to bevacizumab, Grade 2</i>	<ul style="list-style-type: none"> • Reduce infusion rate to ≤50% or interrupt infusion at the discretion of the investigator per medical judgment. • If the infusion is interrupted, it may be resumed at ≤50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reaction (cont.)	
IRR to bevacizumab, Grade 3 or 4	<ul style="list-style-type: none"> • Stop infusion and permanently discontinue bevacizumab. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen) if clinically indicated.
Hemophagocytic lymphohistiocytosis or macrophage activation syndrome	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Withhold all treatment. The Medical Monitor is available to advise as needed.
Pancreatic events	
Amylase and/or lipase elevation, Grade 3 or 4	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Pancreatitis, Grade 2–4	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a • For Grade 2 events, camonsertib may be continued as per investigator's discretion. • For Grade ≥ 3 events, for camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Dermatologic events	
General guidance	<ul style="list-style-type: none"> • A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
Dermatologic events (cont.)	
Dermatologic event, Grade 1 or 2	<ul style="list-style-type: none"> • Continue atezolizumab and bevacizumab. • Initiate supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids. • For Grade 2 rash, consider referral to dermatologist. • Continue camonsertib as per investigator's discretion. <p>Acneiform rash:</p> <ul style="list-style-type: none"> • Consider initiating treatment with topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.
Dermatologic event, Grade 3	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Dermatologic event, Grade 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab, and contact Medical Monitor ^b. • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^a • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Stevens-Johnson syndrome or toxic epidermal necrolysis, any grade	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Withhold bevacizumab. ^a • If event resolves to Grade 1 or better, resume bevacizumab.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

<i>Event</i>	<i>Action to Be Taken</i>
<i>Dermatologic events (cont.)</i>	
<i>Stevens-Johnson syndrome or toxic epidermal necrolysis, any grade (cont.)</i>	<ul style="list-style-type: none"> • Permanently discontinue bevacizumab if withheld for > 42 days or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Neurologic disorders</i>	
<i>Immune-mediated neuropathy, Grade 1</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue bevacizumab. • Continue camonsertib at investigator's discretion. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
<i>Immune-mediated neuropathy, including facial paresis, Grade 2</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Withhold bevacizumab. ^a • Continue camonsertib at investigator's discretion.
<i>Immune-mediated neuropathy, including facial paresis, Grade 3 or 4</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue bevacizumab. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Myasthenia gravis or Guillain-Barré syndrome, all grades</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue bevacizumab.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
Neurologic disorders (cont.)	
<i>Myasthenia gravis or Guillain-Barré syndrome, all grades (cont.)</i>	<ul style="list-style-type: none"> • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Immune-mediated myelitis, Grade 1</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue bevacizumab. • Continue camonsertib at investigator's discretion.
<i>Immune-mediated myelitis, Grade 2</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue bevacizumab. • Continue camonsertib at investigator's discretion.
<i>Immune-mediated myelitis, Grade 3 or 4</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue bevacizumab. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Immune-related meningoencephalitis, any grade</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Withhold bevacizumab.^a • If patient stabilizes within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab.^a • Continue camonsertib at investigator's discretion, and refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm**Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)**

<i>Event</i>	<i>Action to Be Taken</i>
<i>Hypertension</i>	
<i>General guidance</i>	<ul style="list-style-type: none">• <i>Treat with antihypertensive medication as needed.</i>
<i>Hypertension, Grade 1</i>	<ul style="list-style-type: none">• <i>Continue atezolizumab, bevacizumab, and camonsertib.</i>• <i>Consider increased blood pressure measuring.</i>
<i>Hypertension, Grade 2</i>	<ul style="list-style-type: none">• <i>Atezolizumab and camonsertib may continue without interruption at the discretion of the investigator per medical judgment.</i>• <i>If asymptomatic, begin or modify baseline antihypertensive therapy and continue bevacizumab.</i>• <i>If symptomatic, start or adjust antihypertensive therapy.</i>
<i>Hypertension, Grade 3</i>	<ul style="list-style-type: none">• <i>Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.</i>• <i>Withhold bevacizumab until symptoms resolve to Grade 1 or better <u>and</u> blood pressure <160/90 mmHg.</i>• <i>For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above.</i>• <i>Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.</i>• <i>Modify existing antihypertensive therapy (more than one drug or more intensive therapy than previously indicated).</i>

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
Hypertension (cont.)	
Hypertension, Grade 4	<ul style="list-style-type: none"> • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. • Discontinue bevacizumab. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Hemorrhage	
Hemorrhage, Grade 3 or 4 (excluding cerebral hemorrhage)	<ul style="list-style-type: none"> • Continue atezolizumab. • Permanently discontinue bevacizumab. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Cerebral hemorrhage, any grade	<ul style="list-style-type: none"> • Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
Hemorrhage (cont.)	
Grade ≥ 2 hemoptysis (≥ 2.5 mL of bright red blood per episode)	<ul style="list-style-type: none"> • Continue atezolizumab. • Permanently discontinue bevacizumab. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Bleeding in patients on full-dose anticoagulant therapy	<ul style="list-style-type: none"> • Continue atezolizumab. • Permanently discontinue bevacizumab. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Venous thromboembolic events	
Venous thromboembolic event, Grade 3	<ul style="list-style-type: none"> • Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be withheld until the full-dose anticoagulation period is over. The use of direct oral anticoagulants is not recommended. • If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed during full-dose anticoagulation <u>if</u> all of the criteria below are met: <ul style="list-style-type: none"> – The patient must not have pathological conditions that carry high risk of bleeding (e.g., tumor involving major vessels or other conditions). – The patient must not have had Grade > 2 hemorrhagic events while in the study. – The patient must be on stable dose of heparin, low-molecular-weight heparin, or have an in-range INR (usually 2 to 3) on a stable dose of warfarin prior to restarting bevacizumab.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm**Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)**

Event	Action to Be Taken
<i>Venous thromboembolic events (cont.)</i>	
<i>Venous thromboembolic event, Grade 3 (cont.)</i>	<ul style="list-style-type: none">• <i>If thromboemboli worsen or recur upon resumption of study therapy, discontinue bevacizumab.</i>• <i>For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above.</i>• <i>Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.</i>
<i>Venous thromboembolic event, Grade 4</i>	<ul style="list-style-type: none">• <i>Atezolizumab may be continued at the discretion of the investigator.</i>• <i>Permanently discontinue bevacizumab.</i>• <i>For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above.</i>• <i>Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.</i>
<i>Arterial thromboembolic events</i>	
<i>Arterial thromboembolic event, any grade</i>	<ul style="list-style-type: none">• <i>Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.</i>• <i>Permanently discontinue bevacizumab.</i>• <i>For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above.</i>• <i>Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.</i>

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Event	Action to Be Taken
Proteinuria	
Proteinuria, Grade 1 (1+ by dipstick; urinary protein <1.0 g/24 hr)	<ul style="list-style-type: none"> Continue atezolizumab, bevacizumab, and camonsertib.
Proteinuria, Grade 2 (2+ and 3+ by dipstick; urinary protein 1.0–3.4 g/24 hr)	<ul style="list-style-type: none"> Continue atezolizumab and camonsertib at investigator's discretion. For 2+ dipstick: Continue bevacizumab and collect 24-hour urine protein prior to subsequent bevacizumab administration. For 3+ dipstick: Obtain 24-hour urine prior to administering bevacizumab. Withhold bevacizumab for urinary protein ≥ 2 g/24 hr. If bevacizumab is withheld and urine protein improves to <2 g/24 hr within 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab.
Proteinuria, Grade 3 (4+ by dipstick; urinary protein ≥ 3.5 g/24 hr) with no diagnosis of nephrotic syndrome	<ul style="list-style-type: none"> Atezolizumab may be continued at the discretion of the investigator. Withhold bevacizumab. If urine protein improves to <2 g/24 hr within 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
Nephrotic syndrome, Grade 3 or 4	<ul style="list-style-type: none"> Atezolizumab may be continued at the discretion of the investigator. Permanently discontinue bevacizumab. For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

<i>Event</i>	<i>Action to Be Taken</i>
<i>Fistula</i>	
<i>Tracheoesophageal fistula, any grade</i>	<ul style="list-style-type: none"> • Withhold atezolizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. • Permanently discontinue bevacizumab. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Fistula (non-tracheoesophageal), Grade 4</i>	<ul style="list-style-type: none"> • Withhold atezolizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. • Permanently discontinue bevacizumab. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Wound dehiscence</i>	
<i>Wound dehiscence, any grade requiring medical or surgical therapy</i>	<ul style="list-style-type: none"> • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. • Permanently discontinue bevacizumab. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

<i>Event</i>	<i>Action to Be Taken</i>
<i>Posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome</i>	
<i>PRES/RPLS, any grade confirmed by MRI</i>	<ul style="list-style-type: none"> • Withhold atezolizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. • Permanently discontinue bevacizumab. • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Atezolizumab-related events not described above</i>	
<i>Grade 1 or 2</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue bevacizumab. • Continue camonsertib at investigator's discretion.
<i>Grade 3</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Withhold bevacizumab. If toxicity resolves to Grade ≤ 1, resume bevacizumab. ^a • For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above. • Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Grade 4</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Withhold bevacizumab. • If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. ^a

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm**Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)**

<i>Event</i>	<i>Action to Be Taken</i>
<i>Atezolizumab-related events not described above (cont.)</i>	
<i>Grade 4 (cont.)</i>	<ul style="list-style-type: none">• For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above.• Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Bevacizumab-related events not described above</i>	
<i>Grade 1 or 2</i>	<ul style="list-style-type: none">• Continue atezolizumab, camonsertib, and bevacizumab at investigator's discretion.
<i>Grade 3</i>	<ul style="list-style-type: none">• Follow guidelines for atezolizumab in Appendix 6.• Withhold bevacizumab. ^a• If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. ^a• For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above.• Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.
<i>Grade 4</i>	<ul style="list-style-type: none">• Follow guidelines for atezolizumab in Appendix 6.• Withhold bevacizumab. ^a• If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. ^a• For camonsertib, refer to "Management guidelines for other adverse events while receiving camonsertib" row above.• Dose adjustment with camonsertib may be considered at the discretion of investigator. The Medical Monitor is available to advise as needed.

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

Table A14-6 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+Camon Arm (cont.)

Atezo = atezolizumab; Bev = bevacizumab; Camon = camonsertib; CRS = cytokine release syndrome; IRR = infusion-related reaction; MRI = magnetic resonance imaging; PRES = posterior reversible encephalopathy syndrome; QTcF = QT interval corrected through use of Fridericia's formula; RPLS = reversible posterior leukoencephalopathy syndrome; ULN = upper limit of normal.

- ^a If bevacizumab is delayed due to toxicity for ≥ 42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab.*
- ^b Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A14-5.3 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO+BEV+CAMON ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo+Bev+Camon arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7).
- Suspected transmission of an infectious agent by the study treatment, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia

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- *Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)*
- *Leukemias*
- *Myelodysplastic syndrome (MDS)*
- *Grade ≥ 3 anemia, neutropenia, and thrombocytopenia*
- *Any grade febrile neutropenia or neutropenic sepsis*
- *Grade ≥ 3 dyspnea*
- *Myelitis*
- *Facial paresis*
- *Grade ≥ 3 hypertension*
- *Grade ≥ 3 proteinuria*
- *Any grade GI perforation, abscesses, or GI fistulae*
- *Grade ≥ 2 non-GI fistula or abscess*
- *Grade ≥ 3 wound-healing complication*
- *Any grade CNS bleeding*
- *Grade ≥ 2 hemoptysis*
- *Other Grade ≥ 3 hemorrhagic event*
- *Any grade arterial thromboembolic event*
- *Grade ≥ 3 venous thromboembolic event*
- *Any grade posterior reversible encephalopathy syndrome (PRES)*
- *Grade ≥ 3 congestive heart failure*

A14-5.4 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+BEV+CAMON ARM

A14-5.4.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab and 6 months after the final dose of camonsertib and bevacizumab. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue atezolizumab and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events

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associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A14-5.4.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the final dose of camonsertib and bevacizumab. The investigator should report the pregnancy on the Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to docetaxel. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A14-5.4.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A14-5.4.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

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A14-6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+BEV+CAMON ARM

Table A14-7 Schedule of Activities for Atezo+Bev+Camon Arm

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-day cycles) ^a						Stage 2 Screen. (see Appendix 2) ^c or Treat. Discon. ^d (see below)	Follow-Up ^d Every 3 Months (± 7 days)
		Cycle 1 ^b			Cycles 2–3		Cycles ≥ 4		
	Day –28 to –1								
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available							
Vital signs ^e		x	x	x	x	x	x	x	
Weight ^f		x			x		x	x	
Complete physical examination ^g								x	
Limited physical examination ^{f, h}		x	x	x	x	x	x		
ECOG Performance Status ^f		x			x		x	x	
ECG ^{f, i}		x			<i>xⁱ</i>				
Hematology ^j		<i>x^k</i>	x	x	x	x	x	x	
Chemistry ^l		<i>x^k</i>			x		x	x	
Coagulation (INR and aPTT)		<i>x^k</i>			x		x	x	
TSH, free T3 (or total T3), free T4 ^m		<i>x^k</i>						x	
Pregnancy test ⁿ		<i>x^k</i>			x		x	x	x
Urinalysis ^o		Perform as clinically indicated							
Serum autoantibody sample ^p		Perform if a patient experiences a suspected immune-mediated adverse event							

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Table A14-7 Schedule of Activities for Atezo + Bev + Camon Arm (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-day cycles) ^a						Stage 2 Screen. (see Appendix 2) ^c or Treat. Discon. ^d (see below)	Follow- Up ^d Every 3 Months (± 7 days)
		Cycle 1 ^b			Cycles 2–3		Cycles ≥ 4		
	Day –28 to –1								
PK samples	See Appendix 2	Refer to Table A14-8 .							
ADA samples		Refer to Table A14-8 .							
Biomarker samples		Refer to Table A14-8 .							
Blood sample for RBR (optional) ^q		x							
Tumor biopsy		x ^r							
Tumor biopsy (optional)		x ^s							
Tumor response assessments		x ^{t, u, v}							
Concomitant medications ^w		x	x	x	x	x	x	x	
Adverse events ^x		x	x	x	x	x	x	x ^x	x ^x
Atezolizumab administration ^{y, z}		x			x		x		
Bevacizumab administration ^{y, aa}		x			x		x		
Dispense camonsertib ^{y, bb}		x			x		x		
Survival follow-up and anti-cancer treatment									x ^{cc}

Appendix 14: Study Details Specific to Atezo + Bev + Camon Arm

Table A14-7 Schedule of Activities for Atezo + Bev + Camon Arm (cont.)

ADA=anti-drug antibody; Atezo=atezolizumab; CT=computed tomography; Discon.=discontinuation; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; NGS=next generation sequencing; PK=pharmacokinetic; QTcF=QT interval corrected through use of Fridericia's formula; RBR=Research Biosample Repository; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen.=screening; T3=triiodothyronine; T4=thyroxine; Treat.=treatment; TSH=thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

- ^a If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. The Medical Monitor is available to advise as needed.
- ^b It is recommended that treatment be initiated no later than 7 days after randomization.
- ^c Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) or unacceptable toxicity to camonsertib will be given the option of receiving a different treatment combination in Stage 2 of the study (as outlined in Section 3.1.4) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.
- ^d Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the final dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments.
- ^e Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (\pm 5) minutes during and 30 (\pm 10) minutes after the infusion. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (\pm 10) minutes after the infusion. For the first infusion of bevacizumab, vital signs should be measured within 60 minutes prior to the infusion, at the end of the infusion, and 2 (\pm 1) hours after the infusion. For subsequent bevacizumab infusions, vital signs should be measured within 60 minutes prior to the infusion and within 30 minutes after completion of the infusion.
- ^f Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^g Physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Appendix 14: Study Details Specific to Atezo + Bev + Camon Arm

Table A14-7 Schedule of Activities for Atezo + Bev + Camon Arm (cont.)

- ^h Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ⁱ Triplicate ECG should be performed at baseline prior to receiving Cycle 1. Subsequently, single ECGs should be performed on Day 1 of odd-numbered cycles for the first 15 cycles of treatment (i.e., Cycles 3, 5, 7, 9, 11, 13 and 15). Subsequently, ECGs can be performed every 3 months. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording. If at a particular timepoint (if applicable) the mean QTcF is >500 ms and/or >60 ms longer than the baseline value, another ECG must be recorded more than 30 minutes apart to confirm the QTcF prolongation and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard of care treatment may be instituted per the discretion of the investigator. Additional unscheduled ECGs (triplicate or single) should be performed if clinically indicated.
- ^j Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, reticulocytes, other cells). If clinically indicated, a more frequent hematologic testing may be required beyond Cycle 1.
- ^k If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.
- ^l Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, direct bilirubin, ALP, ALT, and AST. Amylase and lipase will be included on Day 1 of each treatment cycle.
- ^m TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).
- ⁿ All women of childbearing potential will have a urine or serum pregnancy test performed at specified visits during treatment and at 3 months and 6 months after the final dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^o Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ^p Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Serum samples collected for the assessment of PK, ADAs, or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment, may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.
- ^q Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

Appendix 14: Study Details Specific to Atezo + Bev + Camon Arm

Table A14-7 Schedule of Activities for Atezo + Bev + Camon Arm (cont.)

- ^r Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see Section 3.1.2) will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible). See Section 4.5.6 for tissue sample requirements.
- ^s Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation, if deemed clinically feasible and may undergo additional on-treatment biopsies at any other time during Stage 1 or Stage 2 at the investigator's discretion.
- ^t Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of atezolizumab-treated patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.
- ^u All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).
- ^v For patients who undergo screening for Stage 2: Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.
- ^w Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

Appendix 14: Study Details Specific to Atezo + Bev + Camon Arm

Table A14-7 Schedule of Activities for Atezo + Bev + Camon Arm (cont.)

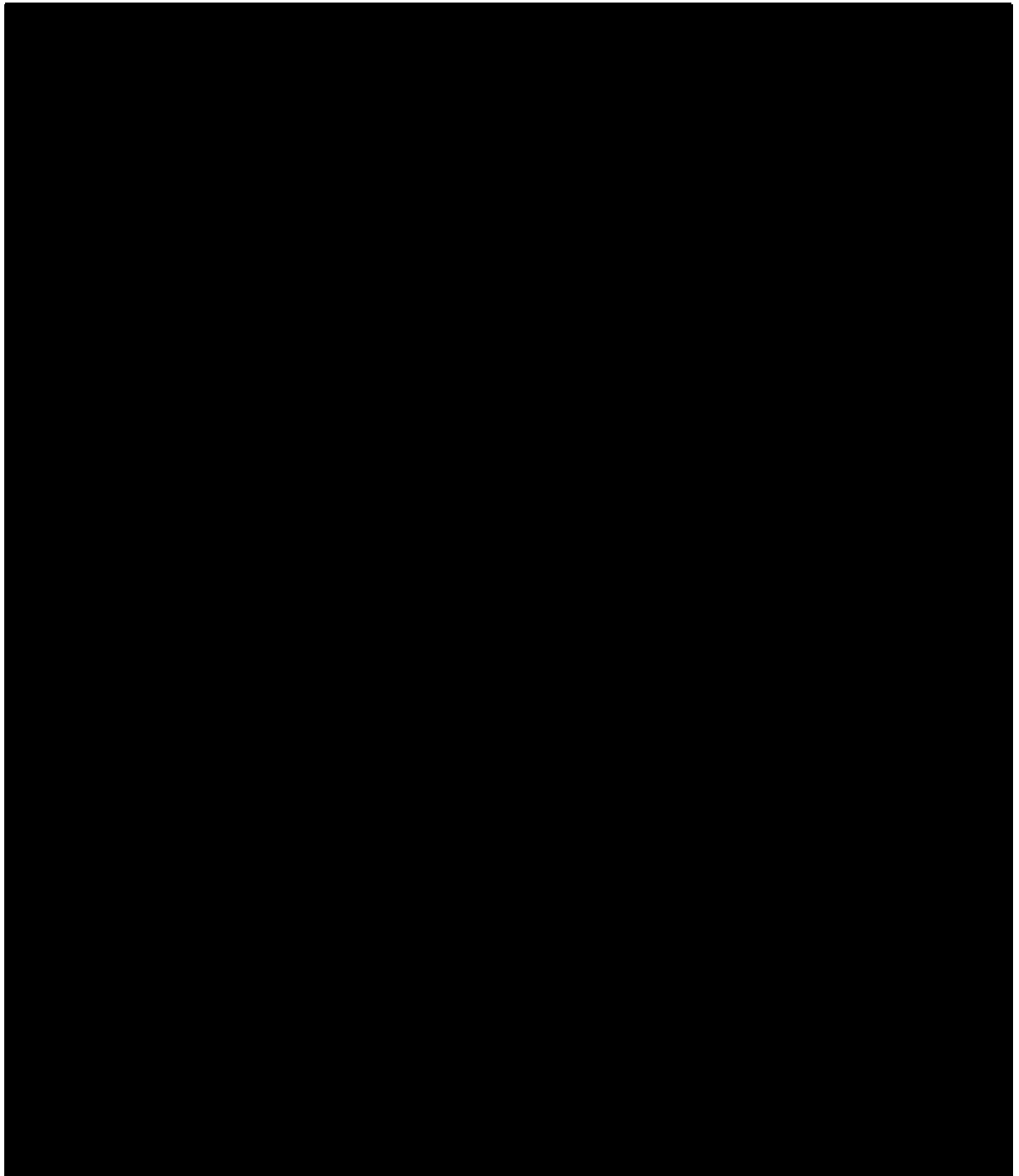
- ^x After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.
- ^y Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).
- ^z Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Refer to Section A14-4.1.2.1 for details on atezolizumab infusions (including measurement of vital signs).
- ^{aa} Bevacizumab will be administered by IV infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle. The initial dose of bevacizumab will be delivered over 90 (±15) minutes. If the first bevacizumab infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (±10) minutes. If the 60 (±10) minute infusion was tolerated without infusion-associated adverse events, the third infusion may be delivered over 30 (±15) minutes. If the 30-minute bevacizumab infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. Bevacizumab will be administered after completion of the atezolizumab infusion. Bevacizumab must be administered ±3 days after any on-treatment biopsy, but only after adequate wound healing has been demonstrated.
- ^{bb} Camonsertib will be self-administered by patients orally at home (except on clinic days) at a dose of [REDACTED] mg (safety run-in)/[REDACTED] mg daily for [REDACTED] consecutive days per week followed by [REDACTED] off-treatment days ([REDACTED]) of each 21-day treatment cycle (Days 1–3 and Days 8–10). The cycle visit Day 1 should remain on schedule as planned starting from actual Day 1 of Cycle 1. Day 1 of every cycle is independent of missed doses or dose delays. Camonsertib should be taken in the morning at approximately the same time each day. Cycle dosing must start on either Monday, Tuesday, or Wednesday if unable to accommodate weekend visits and should be taken on the same consecutive days each week. On clinic visit days, patients should take their tablets in the clinic. To assess patient compliance with self-administration of camonsertib, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

Appendix 14: Study Details Specific to Atezo + Bev + Camon Arm

Table A14-7 Schedule of Activities for Atezo + Bev + Camon Arm (cont.)

^{cc} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm



Appendix 14: Study Details Specific to Atezo+Bev+Camon Arm

[REDACTED]

[REDACTED]

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Appendix 15

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A15-1 BACKGROUND ON ATEZO +BEV+TIRA ARM

A15-1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, myocarditis, and nephritis have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma (in the European Union), non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer (in the European Union), hepatocellular carcinoma (HCC), melanoma (in the United States), and alveolar soft part sarcoma (in the United States).

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A15-1.2 BACKGROUND ON BEVACIZUMAB

Bevacizumab is a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF) that recognizes all isoforms of VEGF. It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor environment. Additional anti-tumor activity may be on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

Bevacizumab has been tested in Phase II and III studies in a variety of solid tumors in combination with chemotherapy. Bevacizumab is registered in over 40 countries worldwide for the first-line treatment of metastatic colorectal cancer (CRC) in combination with chemotherapy, as second-line CRC treatment, and first-line treatment of advanced NSCLC, metastatic breast cancer, advanced renal cell carcinoma (RCC), ovarian cancer, and glioblastoma (Reck and Crinò 2009).

In NSCLC, the Phase II/III Study E4599 showed that the addition of bevacizumab (15 mg/kg every 3 weeks [Q3W]) to the paclitaxel and carboplatin regimen led to a clinically relevant and statistically significant prolongation of overall survival ([OS] primary endpoint) compared with patients who were treated with paclitaxel and carboplatin alone (hazard ratio [HR] =0.80; 95% CI: 0.69 to 0.93; $p=0.003$; Kaplan-Meier [KM]-estimated median: 12.3 vs. 10.3 months). The OS benefit was supported by the results of progression-free survival (PFS) (HR =0.65; 95% CI: 0.56 to 0.76; KM-estimated median: 6.4 vs. 4.8 months) and response rate (29.0% vs. 12.9%).

In addition, data from the protocol-defined final PFS (primary efficacy parameter) analysis of Study BO17704 (AVAIL; Roche Report No. 1023798) showed that the addition of bevacizumab (7.5 or 15 mg/kg Q3W) to cisplatin/gemcitabine chemotherapy resulted in a clinically relevant and statistically significant improvement in PFS (bevacizumab 7.5 mg/kg: HR =0.75; 95% CI: 0.62 to 0.91; $p=0.0026$; KM-estimated median PFS: 6.7 vs. 8.1 months) (bevacizumab 15 mg/kg: HR =0.82; 95% CI: 0.68 to 0.98; $p=0.0301$; KM-estimated median PFS: 6.5 vs. 6.1 months). Objective response rate (ORR) was also significantly increased in both bevacizumab-containing arms (7.5 mg/kg: 34.1% vs. 20.1%; bevacizumab 15 mg/kg: 30.4% vs. 20.1%).

Bevacizumab is currently being tested in combination with atezolizumab across different indications in Phase I, II, and III clinical studies. Atezolizumab plus bevacizumab has been approved as the first-line standard of care for patients with metastatic HCC.

Refer to the Bevacizumab Investigator's Brochure for details on nonclinical and clinical studies.

A15-1.3 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/ κ monoclonal antibody that binds to T-cell immunoreceptor with Ig and ITIM domains (TIGIT) and prevents its interaction with CD155 (also known as poliovirus receptor [PVR]). Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of tumor-specific T-cell responses. This may result in improved meaningful anti-tumor activity when tiragolumab is used in combination with other cancer immunotherapies and administered with chemotherapy. The available

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in patients with cancer.

Refer to the Tiragolumab Investigator's Brochure for details on nonclinical and clinical studies.

A15-2 RATIONALE FOR ATEZO +BEV +TIRA ARM

A15-2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses by binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, RCC, melanoma, CRC, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors (CPIs), have had a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active as monotherapy for many patients.

A15-2.2 ANTI-VEGF CANCER TREATMENT

In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggested that VEGF may reduce lymphocyte adhesion to vessel walls in the tumor microenvironment, thus contributing to decreased immune cell recruitment to the tumor site (Bouzin et al. 2007). Mice exposed to pathophysiologic levels of VEGF exhibited impaired dendritic cell (DC) function, which could be restored by blockade of VEGF receptor 2 (Huang et al. 2007). In addition, VEGF recruits macrophages into the tumor microenvironment that have an M2 polarization state, which is typically involved in wound healing. These M2 tumor-associated macrophages ultimately help establish and maintain an immunosuppressive microenvironment (Chen and Mellman 2013). In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). Synergistic effects have also been observed in a clinical study combining an immune-modulatory antibody (anti-cytotoxic T lymphocyte-associated protein 4; ipilimumab) and bevacizumab: Hodi et al. (2010) described increased T-cell trafficking in post-treatment biopsies, as well as marked increases in central memory cells in peripheral blood in the majority of patients.

A15-2.3 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin super family (Yu et al. 2009). TIGIT is expressed on the surface of activated T-cell and natural killer (NK)-cell subsets and interacts with high affinity with CD155 (also known as PVR) (Yu et al. 2009). Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses in nonclinical models of autoimmune and viral infections, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; Johnston et al. 2014). TIGIT expression is elevated in the tumor microenvironment in many human tumors, is concordantly expressed with other checkpoint immune receptors such as PD-1 on the surface of T cells, and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014; Manieri et al. 2017). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (Stanietzky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017).

TIGIT is expressed by a wide variety of human tumors. It is expressed in most solid tumors, such as NSCLC, breast cancer, head and neck cancer, and melanoma, as well as in hematologic tumors, such as multiple myeloma and non-Hodgkin lymphoma. Fluorescence activated cell-sorting analysis of T cells isolated from fresh tumor samples

revealed that TIGIT and PD-1 are also co-expressed on tumor-infiltrating T cells (Johnston et al. 2014; Yadav et al. 2016; Yang 2016; Guillerey et al. 2018). TIGIT was expressed in 30%–80% of tumor-infiltrating CD4⁺ T cells and in 50%–80% of tumor-infiltrating CD8⁺ T cells (Johnston et al. 2014).

Therefore, TIGIT is a potential target for therapeutic interventions that aim to restore the immune response against the tumor. Agents that inhibit TIGIT interaction with PVR may inhibit an important source of tumor-associated immune suppression, thereby enhancing the activity of other immune-based therapies. Nonclinical studies using genetically deficient mice and blocking antibodies have revealed a key role for TIGIT in regulating T-cell responses in cancer. Taken together, the data support the hypothesis that anti-TIGIT therapy may reactivate anti-tumor immunity and provide clinical benefits to patients with cancer.

A15–2.4 RATIONALE FOR COMBINING ATEZOLIZUMAB WITH BEVACIZUMAB AND TIRAGOLUMAB

Durable clinical benefit is limited to a minority of patients treated with single-agent PD-L1/PD-1 inhibitors. Therapies targeting the mechanisms of resistance to anti-PD-L1/PD-1 therapies are needed to improve outcomes in patients with solid-tumor cancers. A strong scientific rationale and emerging clinical data suggest that combined PD-L1, VEGF, and TIGIT inhibition may be clinically beneficial in a number of tumor types.

Anti-VEGF agents promote the normalization of tumor vasculature, thereby increasing access of therapeutic agents (Jain 2001). In addition, bevacizumab can restore and/or maintain the antigen-presentation capacity of DCs, leading to enhanced T-cell infiltration in tumors (Oelkrug and Ramage 2014; Wallin et al. 2016). Administration of anti-VEGF-A has been shown to attenuate tumor endothelial FasL expression and produce a significant increase in the influx of tumor-rejecting CD8⁺ T cells, leading to tumor growth suppression (Motz et al. 2014). Anti-VEGF therapies can also reduce the frequency of myeloid-derived suppressor cells, decrease production of suppressive cytokines, and lower expression of inhibitory checkpoints on CD8⁺ T cells in tumors (Roland et al. 2009; Voron et al. 2015).

The immunomodulatory effects of bevacizumab are anticipated to increase CD8⁺ T-cell recruitment and relieve intratumoral immunosuppression, thereby boosting the effects of immunotherapy. Indeed, clinical data have demonstrated a beneficial effect of anti-angiogenesis and immunomodulation within the context of atezolizumab treatment. The activity of combination treatment with atezolizumab and bevacizumab has been demonstrated in multiple, large, randomized Phase III clinical studies in patients with NSCLC, RCC, and HCC.

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

In chemotherapy-naïve patients with Stage IV NSCLC, results from Study GO29436 (IMpower150) have shown that atezolizumab plus bevacizumab and chemotherapy results in significantly longer OS compared with bevacizumab and chemotherapy alone (Socinski et al. 2018). For patients with inoperable, locally advanced, or metastatic RCC, results from Study WO29637 (IMmotion151) demonstrated improved PFS after treatment with the combination of atezolizumab and bevacizumab compared with sunitinib in a treatment-naïve patient population (Rini et al. 2019). Recently, the combination of atezolizumab plus bevacizumab has demonstrated superiority over sorafenib in HCC and has been approved and become standard of care for the first-line treatment of patients with metastatic HCC (Finn et al. 2020). Data from Morpheus platform presented at American Society of Clinical Oncology (ASCO) 2023, showed that the addition of tiragolumab to atezolizumab and bevacizumab resulted in higher ORR and longer PFS compared with atezolizumab and bevacizumab (Finn et al. 2023).

Resistance to PD-L1/PD-1 blockade may result in the expression of multiple co-inhibitory receptors on the surface of effector T cells. Nonclinical tumor models have shown that TIGIT selectively suppresses the effector function of chronically stimulated CD8⁺ T cells, and that inhibiting both TIGIT and PD-L1/PD-1 results in superior efficacy compared with single-agent treatments (Johnston et al. 2014). Higher levels of PD-1⁺, TIGIT⁺, CD8⁺ T cells have been reported in patients with advanced HCC and are associated with poor clinical outcomes, including accelerated disease progression and death (Liu et al. 2019). Hence, targeting TIGIT and PD-L1 with tiragolumab and atezolizumab, respectively, may enhance the efficacy of PD-L1/PD-1 blockade across different cancer types, including NSCLC (see Section A15-2.6 for a description of clinical studies of tiragolumab combined with atezolizumab). The combination of atezolizumab and bevacizumab with or without stereotactic body radiotherapy showed promising activity in patients with metastatic non-squamous NSCLC who progressed during or following a PD-L1/PD-1 CPI given in combination as one line of therapy or as two separate lines of therapy (Ghiringhelli et al. 2023).

Based on the above-described data, it is hypothesized that combination treatment with atezolizumab, bevacizumab, and tiragolumab may augment the anti-tumor immune response, resulting in an improved and more durable clinical benefit in patients with non-squamous NSCLC who progressed on or following CPI.

A15-2.5 CLINICAL STUDIES OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB

Study GP28328 is an ongoing, Phase Ib, open-label, multicenter study combining atezolizumab (1200 mg Q3W) with bevacizumab (15 mg/kg Q3W) in patients with advanced solid tumors, with expansion arms for patients with RCC, metastatic CRC, gastric cancer, and ovarian cancer. Safety findings have been consistent with the

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

known single-agent safety profiles for each drug; no new safety signals have been identified. The regimen has been well tolerated, and adverse events have been manageable. Another Phase Ib, open-label, multicenter study (GO30140) is investigating a similar dose of atezolizumab combined with bevacizumab in patients with HCC. In addition, this combination is being tested in a Phase II randomized study (WO29074) in which atezolizumab is administered as monotherapy or in combination with bevacizumab, compared with sunitinib, in patients with untreated advanced RCC.

In chemotherapy-naïve patients with Stage IV NSCLC, results from Phase III Study GO29436 (IMpower150) have shown that atezolizumab in combination with carboplatin+paclitaxel and bevacizumab results in significantly longer OS compared with carboplatin+paclitaxel and bevacizumab alone (Socinski et al. 2018). For inoperable, locally advanced, or metastatic RCC, Phase III Study WO29637 (IMmotion151) demonstrated improved PFS after treatment with the combination of atezolizumab plus bevacizumab compared with sunitinib treatment in treatment-naïve patients (Motzer et al. 2018). Phase Ib Study GO30140 in HCC first-line treatment found an ORR of 65% in 23 evaluable patients, across etiology, geography, baseline α -fetoprotein levels, and extrahepatic spread. The combination has been explored in a randomized Phase III study YO40245 (IMbrave150) versus sorafenib in first-line treatment for HCC (Stein et al. 2018). In this study, atezolizumab combined with bevacizumab resulted in better overall and PFS outcomes than sorafenib (Finn et al. 2020). Consequently, atezolizumab combined with bevacizumab has been approved and became standard of care for the first-line treatment of patients with metastatic HCC. Recently, the addition of tiragolumab to atezolizumab plus bevacizumab has demonstrated an additional increase in ORR and median PFS as compared with the combination of atezolizumab and bevacizumab (Finn et al. 2023). These are examples of clear synergy between atezolizumab and bevacizumab in different tumor types, which support further exploration of the combination in NSCLC.

Detailed clinical study results for atezolizumab and bevacizumab can be found in the Atezolizumab Investigator's Brochure and the Bevacizumab Investigator's Brochure, respectively.

A15-2.6 CLINICAL STUDIES OF TIRAGOLUMAB AS A SINGLE AGENT OR IN COMBINATION WITH ATEZOLIZUMAB

Tiragolumab is currently under investigation in patients with solid tumors, for example, in the ongoing Phase Ia/Ib study GO30103, the Phase II studies GO40290 (CITYSCAPE) and GO42501 (SKYSCRAPER-05), and the Phase III study GO41854 (SKYSCRAPER-03).

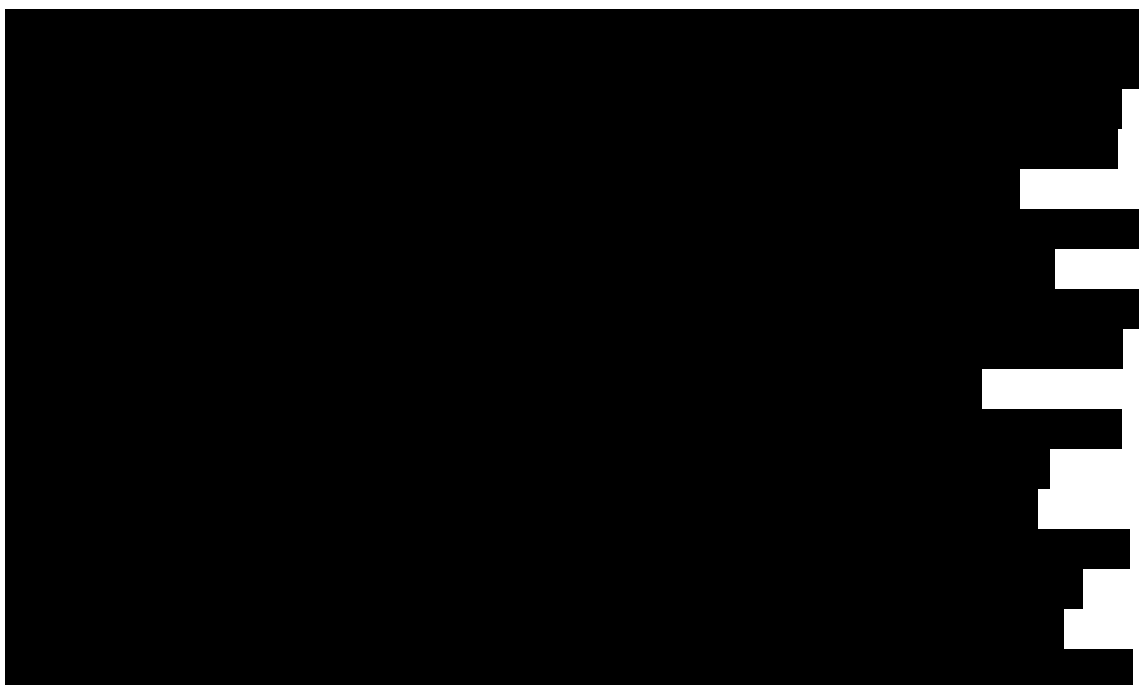
Clinical data for Studies GO30103 and GO40290 are reported below.

A15-2.6.1 Study GO30103

Study GO30103 is a first in human Phase Ia/Ib open-label, dose-escalation study of the safety and pharmacokinetics of tiragolumab as a single agent and in combination with atezolizumab in patients with locally advanced or metastatic tumors. As of the clinical cutoff date of 1 October 2021, 42 patients were enrolled in the Phase Ia portion of the study to receive single-agent tiragolumab, and 200 patients were enrolled in the Phase Ib portion of the study to receive tiragolumab in combination with atezolizumab at dose levels of 2–1200 mg tiragolumab and 1200 mg atezolizumab. Of the 42 patients enrolled in the Phase Ia portion of the study, 23 patients crossed over to the Phase Ib portion of the study after disease progression.

Tiragolumab as a single-agent or in combination with atezolizumab was tolerated across all administered dose levels in Study GO30103. The maximum tolerated dose (MTD) was not reached, and the maximum administered dose was 1200 mg. No dose-limiting toxicities (DLTs) or clear dose-related trends in the incidence of adverse events have been observed in the Phase Ia or Phase Ib portions of Study GO30103.

As of 1 October 2021, in the Phase Ia portion of the study, the most commonly reported Grade 3 or 4 adverse events ($\geq 5\%$ of patients) were anemia (4 patients; 9.5%), and dyspnea (3 patients; 7.1%). Overall, 54.8% of patients reported adverse events considered related to tiragolumab by the investigator. Tiragolumab-related adverse events reported in $\geq 5\%$ of patients were fatigue, pruritus, and infusion-related reaction (IRR) (11.9% each), and rash (9.5%).



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[REDACTED]

In the Phase Ib part of the study, the majority of Grade 3 or 4 adverse events reported occurred in 1 patient each, with anemia (7.5%) as the only Grade 3 or 4 adverse event reported in $\geq 5\%$ of patients.

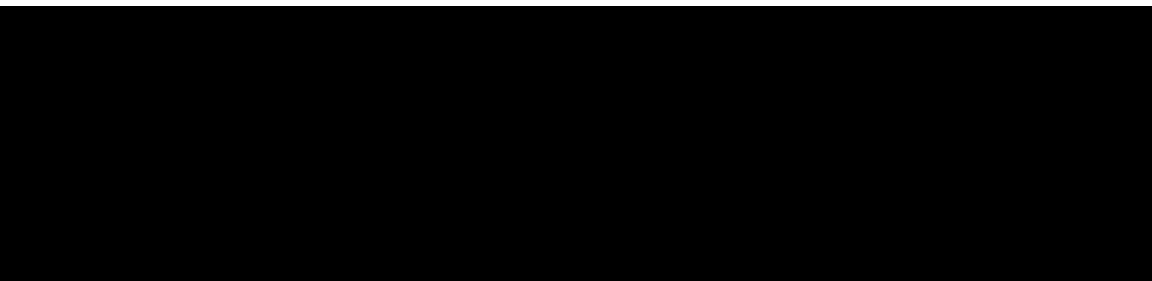
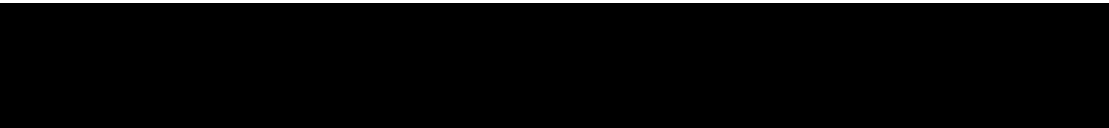
[REDACTED]

[REDACTED]

As of 1 October 2021, the anti-tumor activity of tiragolumab as a single-agent and in combination with atezolizumab in patients with advanced solid tumors has been investigated in the Phase Ia/Ib study GO30103.

[REDACTED]

[REDACTED]



A15-2.6.2 Study GO40290

Study GO40290 is a Phase II randomized, blinded, placebo-controlled study to evaluate the safety and efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated, locally advanced unresectable or metastatic PD-L1-selected NSCLC. A total of 135 patients were enrolled in this study (last patient was enrolled in March 2019). As of the clinical cutoff date of 16 August 2021, 12 patients were still receiving study treatment in the intent-to-treat (ITT) population.

As of the clinical cutoff date of 16 August 2021, 66 of 67 patients (98.5%) in the tiragolumab plus atezolizumab arm and 66 of 68 patients (97.1%) in the placebo plus atezolizumab arm reported at least one adverse event.

The most common adverse events reported in $\geq 15\%$ of all patients who received tiragolumab plus atezolizumab, regardless of attribution to study treatments included: IRR (31.3%), arthralgia (29.9%), asthenia and pruritus (28.4% each), fatigue (25.4%), rash (23.9%), decreased appetite (22.4%), diarrhea (20.9%), constipation (17.9%), and cough and pneumonia (16.4% each). The most common adverse events in patients who received placebo plus atezolizumab included asthenia (27.9%), dyspnea (25.0%), decreased appetite (23.5%), arthralgia (17.6%), and fatigue, pruritus, and diarrhea (16.2% each).

The adverse events experienced by a higher proportion of patients in the tiragolumab plus atezolizumab arm than the placebo plus atezolizumab arm (preferred term; $\geq 10\%$ difference) were (tiragolumab plus atezolizumab and placebo plus atezolizumab, respectively): IRR (31.3% and 10.3%), arthralgia (29.9% and 17.6%), pruritus (28.4% and 16.2%), and rash (23.9% and 10.3%). The only adverse event experienced more frequently ($\geq 10\%$ difference) in the placebo plus atezolizumab arm was dyspnea (14.9% and 25.0%).

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A total of 55 of 67 patients (82.1%) in the tiragolumab plus atezolizumab arm and 48 of 68 patients (70.6%) in the placebo plus atezolizumab arm experienced at least one adverse event that was assessed by the investigator to be related to the study treatments. The most common related adverse events reported in $\geq 10\%$ of patients who received tiragolumab plus atezolizumab and placebo plus atezolizumab, respectively, were IRR (31.3% and 10.3%), pruritus (26.9% and 14.7%), rash (20.9% and 5.9%), asthenia (17.9% and 17.6%), fatigue (17.9% and 7.4%), arthralgia (16.4% and 7.4%), lipase increased (11.9% and 2.9%), hypothyroidism (10.4% and 5.9%), and decreased appetite (9% and 17.6%).

A total of 35 of 67 patients (52.2%) in the tiragolumab plus atezolizumab arm and 27 of 68 patients (39.7%) in the placebo plus atezolizumab arm experienced at least one Grade 3 or 4 adverse event regardless of attribution to study treatments. The Grade 3 or 4 adverse events experienced by a higher proportion of patients in the tiragolumab plus atezolizumab arm than the placebo plus atezolizumab arm ($\geq 2\%$ difference) were pneumonia (11.9% and 5.9%), increased lipase (9.0% and 4.4%), pleural effusion (6.0% and 2.9%), and blood ALP increased, hemoptysis, hepatitis, and hypokalemia (3.0% and 0%, each). The Grade 3 or 4 adverse events experienced by a higher proportion of patients in the placebo plus atezolizumab arm than the tiragolumab plus atezolizumab arm ($\geq 2\%$ difference) were (tiragolumab plus atezolizumab and placebo plus atezolizumab, respectively) increased amylase (1.5% and 4.4%) and asthenia (0% and 2.9%).

The data analysis (clinical cutoff date of 16 August 2021) showed that the combination of tiragolumab plus atezolizumab improved ORR and PFS compared with placebo plus atezolizumab in the ITT population. ORR for tiragolumab plus atezolizumab was 38.8% (95% CI: 26.4% to 51.2%) compared with placebo plus atezolizumab, which was 20.6% (95% CI: 10.2% to 30.9%). This was associated with a 38% relative risk reduction in disease worsening or death (median investigator-assessed PFS for tiragolumab plus atezolizumab was 5.6 months (95% CI: 4.2 to 10.4 months) compared with placebo plus atezolizumab, which was 3.9 months (95% CI: 2.7 to 4.5 months), with a HR of 0.62 (95% CI: 0.42 to 0.91).

A15-2.7 BENEFIT-RISK ASSESSMENT

The preliminary safety and efficacy data from the ongoing studies of tiragolumab as a single agent or in combination with atezolizumab across different solid tumor indications, including treatment naive NSCLC, support a favorable benefit–risk profile for tiragolumab and atezolizumab. Because of the reinvigoration of an anti-tumor immune response by immune-modulating radiotherapy and the potential synergism with immune CPI treatment, the potentially synergistic mechanisms of action of atezolizumab and tiragolumab, as well as their manageable and tolerable safety profiles,

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

combination treatment with these two treatment modalities appears to have promising therapeutic potential in solid tumors and may reinvigorate and augment the anti-tumor immune response, potentially resulting in improved and more durable clinical benefit for patients with treatment naïve NSCLC.

Preclinical data indicate promising activity for the triple combination in metastatic setting. Results from the Morpheus HCC study (GO42216) presented at the ASCO 2023 showed that atezolizumab in combination with bevacizumab and tiragolumab had higher ORR and longer PFS compared with the current standard of care of atezolizumab in combination with bevacizumab and identified no new safety signals (Finn et al. 2023). Fifty-eight patients with unresectable, locally advanced or metastatic HCC who were randomized into atezolizumab in combination with bevacizumab and tiragolumab arm showed a confirmed ORR of 42.5% and a PFS of 11.1 months (95% CI: 8.2 months to not estimable) compared with an ORR of 11.1% and a PFS of 4.2 months (95% CI: 1.6 to 7.4 months) in the atezolizumab plus bevacizumab arm, corresponding to a PFS HR of 0.42 (95% CI: 0.22 to 0.82).

Furthermore, the current study (BO39610) contains all safety measures of an early development study in that it enrolls only a well-defined patient population with good performance status selected on the basis of the known safety profile of the combination partners. In addition, the study implements close safety monitoring, including frequent visits of patients to the site, strict inclusion and exclusion criteria, regular investigator calls, and the implementation of an Internal Monitoring Committee and a Scientific Oversight Committee.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.4.

A15–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO +BEV +TIRA ARM

A15–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab (Tecentriq® U.S. Prescribing Information).

A15–3.2 RATIONALE FOR BEVACIZUMAB DOSE AND SCHEDULE

Bevacizumab will be administered by infusion at a fixed dose of 15 mg/kg Q3W (15 mg/kg on Day 1 of each 21-day cycle), which is an approved dosage for bevacizumab (Avastin® U.S. Prescribing Information).

[REDACTED]

[REDACTED]

[REDACTED]

Refer to the Tiragolumab Investigator's Brochure for additional details.

**A15-4 MATERIALS AND METHODS SPECIFIC TO
ATEZO +BEV +TIRA ARM**

A15-4.1 TREATMENT IN ATEZO +BEV +TIRA ARM

A15-4.1.1 Formulation, Packaging, and Handling

A15-4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the atezolizumab formulation, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A15-4.1.1.2 Bevacizumab

The bevacizumab drug product will be supplied by the Sponsor as a sterile solution in a single-use, 4-mL or 16-mL, preservative-free glass vial. The 4-mL vial contains 100 mg of bevacizumab (25 mg/mL), and the 16-mL vial contains 400 mg of bevacizumab (25 mg/mL).

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For information on the bevacizumab formulation, see the pharmacy manual and the Bevacizumab Investigator's Brochure.

A15-4.1.1.3 Tiragolumab

The tiragolumab drug product will be supplied by the Sponsor [REDACTED]

For information on the tiragolumab formulation, see the pharmacy manual and the Tiragolumab Investigator's Brochure.

A15-4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo +Bev +Tira arm will receive treatment as outlined in [Table A15-1](#) until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see [Section 3.1.1](#) for details). [REDACTED]

Table A15-1 Treatment Regimen for Atezo +Bev +Tira Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none">• Atezolizumab 1200 mg by IV infusion on Day 1 of each cycle• Bevacizumab 15 mg/kg by IV infusion on Day 1 of each cycle ^a• Tiragolumab 600 mg by IV infusion on Day 1 of each cycle ^b

Atezo +Bev +Tira =atezolizumab plus bevacizumab plus tiragolumab;

IRR =infusion-related reaction.

^a On Day 1 of each cycle, bevacizumab will be administered at least 5 minutes after completion of the atezolizumab infusion.

^b [REDACTED]

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any

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associated adverse events, should be reported as described in Section 5.3.5.12.

No safety data related to overdosing of atezolizumab, bevacizumab, or tiragolumab are available to date.

A15-4.1.2.1 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5.

Atezolizumab infusions will be administered per the instructions outlined in Table A15-2.

Table A15-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
<ul style="list-style-type: none">No premedication is permitted prior to the atezolizumab infusion.Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion.Atezolizumab should be infused over 60 (± 15) minutes.If clinically indicated, vital signs should be measured every 15 (± 5) minutes during the infusion and at 30 (± 10) minutes after the infusion.Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	<ul style="list-style-type: none">If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for subsequent doses at the discretion of the investigator.Vital signs should be measured within 60 minutes prior to the infusion.Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an IRR or 60 (± 15) minutes if the patient experienced an IRR with the previous infusion.If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (± 10) minutes after the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of IRRs for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A15-5.1.5.2. Atezolizumab treatment may be suspended for reasons other than

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toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A15-4.1.2.2 Bevacizumab Administration

Bevacizumab will be administered by IV infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle. On Day 1 of each cycle, bevacizumab will be administered at least 5 minutes after completion of the atezolizumab infusion.

Administration of bevacizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#).

Bevacizumab infusions will be administered per the instructions outlined in [Table A15-3](#).

Table A15-3 Administration of First and Subsequent Bevacizumab Infusions

First Infusion	Subsequent Infusions
<ul style="list-style-type: none">No premedication is permitted prior to the bevacizumab infusion.Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) should be measured within 60 minutes prior to the infusion.Bevacizumab should be infused over 90 (\pm15) minutes.Vital signs should be measured at the end of infusion and 2 (\pm1) hours after the infusion.Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	<ul style="list-style-type: none">If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for subsequent doses at the discretion of the investigator.Vital signs should be recorded within 60 minutes prior to the infusion.Bevacizumab should be infused over 60 (\pm10) minutes if the previous 90-minute infusion was tolerated without an IRR, or 90 (\pm15) minutes if the patient experienced an IRR with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (\pm5) minutes thereafter.Vital signs should be measured within 30 minutes after completion of the infusion.

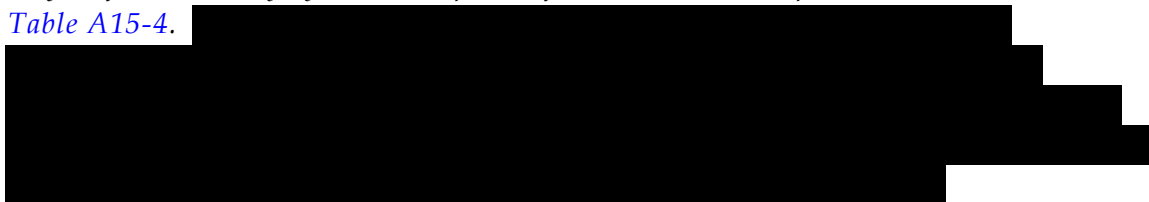
IRR = infusion-related reaction.

Guidelines for medical management of IRRs for bevacizumab are provided in [Section A15-5.1.5](#).

No dose modification for bevacizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section [A15-5.1.5.2](#). Bevacizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A15-4.1.2.3 Tiragolumab Administration

Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle with a post-infusion observation period as described in [Table A15-4](#).



Administration of tiragolumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#). Tiragolumab infusions will be administered according to the instructions outlined in [Table A15-4](#).

Table A15-4 Administration of First and Subsequent Tiragolumab Infusions

<ul style="list-style-type: none">••••••	<ul style="list-style-type: none">••••••

Guidelines for medical management of IRRs for tiragolumab are provided in [Appendix 6](#).

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in [Section A15-5.1.5.2](#). Tiragolumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A15-4.1.3 Stage 2 Treatment

Patients in Cohort 2, Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in [Section 3.1.1](#)) or unacceptable toxicity related to atezolizumab will be given the option of receiving a different treatment combination

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during Stage 2, as outlined in [Table A15-5](#), provided they meet the eligibility criteria for Stage 2 (see [Section 4.1](#)) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A15-5 Stage 2 Treatment Regimens Available for Atezo +Bev +Tira Arm

Study Treatment	Appendix
Atezo + Docetaxel	Appendix 16

Atezo = atezolizumab; Bev = bevacizumab; Tira = tiragolumab.

Refer to [Appendix 16](#) for details specific to the atezolizumab plus docetaxel arm.

A15-4.2 CONCOMITANT THERAPY FOR ATEZO +BEV +TIRA ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A15-4.2.1 Permitted Therapy for Atezo +Bev +Tira Arm

Patients are permitted to use the following therapies during the study:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

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- [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]

[REDACTED]

 - [REDACTED]

[REDACTED]

 - [REDACTED]

[REDACTED]

 - [REDACTED]
 - [REDACTED]

[REDACTED]

 - [REDACTED]

[REDACTED]

Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for the second atezolizumab, bevacizumab, and tiragolumab infusions only, at the discretion of the investigator. [REDACTED]



In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 -adrenergic agonists; refer to [Appendix 5](#) for details).

A15-4.2.2 Cautionary Therapy for Atezo +Bev +Tira Arm

A15-4.2.2.1 Corticosteroids and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and/or tiragolumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab and/or tiragolumab therapy (refer to [Appendix 6](#) for details).

The above list of cautionary medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor is available to advise as needed if questions arise regarding medications not listed above.

A15-4.2.2.2 Herbal Therapies

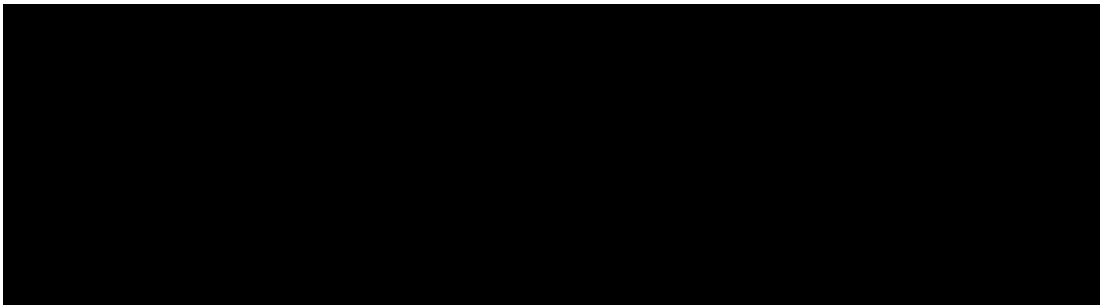

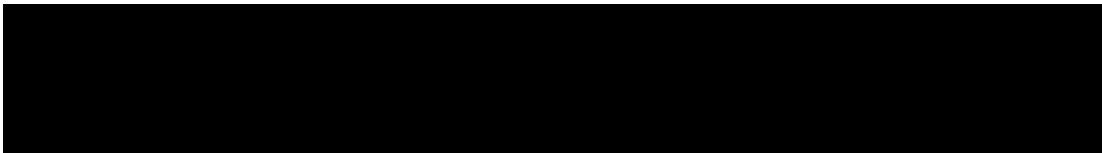
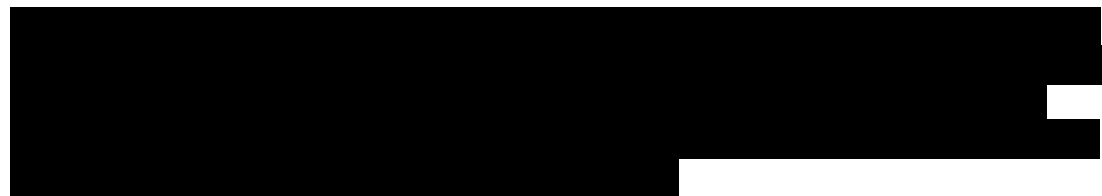


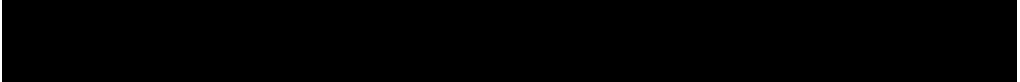
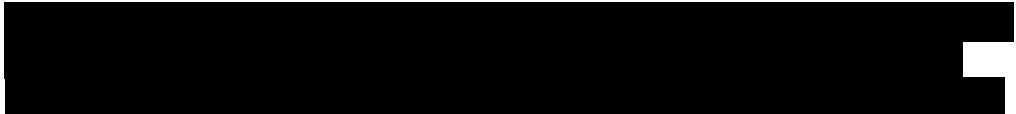
Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section [A15-4.2.3](#)) may be used during the study at the discretion of the investigator.

A15-4.2.2.3 Bisphosphonates

Osteonecrosis of the jaw has been reported in patients receiving bevacizumab, mainly in combination with bisphosphonates. Thus, caution must be exercised in using bevacizumab in patients receiving concomitant bisphosphonates.

A15-4.2.3 Prohibited Therapy for Atezo +Bev +Tira Arm

Use of the following concomitant therapies is prohibited as described below:

- 
- 
- 
- 
- 




A15-4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO +BEV +TIRA ARM

Contraception requirements for women and men in the Atezo +Bev +Tira arm are outlined below.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 5 months after the final dose of atezolizumab, for 6 months after the final dose of bevacizumab, and for 90 days after the final dose of tiragolumab.

A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

Hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of bevacizumab and for 90 days after the final dose of tiragolumab to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of

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preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

A15-5 ASSESSMENT OF SAFETY FOR ATEZO +BEV +TIRA ARM

A15-5.1 SAFETY PLAN FOR ATEZO +BEV +TIRA ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab, bevacizumab, and tiragolumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections [A15-5.1.1](#), [A15-5.1.2](#), [A15-5.1.3](#), and [A15-5.1.4](#)). Guidelines for management of patients who experience specific adverse events are provided in Section [A15-5.1.5](#).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study.

Administration of study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections [5.2–5.6](#).

A15-5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial palsy, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A15-5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: GI perforations, hemorrhage, arterial thromboembolic events, fistulae, wound-healing complications, hypertension, venous thromboembolism, proteinuria, congestive heart failure, and posterior reversible encephalopathy syndrome.

Refer to Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for bevacizumab.

A15-5.1.3 Risks Associated with Tiragolumab

IRRs and [REDACTED] are identified risks of tiragolumab. [REDACTED]
[REDACTED] Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events).

Refer to [Appendix 6](#) of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for details on nonclinical and clinical safety assessments.

A15-5.1.3.1 Infusion-Related Reactions

Because tiragolumab is a therapeutic monoclonal antibody and targets immune cells, IRRs associated with hypersensitivity reactions and/or target-mediated cytokine release may occur. Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

IRRs have been reported in patients treated with tiragolumab, with or without atezolizumab. The majority of events were mild to moderate and manageable.

[REDACTED] Subsequent infusions and observation times may be shortened if the preceding infusion was well tolerated. All infusions of tiragolumab will be administered in an appropriate medical setting.

Refer to Section [A15-4.1.2.3](#) for detailed guidance on administration of tiragolumab in this study. Please see [Appendix 5](#) for guidance on anaphylaxis precautions and [Table A15-6](#) and [Appendix 6](#) for guidance on the management of IRRs.

[REDACTED]

[REDACTED]

The IgG1 backbone of tiragolumab with the intact Fc-effector function may lead to antibody-dependent cell-mediated cytotoxicity-mediated reduction in lymphocyte

count. [REDACTED]

[REDACTED] Patients with a lymphocyte count <500 cells/mL will be excluded from the study (Section 4.1.2) and complete blood counts will be monitored regularly during the study.

A15-5.1.3.4 Immune-Mediated Adverse Events

Nonclinical models have suggested a role of TIGIT signaling interruption in autoimmunity. In a knockout model (TIGIT^{-/-}), loss of TIGIT signaling resulted in hyperproliferative T-cell responses and exacerbation of experimental autoimmune encephalitis (EAE). TIGIT^{-/-} and wild-type B6 mice were immunized with myelin oligodendrocyte glycoprotein peptide in an EAE using suboptimal doses. In contrast to the wild-type B6 mice, the majority of the TIGIT^{-/-} mice developed severe EAE (Joller et al. 2011).

Clinical experience with therapeutics intended to enhance anti-tumor T-cell responses has demonstrated that development of autoimmune inflammatory conditions is a general risk and may therefore be considered a potential risk of tiragolumab. Such immune-mediated adverse events have been described for virtually all organ systems and include, but are not limited to, colitis, pneumonitis, endocrinopathies, ocular toxicity, pancreatic toxicity, neurologic toxicity, cardiac toxicity, nephritis, myositis, and severe cutaneous adverse reactions.

Patients with a history of autoimmune disease will be excluded from this study. Refer to Section 4.1.2 for details.

In this study, immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A15-5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

Suggested management guidelines for individual suspected immune-mediated adverse events are provided in Appendix 6.

A15-5.1.3.5 Embryofetal Toxicity

[REDACTED]. Administration of tiragolumab is expected to have adverse effects on pregnancy based on the expression of TIGIT on decidual NK and CD8⁺ T cells (Powell et al. 2017; van der Zwan et al. 2018; Vento-Tormo et al. 2018), and the expected role of these cells in the recognition and response to foreign fetal, placental, and viral antigens at the maternal-fetal interface as well as maintenance of maternal-fetal tolerance. No reproductive or teratogenicity studies in animals have been conducted with tiragolumab. There are no clinical studies

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of tiragolumab in pregnant women. Tiragolumab should not be administered to pregnant women.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of embryofetal toxicity.

A15-5.1.4 Risks Associated with Combination Use of Atezolizumab, Bevacizumab, and Tiragolumab

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab, bevacizumab, and tiragolumab: IRRs and immune-mediated toxicities (including HLH).

A15-5.1.5 Management of Patients Who Experience Specific Adverse Events in Atezo+Bev +Tira Arm

A15-5.1.5.1 Dose Modifications

There will be no dose modifications for atezolizumab, bevacizumab, and tiragolumab in this study.

A15-5.1.5.2 Treatment Interruption for Toxicities

Atezolizumab and tiragolumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see [Table A15-6](#)).

On the basis of the available characterization of mechanism of action, tiragolumab may cause adverse events similar to, but independent of, atezolizumab. Tiragolumab may also exacerbate the frequency or severity of atezolizumab-related adverse events or may have non-overlapping toxicities with atezolizumab. Because these scenarios may not be distinguishable from each other in the clinical setting, adverse events should generally

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be attributed to both agents, and dose interruptions or treatment discontinuation in response to adverse events should be applied to both tiragolumab and atezolizumab.

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 non-serious adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤ 1 , bevacizumab may be restarted at the same dose level. If bevacizumab is delayed due to toxicity for >42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab. Bevacizumab can be resumed after being withheld for >42 days if the patient is likely to derive clinical benefit. The decision to re-challenge patients with bevacizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.



Refer to Section [A15–4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A15–5.1.5.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in [Table A15-6](#). These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

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Table A15-6 Guidelines for Management of Patients Who Experience Adverse Events in Atezo +Bev +Tira Arm

[illegible]

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

Table A15-6 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev +Tira Arm (cont.)

<i>Event</i>	<i>Action to Be Taken</i>
<i>Gastrointestinal events (cont.)</i>	

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Table A15-6 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev +Tira Arm (cont.)

<i>Event</i>	<i>Action to Be Taken</i>
[REDACTED]	
[REDACTED]	• [REDACTED]
[REDACTED]	• [REDACTED] • [REDACTED]
[REDACTED]	• [REDACTED] • [REDACTED]
[REDACTED]	• [REDACTED] • [REDACTED]
[REDACTED]	• [REDACTED] • [REDACTED]
[REDACTED]	
[REDACTED]	

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Table A15-6 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev +Tira Arm (cont.)

[illegible]

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

Table A15-6 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev +Tira Arm (cont.)

Event	Action to Be Taken
[REDACTED]	
[REDACTED]	<ul style="list-style-type: none"> [REDACTED] [REDACTED]
[REDACTED]	<ul style="list-style-type: none"> [REDACTED] [REDACTED]^a
[REDACTED]	
[REDACTED]	<ul style="list-style-type: none"> [REDACTED] [REDACTED]
[REDACTED]	<ul style="list-style-type: none"> [REDACTED] [REDACTED]
[REDACTED]	
[REDACTED]	<ul style="list-style-type: none"> [REDACTED] [REDACTED] [REDACTED]
[REDACTED]	<ul style="list-style-type: none"> [REDACTED] [REDACTED]

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

Table A15-6 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev +Tira Arm (cont.)

<i>Event</i>	<i>Action to Be Taken</i>
<i>IRRs, [REDACTED], anaphylaxis, and hypersensitivity reaction (cont.)</i>	
[REDACTED]	
<i>Pancreatic events</i>	
[REDACTED]	
<i>Dermatologic events</i>	
[REDACTED]	

Appendix 15: Study Details Specific to Atezo + Bev + Tira Arm

Table A15-6 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev +Tira Arm (cont.)

[illegible]

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

Table A15-6 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev +Tira Arm (cont.)

Event	Action to Be Taken
Neurologic disorders	

Appendix 15: Study Details Specific to Atezo + Bev + Tira Arm

Table A15-6 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev +Tira Arm (cont.)

[illegible]

Appendix 15: Study Details Specific to Atezo + Bev + Tira Arm

Table A15-6 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev +Tira Arm (cont.)

[illegible]

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

Table A15-6 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev +Tira Arm (cont.)

Event	Action to Be Taken
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

Table A15-6 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev +Tira Arm (cont.)

<i>Event</i>	<i>Action to Be Taken</i>
[REDACTED]	
[REDACTED]	<ul style="list-style-type: none"> • [REDACTED] • [REDACTED]
[REDACTED]	
[REDACTED]	<ul style="list-style-type: none"> • [REDACTED] • [REDACTED] • [REDACTED]
[REDACTED]	
[REDACTED]	<ul style="list-style-type: none"> • [REDACTED] • [REDACTED]
[REDACTED]	<ul style="list-style-type: none"> • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED]
[REDACTED]	
[REDACTED]	<ul style="list-style-type: none"> • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED]
[REDACTED]	

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

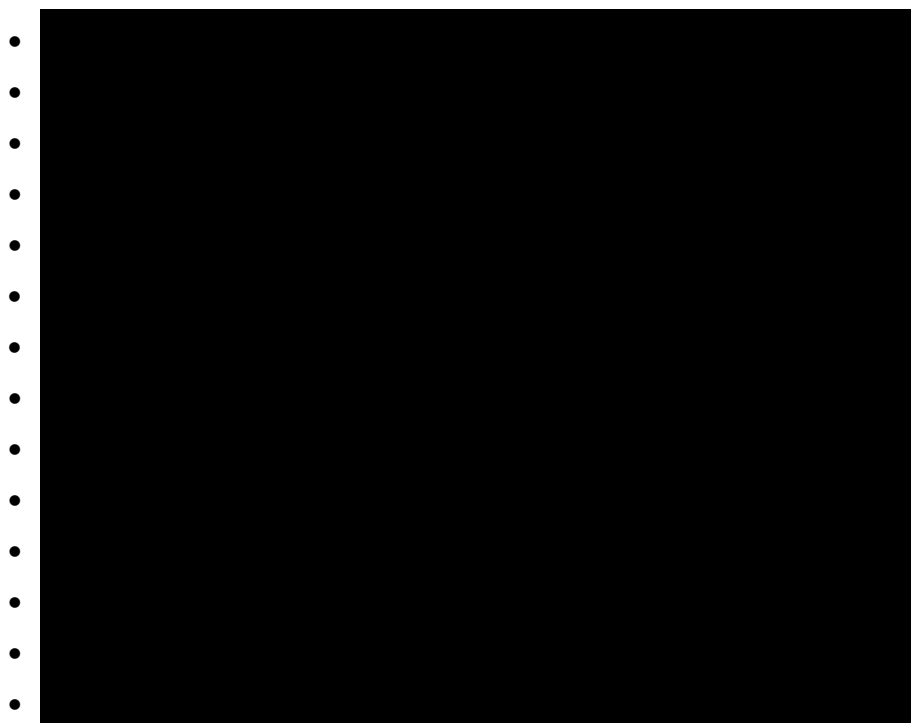
Table A15-6 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev +Tira Arm (cont.)

<i>Event</i>	<i>Action to Be Taken</i>
	<ul style="list-style-type: none">
<i>a</i>	
<i>b</i>	
<i>c</i>	

A15-5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + BEV + TIRA ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.2.3 for reporting instructions). Adverse events of special interest for the Atezo + Bev + Tira arm are as follows:

- [illegible]



A15-5.3 *REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO +BEV +TIRA ARM*

A15-5.3.1 *Pregnancies in Female Patients*

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab, 6 months after the final dose of bevacizumab, or 90 days after the final dose of tiragolumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A15-5.3.2 *Pregnancies in Female Partners of Male Patients*

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within

6 months after the final dose of bevacizumab or 90 days after the final dose of tiragolumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A15-5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A15-5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

A15-6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO +BEV +TIRA ARM

Table A15-7 Schedule of Activities for Atezo +Bev +Tira Arm

Assessment/Procedure	Stage 1 Screening (see Appendix 2)	Treatment Cycles (21-day cycles) ^a		Stage 2 Screen. (see Appendix 2) ^c or Treatment Discontinuation ^d (see below)	Follow-Up ^d
		Cycle 1 ^b	Cycles ≥2		
	Days −28 to −1	Day 1	Day 1 (±3 days)		Every 3 Months
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available			
Vital signs ^e		<i>x</i>	<i>x</i>	<i>x</i>	
Weight		<i>x</i> ^f	<i>x</i> ^f	<i>x</i>	
Complete physical examination ^g				<i>x</i>	
Limited physical examination ^h		<i>x</i> ^f	<i>x</i> ^f		
ECOG Performance Status		<i>x</i> ^f	<i>x</i> ^f	<i>x</i>	
ECG ^{f, i}		Perform as clinically indicated.			
Hematology ^j		<i>x</i> ^{k, l}	<i>x</i> ^k	<i>x</i>	
Chemistry panel ^m		<i>x</i> ^{k, l}	<i>x</i> ^k	<i>x</i>	
Coagulation (INR and aPTT)		<i>x</i> ^{k, l}	<i>x</i> ^k	<i>x</i>	
TSH, free T3 (or total T3), free T4 ⁿ		<i>x</i> ^l		<i>x</i>	
Pregnancy test ^o		<i>x</i> ^{k, l}	<i>x</i> ^k	<i>x</i>	<i>x</i> ^o
Urinalysis ^p		<i>x</i> ^q	<i>x</i> ^q	<i>x</i>	
Serum autoantibody analysis ^r		Perform if a patient experiences a suspected immune-mediated adverse event.			

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

Table A15-7 Schedule of Activities for Atezo +Bev +Tira Arm

Assessment/Procedure	Stage 1 Screening (see <i>Appendix 2</i>)	Treatment Cycles (21-day cycles) ^a		Stage 2 Screen. (see <i>Appendix 2</i>) ^c or Treatment Discontinuation ^d (see below)	Follow-Up ^d
		Cycle 1 ^b	Cycles ≥2		
	Days −28 to −1	Day 1	Day 1 (±3 days)		Every 3 Months
PK samples	See <i>Appendix 2</i>	Refer to <i>Table A15-8</i> .			
ADA samples		Refer to <i>Table A15-8</i> .			
Biomarker samples		Refer to <i>Table A15-8</i> .			
Blood sample for RBR (optional) ^s		<i>x</i>			
Tumor biopsy		<i>x</i> ^{t, u}			
Tumor biopsy (optional)		<i>x</i> ^{u, v}			
Tumor response assessments		<i>x</i> ^{w, x, y}			
Concomitant medications ^z		<i>x</i>	<i>x</i>	<i>x</i>	
Adverse events ^{aa}		<i>x</i>	<i>x</i>	<i>x</i> ^{aa}	<i>x</i> ^{aa}
Atezolizumab administration ^{bb, cc}		<i>x</i>	<i>x</i>		
Bevacizumab administration ^{bb, dd}		<i>x</i>	<i>x</i>		
Tiragolumab administration ^{bb, ee}		<i>x</i>	<i>x</i>		
Survival follow-up and anti-cancer treatment				<i>x</i> ^{ff}	

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

Table A15-7 Schedule of Activities for Atezo +Bev +Tira Arm

ADA =anti-drug antibody; Atezo +Bev +Tira =atezolizumab plus bevacizumab plus tiragolumab; CT =computed tomography; ECOG =Eastern Cooperative Oncology Group; eCRF =electronic Case Report Form; PK =pharmacokinetic; RBR =Research Biosample Repository; RECIST v1.1 =Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen. =screening; T3 =triiodothyronine; T4 =thyroxine; TSH =thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

- ^a If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. The Medical Monitor is available to advise as needed.
- ^b It is recommended that treatment be initiated no later than 7 days after randomization.
- ^c Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.4) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.
- ^d Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the final dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments.
- ^e Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (\pm 5) minutes during and 30 (\pm 10) minutes after the infusion. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (\pm 10) minutes after the infusion.
- ^f Assessment may be performed within 24 hours prior to dosing during the treatment period.

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

Table A15-7 Schedule of Activities for Atezo +Bev +Tira Arm

- ^g Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^h Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ⁱ It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.
- ^j Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).
- ^k Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.
- ^l If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.
- ^m Chemistry panel (serum or plasma) includes bicarbonate or carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included on Day 1 of each treatment cycle.
- ⁿ TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).
- ^o All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum pregnancy tests will be performed at specified subsequent visits and at 3 months and 6 months after the final dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^p Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ^q Urinalysis may be performed up to 72 hours prior to Day 1 of each cycle, as results must be available prior to treatment administration. See [Table A15-6](#) for management guidelines for proteinuria.
- ^r Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Serum samples collected for the assessment of PK, ADAs, or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment, may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.
- ^s Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

Table A15-7 Schedule of Activities for Atezo +Bev +Tira Arm

- ^t On-treatment biopsies must be performed at least 7 days after the previous bevacizumab dose. Bevacizumab must be administered ≥ 3 days after any on-treatment biopsy, but only after adequate wound healing has been demonstrated. The biopsy should not be performed in an anatomic location at risk for excessive bleeding, as determined by the investigator.
- ^u Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see Section 3.1.2) will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible). See Section 4.5.6 for tissue sample requirements.
- ^v Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.
- ^w Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (± 1 week) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 6 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.
- ^x All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).
- ^y For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).
- ^z Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

Appendix 15: Study Details Specific to Atezo +Bev +Tira Arm

Table A15-7 Schedule of Activities for Atezo +Bev +Tira Arm

- ^{aa} After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until [REDACTED] days after the final dose of study treatment [REDACTED] and serious adverse events and adverse events of special interest will continue to be reported until [REDACTED] days after the final dose of study treatment [REDACTED]. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.
- ^{bb} Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).
- ^{cc} Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.
- ^{dd} Bevacizumab will be administered by IV infusion at a dose of 15mg/kg on Day 1 of each 21-day cycle. The initial dose of bevacizumab will be delivered over 90 (± 15) minutes. If the first bevacizumab infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (± 10) minutes. If the 60 (± 10) minute infusion was tolerated without infusion-associated adverse events, the third infusion may be delivered over 30 (± 15) minutes. If the 30-minute bevacizumab infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. Bevacizumab will be administered after completion of the atezolizumab infusion. Bevacizumab must be administered ≥ 3 days after any on-treatment biopsy, but only after adequate wound healing has been demonstrated.
- ^{ee} [REDACTED]
- ^{ff} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Appendix 15: Study Details Specific to Atezo + Bev +Tira Arm

[REDACTED]

[REDACTED]

[REDACTED]

Appendix 15: Study Details Specific to Atezo + Bev +Tira Arm

[REDACTED]

[REDACTED]

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Appendix 16

Study Details Specific to Atezo + Docetaxel Arm

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A16–1 BACKGROUND ON ATEZO+DOCETAXEL ARM

A16–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, *myocarditis*, and *nephritis*, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma (in the European Union), non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer (in the European Union), hepatocellular carcinoma, melanoma (in the United States), and alveolar soft part sarcoma (in the United States).

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A16–1.2 BACKGROUND ON DOCETAXEL

Docetaxel is a commonly used standard treatment option after failure of platinum-based chemotherapy in patients with locally advanced or metastatic NSCLC. It has demonstrated a survival benefit relative to best supportive care in patients with relapsed NSCLC following first-line therapy and is associated with a response rate of 6%–11% and a median overall survival (OS) of 5–10 months (Stinchcombe and Socinski 2008; Ramlau et al. 2012).

A16–2 RATIONALE FOR ATEZO+DOCETAXEL ARM

A16–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses by binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors, have *had* a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active *as monotherapy* for many patients.

A16–2.2 RATIONALE FOR COMBINING IMMUNE CHECKPOINT INHIBITORS WITH CHEMOTHERAPY

Tumor-cell killing by cytotoxic chemotherapy can reasonably be expected to expose the immune system to high levels of tumor antigens, and invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007). Evaluating the safety and efficacy of these treatment combinations in patients with NSCLC will enable this hypothesis to be tested.

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Recently, the combination of pembrolizumab with carboplatin/cisplatin and pemetrexed was approved by the U.S. FDA for patients with non-squamous NSCLC based on the Phase II study KEYNOTE-021. The objective response rate (ORR) for pembrolizumab in combination with pemetrexed and carboplatin (55%; 33 of 60 patients) was nearly double the ORR for pemetrexed and carboplatin alone (29%; 18 of 63 patients). In addition, 92% of patients treated with pembrolizumab plus chemotherapy had a duration of response of 6 months or more compared with 81% of patients treated with chemotherapy alone. Median PFS was 13.0 months for patients treated with pembrolizumab plus chemotherapy and 8.9 months for patients treated with chemotherapy alone (Langer et al. 2016). The incidence of Grade 3 or higher treatment-related adverse events was similar between groups.

These results have been confirmed for patients with non-squamous NSCLC in the Phase III study KEYNOTE-189. The triplet combination demonstrated a significantly longer median OS in the intent-to-treat population than chemotherapy alone (HR=0.49; $p < 0.0001$). Median PFS was also significantly longer for the experimental arm (8.8 months vs. 4.9 months; HR=0.52, $p < 0.0001$) (Gandhi et al. 2018). This combination may replace platinum-based chemotherapy regimens as a standard of care for patients who were previously untreated with advanced-stage non-squamous NSCLC with low PD-L1 expression.

In the Phase III study KEYNOTE-407, the combination of pembrolizumab with carboplatin plus either paclitaxel or nanoparticle albumin-bound (nab)-paclitaxel demonstrated a statistically significant OS benefit compared with the control arm of carboplatin plus nab-paclitaxel (HR=0.64; 95% CI: 0.49 to 0.85; $p < 0.001$). The OS benefit was consistent across all levels of PD-L1 expression. The median PFS was 6.4 months (95% CI: 6.2 to 8.3) in the pembrolizumab combination group and 4.8 months (95% CI: 4.3 to 5.7) in the placebo combination group (HR=0.56; 95% CI: 0.45 to 0.70; $p < 0.001$) (Paz-Ares et al. 2018). On the basis of these results, the FDA has approved the combination of pembrolizumab plus carboplatin plus nab-paclitaxel for the first-line treatment of patients with squamous NSCLC.

As of 10 February 2015 (data cutoff) in an ongoing Phase Ib study of first-line treatment of NSCLC (Study GP28328), the ORR was 70.6% (12 of 17) for patients treated with atezolizumab plus pemetrexed and carboplatin, 50.0% (8 of 16) for patients treated with atezolizumab plus nab-paclitaxel and carboplatin, and 37.5% (3 of 8) for patients treated with atezolizumab plus paclitaxel and carboplatin. Atezolizumab in combination with chemotherapy was not associated with additive severe (Grade 3 or higher) toxicities. The adverse events observed for atezolizumab in combination with chemotherapy were consistent with the known risks of each study treatment.

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

More recently, in the Phase III Impower150 study, the combination of atezolizumab and bevacizumab plus carboplatin and paclitaxel demonstrated a significant increase in PFS compared with bevacizumab plus carboplatin and paclitaxel in patients with metastatic non-squamous NSCLC (ITT population: HR=0.62; 95% CI: 0.52 to 0.74; $p < 0.001$). Furthermore, a significant and clinically meaningful improvement in median OS was observed for the atezolizumab-containing group at the second interim analysis (19.2 months vs. 14.7 months; stratified HR=0.78; 95% CI: 0.64 to 0.96; $p=0.02$) (Socinski et al. 2018).

Detailed clinical study results for Study GP28328 and Impower150 can be found in the Atezolizumab Investigator's Brochure.

A16–2.3 BENEFIT–RISK ASSESSMENT

The efficacy and safety results for pembrolizumab plus chemotherapy (Langer et al. 2016) and the preliminary efficacy and safety results for atezolizumab plus chemotherapy (Study GP28328), as well as the recent results from the Phase III studies KEYNOTE-189 (Gandhi et al., 2018), KEYNOTE-407 (Paz-Ares et al., 2018), and Impower150 (Socinski et al., 2018) offer evidence of an acceptable safety profile and a very promising therapeutic potential when combining a PD-1 or PD-L1 inhibitor with chemotherapy as treatment for NSCLC.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.4.

A16–3 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab (Tecentriq® U.S. *Prescribing Information*).

A16–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+DOCETAXEL ARM

A16–4.1 TREATMENT IN ATEZO+DOCETAXEL ARM

A16–4.1.1 Formulation, Packaging, and Handling

A16–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the atezolizumab formulation, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

A16–4.1.1.2 Docetaxel

For information on the formulation, packaging, and handling of docetaxel, refer to the local prescribing information.

A16–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus docetaxel (Atezo + Docetaxel) arm will receive treatment as outlined in [Table A16-1](#). Patients will continue atezolizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details) and will continue docetaxel until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1. For Stage 1, it is recommended that treatment be initiated no later than 7 days after randomization. For Stage 2, it is recommended that treatment be initiated no later than 7 days after treatment assignment.

Table A16-1 Treatment Regimen for Atezo + Docetaxel Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none">• Atezolizumab 1200 mg IV on Day 1 of each cycle• Docetaxel 75 mg/m² IV over 1 hour on Day 1 of each cycle

Atezo + Docetaxel = atezolizumab plus docetaxel.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

No safety data related to overdosing of atezolizumab are available. For information on overdosing of docetaxel, refer to the local prescribing information for each agent.

A16–4.1.2.1 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#). Atezolizumab infusions will be administered per the instructions outlined in [Table A16-2](#).

Table A16-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
<ul style="list-style-type: none"> No premedication is permitted prior to the atezolizumab infusion. Vital signs (pulse rate, respiratory rate, <i>pulse oximetry</i>, blood pressure, and temperature) should be <i>measured</i> within 60 minutes prior to the infusion. Atezolizumab should be infused over 60 (± 15) minutes. If clinically indicated, vital signs should be <i>measured</i> every 15 (± 5) minutes during <i>the infusion</i> and at 30 (± 10) minutes after the infusion. Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. 	<ul style="list-style-type: none"> If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic <i>medications</i>, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. Vital signs should be <i>measured</i> within 60 minutes prior to the infusion. Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an IRR or 60 (± 15) minutes if the patient experienced an IRR with the previous infusion. If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be <i>measured</i> during the infusion and at 30 (± 10) minutes after the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in [Appendix 6](#).

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section [A16–5.1.4](#). Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A16–4.1.2.2 Docetaxel Administration

Docetaxel will be administered by IV infusion at a dose of 75 mg/m² over 60 minutes on Days 1 of each 21-day cycle. Docetaxel will be administered approximately 30 minutes after completion of the atezolizumab infusion.

Docetaxel will be administered in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. To reduce the incidence and severity of fluid retention, as well as the severity of hypersensitivity reactions, patients should be premedicated with corticosteroids according to local practice (e.g., 8 mg of oral dexamethasone

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

administered twice daily) for 3 days, starting 1 day prior to docetaxel administration. Anti-emetic medications may be administered prophylactically according to local practice at the investigator's discretion.

Guidelines for docetaxel dose modification and treatment interruption or discontinuation because of toxicities are provided in Section [A16–5.1.4](#). Docetaxel treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A16–4.2 CONCOMITANT THERAPY FOR ATEZO + DOCETAXEL ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

For details regarding the concomitant therapies for docetaxel, refer to the docetaxel prescribing information.

A16–4.2.1 Permitted Therapy for Atezo + Docetaxel Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin at a stable dose)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Inactivated vaccines (such as influenza and COVID-19)
 - Live, attenuated vaccines are not permitted (see [A16–4.2.3](#)).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

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- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy

Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and docetaxel may be continued during palliative radiotherapy.

- Radiotherapy to the brain as outlined below:

Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive limited-field radiotherapy to the brain (stereotactic radiosurgery) provided that all of the following criteria are met:

- The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.
- The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

- Anti-convulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretic *medications*, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator. *Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.*

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections [A16–4.2.2](#) and [A16–4.2.3](#)) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 -adrenergic agonists; see [Appendix 5](#)).

A16–4.2.2 Cautionary Therapy for Atezo + Docetaxel Arm

A16–4.2.2.1 Corticosteroids and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may be administered at the discretion of the investigator. The Medical Monitor is available to advise as needed.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to [Appendix 6](#) for details).

The above list of cautionary medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor is available to advise as needed if questions arise regarding medications not listed above.

A16–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section [A16–4.2.3](#)) may be used during the study at the discretion of the investigator.

A16–4.2.2.3 CYP3A4 Inhibitors and Inducers

The concomitant use of docetaxel with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) and strong CYP3A4 inducers should be avoided.

A16–4.2.3 Prohibited Therapy for Atezo + Docetaxel Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A16–4.2.1.
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the *final* dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

A16–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + DOCETAXEL ARM

Contraception requirements for women and men in the Atezo + Docetaxel arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the *final* dose of atezolizumab and 6 months after the *final* dose of docetaxel.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

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The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below.

With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 6 months after the *final* dose of docetaxel. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the *final* dose of docetaxel to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A16–5 ASSESSMENT OF SAFETY FOR ATEZO + DOCETAXEL ARM

A16–5.1 SAFETY PLAN FOR ATEZO + DOCETAXEL ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and chemotherapy in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections [A16–5.1.1](#), [A16–5.1.2](#), and [A16–5.1.3](#)). Guidelines for management of patients who experience specific adverse events are provided in Section [A16–5.1.4](#). These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections [5.2–5.6](#).

A16–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré

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syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis. Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A16–5.1.2 Risks Associated with Docetaxel

The most common side effects of docetaxel include infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.

For more details regarding the safety profile for docetaxel, refer to the docetaxel prescribing information.

A16–5.1.3 Risks Associated with Combination Use of Atezolizumab and Docetaxel

There are no significant overlapping toxicities associated with combination use of atezolizumab and docetaxel.

A16–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo + Docetaxel Arm

A16–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study.

The dose of docetaxel can be reduced to 55 mg/m² for management of drug-related toxicities. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m².

A16–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see [Table A16-3](#)). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to *the equivalent of* ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's *benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed. *Atezolizumab*

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treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Docetaxel treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment (see [Table A16-3](#)). If docetaxel has been withheld for >63 days because of toxicity, the patient should be discontinued from docetaxel.

If atezolizumab is discontinued, docetaxel can be continued if the patient is likely to derive clinical benefit, as determined by the investigator. If docetaxel is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section [A16–4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A16–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in [Table A16-3](#).

The investigator may use discretion in adhering to the guidelines for docetaxel described below, taking into account the severity of the event and benefit versus risk for the patient, with the goal of maximizing patient compliance and access to supportive care. Additionally, the prescribing information, as well as local hospital or clinical practice must be followed.

Table A16-3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm

Event	Action to Be Taken
Hematologic events	
Nadir ^a ANC $< 0.5 \times 10^9/L$ (500/ μL) for ≥ 7 days ^a or Febrile neutropenia	<p>Any occurrence:</p> <ul style="list-style-type: none"> Withhold atezolizumab. If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. <p>First occurrence:</p> <ul style="list-style-type: none"> Withhold docetaxel. If event resolves to ANC $\geq 1.5 \times 10^9/L$ (1500/μL) within 63 days, ^b and platelet count is $\geq 100 \times 10^9/L$ (100,000/μL), resume docetaxel with dose reduced to 55 mg/m². ^c If not, permanently discontinue docetaxel. <p>Second occurrence:</p> <ul style="list-style-type: none"> Permanently discontinue docetaxel.
Hepatotoxicity	
ALT/AST $> 1.5 \times ULN$ in combination with ALP $> 2.5 \times ULN$	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold docetaxel. If event resolves to baseline within 63 days, ^b resume docetaxel with dose reduced to 55 mg/m². ^c If not, permanently discontinue docetaxel.
Bilirubin $> 1 \times ULN$ or ALT/AST $> 3.5 \times ULN$ in combination with ALP $> 6 \times ULN$	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Permanently discontinue docetaxel.

Atezo + Docetaxel = atezolizumab plus docetaxel; Q2W = every 2 weeks; ULN = upper limit of normal.

^a Nadir of prior cycle.

^b If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for > 63 days. The decision to re-challenge patients with docetaxel should be based on the investigator's *benefit-risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

^c The dose of docetaxel can be reduced to 55 mg/m². If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m².

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Table A16-3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm (cont.)

Event	Action to Be Taken
Neurologic disorders	
Grade 1 or 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue docetaxel.
Grade 3	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. <p>First occurrence:</p> <ul style="list-style-type: none"> Withhold docetaxel. If event resolves to Grade 1 or better within 63 days,^b resume docetaxel with dose reduced to 55 mg/m².^c If not, permanently discontinue docetaxel. <p>Second occurrence:</p> <ul style="list-style-type: none"> Permanently discontinue docetaxel.
Grade 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Permanently discontinue docetaxel.
Hypersensitivity reaction	
Grade 1 or 2	<ul style="list-style-type: none"> Continue docetaxel at the discretion of the investigator.
Grade 3 or 4	<ul style="list-style-type: none"> Immediate discontinuation of the docetaxel infusion and aggressive therapy. Permanently discontinue docetaxel.

Atezo + Docetaxel = atezolizumab plus docetaxel; Q2W = every 2 weeks; ULN = upper limit of normal.

^a Nadir of prior cycle.

^b If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for > 63 days. The decision to re-challenge patients with docetaxel should be based on *the* investigator's *benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

^c The dose of docetaxel can be reduced to 55 mg/m². If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m².

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

Table A16-3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm (cont.)

Event	Action to Be Taken
Pleural effusion	
Grade 1	<ul style="list-style-type: none"> Continue docetaxel and atezolizumab. Monitor patient closely for possible exacerbation.
Grade 2	<ul style="list-style-type: none"> Continue docetaxel and atezolizumab. Monitor patient closely (e.g., by ultrasound Q2W). Consider initiation of standard treatment measures (e.g., salt restriction, oral diuretic). Consider thoracentesis if clinically indicated. Consider consultation with thoracic surgeon.
Grade 3	<p>First occurrence:</p> <ul style="list-style-type: none"> Withhold docetaxel treatment until resolution to Grade ≤ 1. Continue atezolizumab. Initiate standard treatment measures (e.g., salt restriction, oral diuretic). Consider consultation with thoracic surgeon. If event resolves to Grade ≤ 1 within 63 days, ^b resume docetaxel with dose reduced to 55 mg/m². If not, permanently discontinue docetaxel. <p>Second occurrence:</p> <ul style="list-style-type: none"> Permanently discontinue docetaxel. Withhold atezolizumab until resolution to Grade ≤ 1. Consider treatment measures as outlined for first occurrence. If event resolves within 12 weeks, resume atezolizumab at the previous dose level. If not, permanently discontinue atezolizumab.
Grade 4	<ul style="list-style-type: none"> Permanently discontinue docetaxel. Withhold atezolizumab until resolution to Grade ≤ 1. Consider treatment measures as outlined for Grade 3 events. If event resolves within 12 weeks, resume atezolizumab at the previous dose level. If not, permanently discontinue atezolizumab.

Atezo + Docetaxel = atezolizumab plus docetaxel; Q2W = every 2 weeks; ULN = upper limit of normal.

^a Nadir of prior cycle.

^b If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for >63 days. The decision to re-challenge patients with docetaxel should be based on *the* investigator's *benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

^c The dose of docetaxel can be reduced to 55 mg/m². If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m².

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

Table A16-3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm (cont.)

Event	Action to Be Taken
Pericardial effusion	
Grade 2	<ul style="list-style-type: none"> • Continue docetaxel and atezolizumab. • Monitor patient closely for possible exacerbation. • Consider initiation of standard treatment measures. • Consider consultation with cardiologist.
Grade 3	<p>First occurrence:</p> <ul style="list-style-type: none"> • Withhold docetaxel until resolution to Grade ≤ 2. • Continue atezolizumab. • Monitor patient closely (e.g., by ECG and echocardiography weekly). • Initiate standard treatment measures. • Consider consultation with cardiologist. • If event resolves to Grade ≤ 2 within 63 days, ^b resume docetaxel with dose reduced to 55 mg/m². ^c If not, permanently discontinue docetaxel. <p>Second occurrence:</p> <ul style="list-style-type: none"> • Permanently discontinue docetaxel. • Withhold atezolizumab for up to 12 weeks until resolution to Grade ≤ 2. • Consider treatment measures as outlined for first occurrence. • If event resolves within 12 weeks, resume atezolizumab at the previous dose level. If not, permanently discontinue atezolizumab.
Grade 4	<ul style="list-style-type: none"> • Permanently discontinue docetaxel. • Withhold atezolizumab until resolution to Grade ≤ 2. • Consider treatment measures as outlined for Grade 3 events. • If event resolves within 12 weeks, resume atezolizumab at the previous dose level. If not, permanently discontinue atezolizumab.

Atezo + Docetaxel = atezolizumab plus docetaxel; Q2W = every 2 weeks; ULN = upper limit of normal.

^a Nadir of prior cycle.

^b If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for > 63 days. The decision to re-challenge patients with docetaxel should be based on *the* investigator's *benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

^c The dose of docetaxel can be reduced to 55 mg/m². If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m².

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

Table A16-3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm (cont.)

Event	Action to Be Taken
Ascites	
Grade 1	<ul style="list-style-type: none"> Continue docetaxel and atezolizumab. Monitor patient closely for possible exacerbation.
Grade 2	<ul style="list-style-type: none"> Withhold docetaxel until resolution to Grade ≤ 1. Continue atezolizumab. Monitor patient closely (e.g., by ultrasound Q2W). Consider initiation of standard treatment measures (e.g., salt restriction, oral diuretic). Consider paracentesis if clinically indicated.
Grade 3	<p>First occurrence:</p> <ul style="list-style-type: none"> Withhold docetaxel treatment until resolution to Grade ≤ 1. Continue atezolizumab. Initiate standard treatment measures (e.g., salt restriction, oral diuretic). Consider paracentesis if clinically indicated. If event resolves to Grade ≤ 2 within 63 days, ^b resume docetaxel with dose reduced to 55 mg/m². ^c If not, permanently discontinue docetaxel. <p>Second occurrence:</p> <ul style="list-style-type: none"> Permanently discontinue docetaxel. Withhold atezolizumab treatment until resolution to Grade ≤ 1. Consider treatment measures as outlined for first occurrence. If event resolves within 12 weeks, resume atezolizumab at the previous dose level. If not, permanently discontinue atezolizumab.
Grade 4	<ul style="list-style-type: none"> Permanently discontinue docetaxel. Withhold atezolizumab until resolution to Grade ≤ 1. Consider treatment measures as outlined for Grade 3 events. If event resolves within 12 weeks, resume atezolizumab at the previous dose level. If not, permanently discontinue atezolizumab.

Atezo + Docetaxel = atezolizumab plus docetaxel; Q2W = every 2 weeks; ULN = upper limit of normal.

^a Nadir of prior cycle.

^b If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for >63 days. The decision to re-challenge patients with docetaxel should be based on *the* investigator's *benefit-risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

^c The dose of docetaxel can be reduced to 55 mg/m². If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m².

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

Table A16-3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm (cont.)

Event	Action to Be Taken
Fluid retention (other than pleural effusion, pericardial effusion, or ascites)	
Grade 1	<ul style="list-style-type: none"> Continue atezolizumab and docetaxel.
Grade 2	<ul style="list-style-type: none"> Continue atezolizumab and docetaxel. Monitor patient closely. Consider initiation of standard treatment measures (e.g., salt restriction, oral diuretic).
Grade 3	<p>Any occurrence:</p> <ul style="list-style-type: none"> Withhold atezolizumab. If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. <p>First occurrence:</p> <ul style="list-style-type: none"> Withhold docetaxel. Initiate standard treatment measures (e.g., salt restriction, oral diuretic). If event resolves to Grade 1 or better within 63 days,^b resume docetaxel with dose reduced to 55 mg/m².^c If not, permanently discontinue docetaxel. <p>Second occurrence:</p> <ul style="list-style-type: none"> Permanently discontinue docetaxel. Initiate standard treatment measures (e.g., salt restriction, oral diuretic).

Atezo + Docetaxel = atezolizumab plus docetaxel; Q2W = every 2 weeks; ULN = upper limit of normal.

^a Nadir of prior cycle.

^b If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for >63 days. The decision to re-challenge patients with docetaxel should be based on *the* investigator's *benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

^c The dose of docetaxel can be reduced to 55 mg/m². If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m².

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

Table A16-3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm (cont.)

Event	Action to Be Taken
Dermatologic events	
Dermatologic event, Grade 1 or 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue atezolizumab and docetaxel.
Dermatologic event, Grade 3	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. <p>Any occurrence:</p> <ul style="list-style-type: none"> Withhold atezolizumab. If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. <p>First occurrence:</p> <ul style="list-style-type: none"> Withhold docetaxel. If event resolves to Grade 1 or better within 63 days, ^b resume docetaxel with dose reduced to 55 mg/m².^c If not, permanently discontinue docetaxel. <p>Second occurrence:</p> <ul style="list-style-type: none"> Permanently discontinue docetaxel.
Dermatologic event, Grade 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Permanently discontinue docetaxel.
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Permanently discontinue docetaxel.

Atezo + Docetaxel = atezolizumab plus docetaxel; Q2W = every 2 weeks; ULN = upper limit of normal.

^a Nadir of prior cycle.

^b If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for >63 days. The decision to re-challenge patients with docetaxel should be based on *the* investigator's *benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

^c The dose of docetaxel can be reduced to 55 mg/m². If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m².

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

Table A16-3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm (cont.)

Event	Action to Be taken
Docetaxel-related non-hematologic <i>events</i> not described above	
Grade 1 or 2	<ul style="list-style-type: none"> Continue atezolizumab and docetaxel.
Grade 3	<p>Any occurrence:</p> <ul style="list-style-type: none"> Withhold atezolizumab. If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. <p>First occurrence:</p> <ul style="list-style-type: none"> Withhold docetaxel. If event resolves to Grade 1 or better within 63 days,^b resume docetaxel with dose reduced to 55 mg/m².^c If not, permanently discontinue docetaxel. <p>Second occurrence:</p> <ul style="list-style-type: none"> Permanently discontinue docetaxel.
Grade 4	<ul style="list-style-type: none"> Permanently discontinue docetaxel. Withhold atezolizumab. If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab.
Atezolizumab-related <i>events</i> not described above	
Grade 1 or 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue docetaxel.
Grade 3 or 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold docetaxel. If event resolves to Grade 1 or better within 63 days,^b resume docetaxel at current dose or with dose reduced by one level. The Medical Monitor is available to advise as needed. If not, permanently discontinue docetaxel.

Atezo + Docetaxel = atezolizumab plus docetaxel; Q2W = every 2 weeks; ULN = upper limit of normal.

^a Nadir of prior cycle.

^b If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for >63 days. The decision to re-challenge patients with docetaxel should be based on *the* investigator's *benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

^c The dose of docetaxel can be reduced to 55 mg/m². If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m².

A16–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO+DOCETAXEL ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Docetaxel arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 × ULN
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

A16–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+DOCETAXEL ARM

A16–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the *final* dose of atezolizumab and 6 months after the *final* dose of docetaxel. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A16–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the *final* dose of docetaxel. The investigator should report the pregnancy on the Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to docetaxel. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A16–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A16–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

A16–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+DOCETAXEL ARM

Table A16-4 Schedule of Activities for Atezo + Docetaxel Arm

Assessment/Procedure	Stage 2 Screening	Treatment Cycles (21-Day Cycles) ^a			Treat. Discon. ^c	Follow-Up
		Cycle 1 ^b		Cycles ≥ 2		Every 3 Months (± 7 days)
		Day 1	Day 15 (± 3 days)	Day 1 (± 3 days)		
Molecular profile of lung cancer (if applicable)	See Appendix 2	Whenever updated information becomes available				
Vital signs ^d		x	x	x	x	
Weight ^e		x		x	x	
Complete physical examination ^f					x	
Limited physical examination ^{e, g}		x	x	x		
ECOG Performance Status ^e		x		x	x	
ECG ^{e, h}		Perform as clinically indicated				
Hematology ⁱ		x ^j	x	x	x	
Chemistry ^k		x ^j	x	x	x	
TSH, free T3 (or total T3), and free T4 ^l		x ^j			x	
Pregnancy test ^m		x		x	x	
Blood sample for blood-based NGS ctDNA test ⁿ					x	
Urinalysis ^o		Perform as clinically indicated				
Serum autoantibody sample ^p		Perform if a patient experiences a suspected immune-mediated adverse event				

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

Table A16-4 Schedule of Activities for Atezo + Docetaxel Arm (cont.)

Assessment/Procedure	Stage 2 Screening	Treatment Cycles (21-Day Cycles) ^a			Treat. Discon. ^c	Follow-Up
		Cycle 1 ^b		Cycles ≥ 2		Every 3 Months (± 7 days)
		Day 1	Day 15 (± 3 days)	Day 1 (± 3 days)		
PK samples	See Appendix 2	Refer to Table A16-5 .				
ADA samples		Refer to Table A16-5 .				
Biomarker samples		Refer to Table A16-5 .				
Blood sample for RBR (optional) ^q		x				
Tumor biopsy		x ^r				
Tumor biopsy (optional)		x ^s				
Tumor response assessments		x ^{t, u, v}				
Concomitant medications ^x		x	x	x	x	
Adverse events ^y		x	x	x	x	x
Atezolizumab administration ^{z, aa}		x		x		
Docetaxel administration ^{bb}		x		x		
Survival follow-up and anti-cancer treatment						x ^{cc}

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

Table A16-4 Schedule of Activities for Atezo + Docetaxel Arm (cont.)

ADA=anti-drug antibody; Atezo + Docetaxel=atezolizumab plus docetaxel; CT=computed tomography; ctDNA=circulating tumor DNA; Discon.=discontinuation; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; NGS=next-generation sequencing; PK=pharmacokinetic; RBR=Research Biosample Repository; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; T3=triiodothyronine; T4=thyroxine; Treat.=treatment; TSH=thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

- ^a If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. The Medical Monitor is available to advise as needed.
- ^b It is recommended that treatment be initiated no later than 7 days after treatment assignment.
- ^c Patients receiving atezolizumab plus docetaxel as Stage 2 treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the *final* dose of study treatment.
- ^d Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (\pm 5) minutes during and 30 (\pm 10) minutes after the infusion. For subsequent infusions of *atezolizumab*, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (\pm 10) minutes after the infusion.
- ^e Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^f Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^g Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^h ECG recordings will be obtained as clinically indicated. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.
- ⁱ Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).
- ^j If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

Table A16-4 Schedule of Activities for Atezo + Docetaxel Arm (cont.)

- ^k Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included on Day 1 of each treatment cycle.
- ^l TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).
- ^m All women of childbearing potential will have to undergo urine or serum pregnancy tests at specified visits and at 3 months and 6 months after the *final* dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ⁿ Blood samples for blood-based NGS ctDNA test will not be collected from Protocol Version 19 *onward*.
- ^o Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ^p Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Serum samples collected for the assessment of PK, ADAs, or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment, may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.
- ^q Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.
- ^r Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see Section 3.1.2) will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible). See Section 4.5.6 for tissue sample requirements.
- ^s Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

Table A16-4 Schedule of Activities for Atezo + Docetaxel Arm (cont.)

- ^t Tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (± 1 week) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 6 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.
- ^u All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).
- ^w For patients receiving atezolizumab plus docetaxel as Stage 1 treatment who receive a different treatment combination during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).
- ^x Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment *from 7 days prior to* initiation of study treatment until the treatment discontinuation visit.
- ^y After initiation of study treatment, all adverse events will be reported until 30 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

Table A16-4 Schedule of Activities for Atezo + Docetaxel Arm (cont.)

- ^z Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (\pm 15) minutes. Subsequent infusions will be delivered over 30 (\pm 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (\pm 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.
- ^{aa} Atezolizumab treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).
- ^{bb} Docetaxel will be administered by IV infusion at a dose of 75 mg/m² over 60 minutes on Day 1 of each cycle. Docetaxel treatment will continue until unacceptable toxicity or radiographic disease progression according to RECIST v1.1. Docetaxel will be administered approximately 30 minutes after completion of the atezolizumab infusion.
- ^{cc} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Appendix 16: Study Details Specific to Atezo + Docetaxel Arm

Table A16-5 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Docetaxel Arm

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
	30 minutes after atezolizumab infusion	<ul style="list-style-type: none"> • Atezolizumab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycle 8	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after <i>final</i> dose)	At visit	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)

ADA=anti-drug antibody; Atezo + Docetaxel = atezolizumab plus docetaxel;

PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

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A17–1 BACKGROUND ON ATEZO+LINA ARM

A17–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, *myocarditis*, and *nephritis*, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma (in the European Union), non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer (in the European Union), hepatocellular carcinoma, melanoma (in the United States), and alveolar soft part sarcoma (in the United States).

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A17–1.2 BACKGROUND ON LINAGLIPTIN

Linagliptin, marketed under the registered names Tradjenta® (United States) and Trajenta® (worldwide), is a dipeptidyl peptidase-4 (DPP-4) inhibitor developed for the treatment of Type 2 diabetes mellitus. Once a day (QD) linagliptin at a dose of 5 mg was approved by the U.S. Food and Drug Administration on 2 May 2011 for the treatment of Type 2 diabetes mellitus. Linagliptin is being marketed by Boehringer Ingelheim and Eli Lilly.

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DPP-4 (also known as CD26) is an X-prolyl dipeptidyl peptidase capable of enzymatically removing the first two N-terminal amino acids from a protein. DPP-4 is enzymatically active as both a membrane-bound protein and a soluble protein and is expressed in several tissues and biological fluids in the body. DPP-4 expression and/or activity can be affected by inflammation and malignant transformation (Stecca et al. 1997; Kajiyama et al. 2002).

DPP-4 inhibitors are one of the recently developed therapeutic classes for treatment of hyperglycemia in Type 2 diabetes mellitus. The various agents in the class have differing chemical structures but all act by inhibiting the DPP-4 enzyme, thus prolonging the life of incretin hormones, which in turn raise insulin levels and suppress glucagon secretion in a glucose-dependent manner. As a class, DPP-4 inhibitors have been shown to provide significant improvements in glycosylated hemoglobin, and to have a good safety profile. In addition, the glucose-dependent mechanism of action is associated with a low rate of hypoglycemic events (Richter et al. 2008).

A17-2 RATIONALE FOR ATEZO+LINA ARM

A17-2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses by binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head

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and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors (CPIs), have had a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active *as monotherapy* for many patients.

A17-2.2 DPP-4 INHIBITION

In addition to the well-studied ability of DPP-4 to regulate the activity of incretin hormones, DPP-4 has also been shown to regulate the activity of several pro-inflammatory chemokines such as CXCL9, CXCL10, and CXCL11 (Kim et al. 2014). The two chemokines, CXCL9 and CXCL10, and their CXCR3 receptor mediate the recruitment of CXCR3-positive T cells and natural killer (NK) cells into solid cancers (Yang et al. 2006; Gorbachev et al. 2007; Wendel et al. 2008). It has been shown that proteolysis of these chemokines inhibits lymphocyte trafficking, resulting in reduced migration of T cells and NK cells into inflammatory sites such as tumor parenchyma.

Preclinical experiments have shown that DPP-4 inhibition restores CXCL10 activity and promotes immune cell recruitment in the tumor parenchyma, leading to increased tumor control (Barreira da Silva et al. 2015).

A17-2.3 BENEFIT-RISK ASSESSMENT

One potential mechanism to increase responses to a checkpoint-inhibitor is to recruit immune cells to the tumor sites so that an anti-PD-L1 agent can be effective in removing immune inhibitory signals in the tumor microenvironment.

Inhibition of DPP-4 activity is one strategy to promote lymphocyte recruitment in tumors, acting by re-establishing functional chemokine gradients. This strategy has achieved proof of concept in preclinical models in which DPP-4 inhibition improved the anti-tumorigenic activity of anti-PD-L1 (Barreira da Silva et al. 2015). Specifically, it was demonstrated that DPP-4 inhibitors, used in combination with CPIs, resulted in 100% protection of tumor-bearing mice (harboring CT-26 colon carcinoma), rejecting their tumor by Day 21, whereas checkpoint inhibition alone protected only 42% of the mice during the same period of time. DPP-4 inhibition, by regulating lymphocytes trafficking, is therefore postulated to enhance the response to current tumor immunotherapy regimens.

Taking into account the potentially synergistic mechanisms of action of atezolizumab and linagliptin, as well as the well known, manageable, and well-tolerated safety profile for each of these agents, combination treatment with these two agents appears to have a promising and positive benefit-risk in solid tumors such as NSCLC.

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For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.4.

A17–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + LINA ARM

A17–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab (Tecentriq® U.S. *Prescribing Information*).

A17–3.2 RATIONALE FOR LINAGLIPTIN DOSE AND SCHEDULE

The dose of 5 mg once daily (QD), the current approved regimen for patients with Type 2 diabetes (Tradjenta® U.S. *Prescribing Information*), was selected on the basis of PK and pharmacodynamic modeling and preclinical results. Linagliptin was tested at single or multiple oral doses of 1–10 mg in healthy volunteers (Graefe-Mody et al. 2012). At steady state, $\geq 80\%$ inhibition of plasma DPP-4 activity was achieved with 5-mg and 10-mg QD dosing. The 10-mg QD dosage led only to a modest increase in inhibition of DPP-4 compared with the 5-mg dosage.

Evidence correlating 80% DPP-4 inhibition in the plasma with increased immune cell infiltration into tumors comes from preclinical experiments performed in mice (unpublished data), and direct evidence of tissue penetration of the drug comes from rats intravenously dosed with linagliptin (Fuchs et al. 2009). Evidence of effective tissue penetration has also been observed in mice receiving a single dose of linagliptin by oral gavage (unpublished data).

A17–3.3 RATIONALE FOR DPP-4 ACTIVITY AS A BIOMARKER

Preclinical experiments with increasing doses of linagliptin in tumor-bearing mice have shown a positive correlation between the percentage of DPP-4 inhibition in plasma and intra-tumoral lymphocyte infiltration, with 80% plasma inhibition being required to modulate lymphocyte trafficking (unpublished data). To confirm that this inhibition target is indeed achieved, DPP-4 inhibition will be monitored retrospectively in plasma using an enzymatic activity assay (Matheussen et al. 2012).

Plasma samples will also be used for testing other exploratory biomarkers, including, but not limited to, NH₂-truncated forms of CXCL10 (Decalf et al. 2016). Pretreatment tumor samples will be also tested retrospectively by IHC to identify biomarkers that are predictive of clinical benefit with atezolizumab and +linagliptin combination treatment.

A17-4 MATERIALS AND METHODS SPECIFIC TO ATEZO+LINA ARM

A17-4.1 TREATMENT IN ATEZO+LINA ARM

A17-4.1.1 Formulation, Packaging, and Handling

A17-4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the atezolizumab formulation, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A17-4.1.1.2 Linagliptin

For information on the formulation, packaging and handling of linagliptin, refer to the local label.

A17-4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus linagliptin (Atezo+Lina) arm will receive treatment as outlined in [Table A17-1](#) until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see [Section 3.1.1](#) for details). It is recommended that treatment be initiated no later than 7 days after treatment assignment; *however, the first dose of study treatment should not occur within 3 days after a core biopsy or other surgical procedure.*

Table A17-1 Treatment Regimen for Atezo+Lina Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none">• Atezolizumab 1200 mg IV on Day 1 of each cycle• Linagliptin 5 mg by mouth once daily

Atezo = atezolizumab; Lina = linagliptin.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in [Section 5.3.5.12](#). No safety data related to overdosing of atezolizumab are available.

A17–4.1.2.1 Linagliptin Administration

Patients will take linagliptin orally QD, one tablet (5 mg) QD of each 21-day cycle. This is the current dosage approved for linagliptin for the treatment of Type 2 diabetes.

On clinic visit days, patients should take their tablets in the clinic prior to the atezolizumab infusion, as directed by site personnel. Linagliptin can be taken with or without food. Missed or vomited doses will not be made up.

To assess patient compliance with self-administration of linagliptin, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

No dose modification for linagliptin is allowed. Guidelines for linagliptin treatment interruption or discontinuation because of toxicities are provided in Section [A17–5.1.4](#) and the local prescribing information.

Linagliptin treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A17–4.1.2.2 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#). Atezolizumab infusions will be administered per the instructions outlined in [Table A17-2](#).

Table A17-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
<ul style="list-style-type: none"> No premedication is permitted <i>prior to the atezolizumab infusion</i>. Vital signs (pulse rate, respiratory rate, <i>pulse oximetry</i>, blood pressure, and temperature) should be <i>measured</i> within 60 minutes prior to the infusion. Atezolizumab should be infused over 60 (\pm 15) minutes. If clinically indicated, vital signs should be <i>measured</i> every 15 (\pm 5) minutes during the infusion and <i>at</i> 30 (\pm 10) minutes after the infusion. Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. 	<ul style="list-style-type: none"> If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic <i>medications</i>, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. Vital signs should be <i>measured</i> within 60 minutes prior to the infusion. Atezolizumab should be infused over 30 (\pm 10) minutes if the previous infusion was tolerated without an IRR or 60 (\pm 15) minutes if the patient experienced an IRR with the previous infusion. If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be <i>measured</i> during the infusion and at 30 (\pm 10) minutes after the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of infusion-related reactions (IRRs) *for atezolizumab* are provided in [Appendix 6](#).

No dose modification for atezolizumab is allowed. Guidelines for *atezolizumab* treatment interruption or discontinuation *because of toxicities* are provided in [Section A17-5.1.4.2](#). Atezolizumab treatment *may be suspended* for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A17-4.2 CONCOMITANT THERAPY FOR ATEZO+LINA ARM

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A17–4.2.1 Permitted Therapy for Atezo+Lina Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Inactivated vaccines (such as influenza and COVID-19)
 - Live, attenuated vaccines are not permitted (see [A17–4.2.3](#)).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids and mineralocorticoids (e.g., fludrocortisone) administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and linagliptin may be continued during palliative radiotherapy *with sufficient monitoring of hematologic parameters in place*.

- Radiotherapy to the brain as outlined below:

Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

- The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.
- The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

- Anticonvulsant therapy, if required, is administered at a stable dose.

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Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections [A17–4.2.2](#) and [A17–4.2.3](#)) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 -adrenergic agonists; see [Appendix 5](#)).

At this time there is no evidence on potential interactions of COVID-19 vaccines with linagliptin. COVID-19 vaccines must be given in accordance with the approved/authorized vaccine label and official immunization guidance. The decision of administration of a COVID-19 vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

A17–4.2.2 Cautionary Therapy for Atezo+Lina Arm

A17–4.2.2.1 Corticosteroids and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may be administered at the discretion of the investigator. The Medical Monitor is available to advise as needed.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to [Appendix 6](#) for details).

The above list of cautionary medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment.

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In addition, the Medical Monitor is available to advise as needed if questions arise regarding medications not listed above.

A17–4.2.2.2 Medications Given with Precaution due to Effects Related to P-Glycoprotein and Cytochrome P450 3A4

Concomitant use of strong inducers of P-glycoprotein and cytochrome P450 3A4 (e.g., rifampicin) should be avoided during linagliptin treatment because exposure will be decreased in presence of these agents and reduce linagliptin activity. Therefore, use of alternative treatments is strongly recommended during linagliptin treatment.

A17–4.2.2.3 Medications Known to Cause Hypoglycemia

Concomitant use of insulin or insulin-secretagogue drugs are allowed but should be used with caution owing to an increased risk of hypoglycemia. An initial dose decrease in the insulin or insulin-secretagogue drugs should be considered to prevent hypoglycemic events.

A17–4.2.2.4 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section [A17–4.2.3](#)) may be used during the study at the discretion of the investigator.

A17–4.2.3 Prohibited Therapy for Atezo+Lina Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section [4.1.2](#)), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section [A17–4.2.1](#).
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the *final* dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin [IL]-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

A17–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + LINA ARM

Contraception requirements for women and men in the Atezo+Lina arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of < 1% per year during the treatment period and for 5 months after the *final* dose of study treatment.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A17–5 ASSESSMENT OF SAFETY FOR ATEZO + LINA ARM

A17–5.1 SAFETY PLAN FOR ATEZO + LINA ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and linagliptin in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections [A17–5.1.1](#), [A17–5.1.2](#), and [A17–5.1.3](#)). Guidelines for management of patients who experience specific adverse events are provided in Section [A17–5.1.4](#). These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections [5.2–5.6](#).

A17–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus,

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hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis. Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A17–5.1.2 Risks Associated with Linagliptin

Linagliptin is known to cause acute pancreatitis, hypoglycemia, hypersensitivity, arthralgia, bullous pemphigoid, nasopharyngitis, and cough in patients with Type 2 diabetes mellitus. When linagliptin was added to a sulphonylurea (on a background of metformin), the incidence of hypoglycemia was increased over that of placebo. Linagliptin alone showed a comparable incidence of hypoglycemia to placebo.

For more details regarding the safety profile of linagliptin, refer to the local prescribing information.

A17–5.1.3 Risks Associated with Combination Use of Atezolizumab and Linagliptin

The following adverse event is a potential overlapping toxicity associated with combination use of atezolizumab and linagliptin: acute pancreatitis, hypersensitivity, cough, arthralgia, rash, and bullous pemphigoid.

A17–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo+Lina Arm

A17–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab or linagliptin in this study.

A17–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see [Table A17-3](#)). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to *the equivalent of* ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

If atezolizumab is withheld for > 12 weeks *after event onset*, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.* Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures).

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The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Linagliptin treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If linagliptin has been withheld for ≥ 21 days because of toxicity, the patient should be discontinued from linagliptin, unless resumption of treatment is approved at the investigator's discretion. The decision to re-challenge patients should be based on *the investigator's* *benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

If atezolizumab is discontinued, linagliptin should also be discontinued. If linagliptin is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section [A17–4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A17–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events related to linagliptin are provided in the linagliptin prescribing information.

General guidelines for management of patients who experience adverse events in this arm are provided in [Table A17-3](#). In addition, atezolizumab management guidelines for specific atezolizumab-related adverse events can also be found in [Appendix 6](#). For cases in which management guidelines are not covered in [Appendix 6](#), the linagliptin prescribing information, or the protocol, patients should be managed as deemed appropriate by the investigator according to best medical judgment.

Table A17-3 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo +Lina Arm*

Event	Action to Be Taken
Pancreatic events	
Amylase and/or lipase elevation, Grade 2	<ul style="list-style-type: none"> • Continue atezolizumab and linagliptin. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., ≥ 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	<ul style="list-style-type: none"> • Withhold atezolizumab and linagliptin for up to 12 weeks after event onset. • Refer patient to gastrointestinal specialist. • Monitor amylase and lipase every other day. If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks.^{a, b} • Permanently discontinue atezolizumab and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks.^{a, b, c} • For recurrent events, permanently discontinue atezolizumab and linagliptin and contact the Medical Monitor.^c • If event resolves to Grade 1 or better within 21 days, resume linagliptin at the current dose. If not, determine whether linagliptin should continue to be withheld or should be permanently discontinued. The Medical Monitor is available to advise as needed.

Atezo = atezolizumab; Lina = linagliptin.

- ^a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- ^b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A17-3 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo +Lina Arm (cont.)*

Event	Action to Be Taken
Pancreatic events (cont.)	
Pancreatitis, Grade 2 or 3	<ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset. • Permanently discontinue linagliptin. • Refer patient to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. ^{a, b} • Permanently discontinue atezolizumab and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. ^{a, b, c} • For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. ^c
Pancreatitis, Grade 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^c • Permanently discontinue linagliptin. • Refer patient to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Atezo = atezolizumab; Lina = linagliptin.

^a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

^b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on *the investigator's benefit–risk and assessment* documented by the investigator. The Medical Monitor is available to advise as needed.

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Table A17-3 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo +Lina Arm (cont.)*

Event	Action to Be Taken
Linagliptin-related <i>events</i> not described above	
Grade 1 or 2	<ul style="list-style-type: none"> Continue linagliptin and atezolizumab.
Grade 3	<ul style="list-style-type: none"> Withhold linagliptin treatment. Continue atezolizumab. If event resolves to Grade 2 within 21 days, resume linagliptin. If not, permanently discontinue linagliptin. If event resolves to Grade 1 or better within 21 days, resume linagliptin. If not, permanently discontinue linagliptin.
Grade 4	<ul style="list-style-type: none"> Withhold linagliptin and atezolizumab. If event resolves to Grade 2 or better within 21 days, resume linagliptin. If not, permanently discontinue linagliptin. If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab.
Any grade of bullous pemphigoid	<ul style="list-style-type: none"> Permanently discontinue linagliptin. Refer patient to dermatologist. Initiate treatment as per institutional guidelines. For Grade 3 event, withhold atezolizumab for up to 12 weeks after event onset, initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. If event resolves to Grade 1 or better, resume atezolizumab. If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. For Grade 4 event, permanently discontinue atezolizumab and contact Medical Monitor.

Atezo = atezolizumab; Lina = linagliptin.

- ^a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- ^b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A17-3 Guidelines for Management of Patients Who Experience Specific Adverse Events *in Atezo +Lina Arm (cont.)*

Event	Action to Be Taken
Atezolizumab-related <i>events</i> not described above	
Grade 1 or 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue linagliptin.
Grade 3	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue linagliptin.
Grade 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. If atezolizumab is discontinued, linagliptin should also be discontinued.

Atezo = atezolizumab; Lina = linagliptin.

- ^a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- ^b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

A17–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + LINA ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#) for reporting instructions). Adverse events of special interest for the Atezo + Lina arm include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section [5.3.5.7](#))

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- Suspected transmission of an infectious agent by the study treatment, as defined below

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Grade ≥ 3 hypoglycemia
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

A17–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+LINA ARM

A17–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the *final* dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A17–5.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A17–5.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

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A17-6 SCHEDULE OF ACTIVITIES FOR ATEZO+LINA ARM

Table A17-4 Schedule of Activities for Atezo + Lina Arm

Assessment/Procedure	Stage 2 Screening	Treatment Cycle (21-Day Cycles) ^a			Treatment Discon.	Follow-Up Every 3 Months (± 7 days)
		Cycle 1 ^b		Cycles ≥ 2		
		Day 1	Day 15 (± 3 days)	Day 1 (± 3 days)		
Molecular profile of lung cancer (if applicable)	See Appendix 2	Whenever updated information becomes available				
Vital signs ^c		x		x	x	
Weight ^d		x		x	x	
Complete physical examination ^e					x	
Limited physical examination ^{d, f}		x	x	x		
ECOG Performance Status ^d		x		x	x	
ECG ^{d, g}		Perform as clinically indicated				
Hematology ^h		x ⁱ	x	x	x	
Chemistry ^j		x ⁱ	x	x	x	
TSH, free T3 (or total T3), and free T4 ^k		x ⁱ			x	
C-reactive protein					x	
Pregnancy test ^l		x		x	x	
Urinalysis ^m		Perform as clinically indicated			x	
Serum autoantibody sample ⁿ		Perform if a patient experiences a suspected immune-mediated adverse event				

Appendix 17: Study Details Specific to Atezo + Lina Arm

Table A17-4 Schedule of Activities for Atezo + Lina Arm (cont.)

Assessment/Procedure	Stage 2 Screening	Treatment Cycle (21-Day Cycles) ^a			Treatment Discon.	Follow-Up Every 3 Months (± 7 days)
		Cycle 1 ^b		Cycles ≥ 2		
		Day 1	Day 15 (± 3 days)	Day 1 (± 3 days)		
PK samples	See Appendix 2	Refer to Table A17-5.				
ADA samples		Refer to Table A17-5.				
Biomarker samples		Refer to Table A17-5.				
Blood sample for RBR (optional) ^o		x				
Tumor biopsy		x ^p				
Tumor biopsy (optional)		x ^q				
Tumor response assessments		x ^{r, s}				
Concomitant medications ^t		x	x	x	x	
Adverse events ^u		x	x	x	x	
Atezolizumab administration ^{v, w}		x		x		
Dispense linagliptin ^{w, x}		x		x		
Study drug accountability				x ^y		
Survival follow-up and anti-cancer treatment						x ^z

ADA=anti-drug antibody; Atezo + Lina=atezolizumab plus linagliptin; CT=computed tomography; Discon.=discontinuation; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; PK=pharmacokinetic; QD=once a day; RBR=Research Biosample Repository; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

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Table A17-4 Schedule of Activities for Atezo+Lina Arm (cont.)

- ^a If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. The Medical Monitor is available to advise as needed.
- ^b It is recommended that treatment be initiated no later than 7 days after treatment assignment.
- ^c Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (\pm 5) minutes during and 30 (\pm 10) minutes after the infusion. For subsequent infusions of *atezolizumab*, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (\pm 10) minutes after the infusion.
- ^d Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^e Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^f Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^g ECG recordings will be obtained as clinically indicated. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.
- ^h Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).
- ⁱ If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.
- ^j Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included on Day 1 of each treatment cycle.
- ^k TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).
- ^l All women of childbearing potential will undergo urine or serum pregnancy tests at specified visits and at 3 months and 6 months after the *final* dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^m Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

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Table A17-4 Schedule of Activities for Atezo+Lina Arm (cont.)

- ⁿ Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Serum samples collected for the assessment of PK, ADAs, or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment, may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.
- ^o Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.
- ^p Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.6 for tissue sample requirements.
- ^q Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.
- ^r Tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (± 1 week) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 6 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start a new non-protocol-specified anti-cancer therapy.
- ^s All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).
- ^t Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment *from 7 days prior to* initiation of study treatment until the treatment discontinuation visit.

Appendix 17: Study Details Specific to Atezo + Lina Arm

Table A17-4 Schedule of Activities for Atezo + Lina Arm (cont.)

- ^u After initiation of study treatment, all adverse events will be reported until 30 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.
- ^v Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (\pm 15) minutes. Subsequent infusions will be delivered over 30 (\pm 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (\pm 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.
- ^w Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).
- ^x Patients will take one 5-mg tablet of linagliptin orally QD during each 21-day cycle. On clinic visit days, patients should take their tablets in the clinic prior to the atezolizumab infusion, as directed by site personnel.
- ^y Medication diaries should be collected and reviewed, and unused medications should be collected for assessment of compliance.
- ^z After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table A17-5 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Lina Arm

Visit	Time	Sample Type(s)
Day 1 of Cycle 1	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, and PBMC)
	30 minutes after atezolizumab infusion	<ul style="list-style-type: none"> • Atezolizumab PK (serum)
	2 hours postdose oral linagliptin	<ul style="list-style-type: none"> • Biomarkers (plasma and serum) • Linagliptin PK (plasma)
Day 15 of Cycle 1	Prior to study treatment ^a	<ul style="list-style-type: none"> • Linagliptin PK (plasma)
Day 1 of Cycle 2	Prior to study treatment ^a	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Linagliptin PK (plasma) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, and PBMC)
Day 1 of Cycle 3	Prior to study treatment ^a	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Linagliptin PK (plasma) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma and serum)
Day 1 of Cycle 8	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma and serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum)

ADA=anti-drug antibody; Atezo+Lina=atezolizumab plus linagliptin; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

^a On Day 15 of Cycle 1 and Day 1 of Cycle 2 and Cycle 3, patients should take their linagliptin tablet in the clinic after the PK and biomarker samples (if applicable) have been obtained.

Appendix 17: Study Details Specific to Atezo+Lina Arm

Table A17-5 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Lina Arm: Preliminary and Expansion Phases (cont.)

Visit	Time	Sample Type(s)
Treatment discontinuation visit (≤ 30 days after <i>final</i> dose)	At visit	<ul style="list-style-type: none">• Atezolizumab PK (serum)• Atezolizumab ADA (serum)• Biomarkers (plasma, serum)

ADA = anti-drug antibody; Atezo + Lina = atezolizumab plus linagliptin; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

^a On Day 15 of Cycle 1 and Day 1 of Cycles 2 and 3, patients should take their linagliptin tablet in the clinic after the PK and biomarker samples (if applicable) have been obtained.

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Study Details Specific to Atezo+Bev Arm

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A18–1 BACKGROUND ON ATEZO+BEV ARM

A18–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, *myocarditis*, and *nephritis*, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma (in the European Union), non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer (in the European Union), hepatocellular carcinoma (HCC), melanoma (in the United States), and alveolar soft part sarcoma (in the United States).

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A18–1.2 BACKGROUND ON BEVACIZUMAB

Bevacizumab is a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF) that recognizes all isoforms of VEGF. It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor environment. Additional anti-tumor activity may be on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).

Appendix 18: Study Details Specific to Atezo + Bev Arm

Bevacizumab has been tested in Phase II and III studies in a variety of solid tumors in combination with chemotherapy. Bevacizumab is registered in over 40 countries worldwide for the first-line treatment of metastatic colorectal cancer (CRC) in combination with chemotherapy, as second-line CRC treatment, and first-line treatment of advanced NSCLC, metastatic breast cancer, advanced renal cell carcinoma (RCC), ovarian cancer, and glioblastoma (Reck and Crinò 2009).

In NSCLC, the Phase II/III Study E4599 showed that the addition of bevacizumab (15 mg/kg every 3 weeks [Q3W]) to the paclitaxel and carboplatin regimen led to a clinically relevant and statistically significant prolongation of overall survival ([OS] primary endpoint) compared with patients who were treated with paclitaxel and carboplatin alone (hazard ratio [HR]=0.80; 95% CI: 0.69 to 0.93; p=0.003; Kaplan-Meier [KM]-estimated median: 12.3 vs. 10.3 months). The OS benefit was supported by the results of progression-free survival (PFS) (HR=0.65; 95% CI: 0.56 to 0.76; KM-estimated median: 6.4 vs. 4.8 months) and response rate (29.0% vs. 12.9%).

In addition, data from the protocol-defined final PFS (primary efficacy parameter) analysis of Study BO17704 (AVAIL; Roche Report No. 1023798) showed that the addition of bevacizumab (7.5 or 15 mg/kg Q3W) to cisplatin/gemcitabine chemotherapy resulted in a clinically relevant and statistically significant improvement in PFS (bevacizumab 7.5 mg/kg: HR=0.75; 95% CI: 0.62 to 0.91; p=0.0026; KM-estimated median PFS: 6.7 vs. 8.1 months) (bevacizumab 15 mg/kg: HR=0.82; 95% CI: 0.68 to 0.98; p=0.0301; KM-estimated median PFS: 6.5 vs. 6.1 months). Objective response rate (ORR) was also significantly increased in both bevacizumab-containing arms (7.5 mg/kg: 34.1% vs. 20.1%; bevacizumab 15 mg/kg: 30.4% vs. 20.1%).

Bevacizumab is currently being tested in combination with atezolizumab across different indications in Phase I, II, and III clinical studies. *Atezolizumab plus bevacizumab has been approved as the first-line standard of care for patients with metastatic HCC.*

Refer to the Bevacizumab Investigator's Brochure for details on nonclinical and clinical studies.

A18–2 RATIONALE FOR ATEZO+BEV ARM

A18–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

Appendix 18: Study Details Specific to Atezo + Bev Arm

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses by binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, RCC, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors (CPIs), have *had* a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active *as monotherapy* for many patients.

A18–2.2 ANTI-VEGF CANCER TREATMENT

In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggested that VEGF may reduce lymphocyte adhesion to vessel walls in the tumor microenvironment, thus contributing to decreased immune cell recruitment to the tumor site (Bouzin et al. 2007). Mice exposed to pathophysiologic levels of VEGF exhibited impaired dendritic cell (DC) function, which could be restored by blockade of VEGF receptor 2 (Huang et al. 2007). In addition, VEGF recruits macrophages into the tumor microenvironment that have an M2 polarization state, which is typically involved in wound healing. These M2 tumor-associated macrophages ultimately help establish and maintain an immunosuppressive microenvironment (Chen and Mellman 2013). In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). Synergistic effects have also been observed

in a clinical study combining an immune-modulatory antibody (anti-cytotoxic T lymphocyte–associated protein 4; ipilimumab) and bevacizumab: Hodi et al. (2010) described increased T-cell trafficking in post-treatment biopsies, as well as marked increases in central memory cells in peripheral blood in the majority of patients.

A18–2.3 RATIONALE FOR COMBINING ATEZOLIZUMAB WITH BEVACIZUMAB

VEGF-A is a pro-angiogenic molecule produced by endothelium, tumors, and tumor-associated macrophages. The VEGF pathway also plays a crucial role in exerting and maintaining an immunosuppressive tumor microenvironment through several mechanisms. For example, VEGF-A inhibits the maturation of DCs (Gabrilovich et al. 1996), promotes the expression of inhibitory immune checkpoint molecules on intratumoral CD8⁺ T-cells that express VEGF-R2 (Voron et al. 2015), and induces Fas ligand (FasL) expression on endothelial cells, which acquired the ability to kill effector CD8⁺ T cells, but not regulatory T cells (Motz et al. 2014). Anti-VEGF agents such as bevacizumab are well known to promote the normalization of tumor vasculature and thereby increase access of therapeutic agents (Jain 2001). Furthermore, bevacizumab can restore and/or maintain the antigen-presentation capacity of DCs, leading to enhanced T-cell infiltration in tumors (Oelkrug and Ramage 2014; Wallin et al. 2016). Administration of anti-VEGF-A has been shown to attenuate tumor endothelial FasL expression and produce a significant increase in the influx of tumor-rejecting CD8⁺ T cells, leading to tumor growth suppression (Motz et al. 2014). In addition, anti-VEGF therapies can reduce the frequency of myeloid-derived suppressor cells, decrease production of suppressive cytokines, and lower expression of inhibitory checkpoints on CD8⁺ T cells in tumors (Roland et al. 2009; Voron et al. 2015). The immunomodulatory effect of bevacizumab is expected to increase CD8⁺ T-cell recruitment and relieve intratumoral immunosuppression, thereby boosting the effects of atezolizumab.

There is precedence for a beneficial effect of anti-angiogenesis in the context of immunotherapy. In a murine melanoma model, VEGF blockade was shown to synergize with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). High pretreatment serum VEGF was associated with poor survival following ipilimumab (anti-CTLA-4) monotherapy (Yuan et al. 2014), and synergistic effects were observed in a clinical study combining ipilimumab and bevacizumab, as shown by increased T-cell frequency in post-treatment biopsies, as well as marked increases in central memory cells in peripheral blood in the majority of patients (Hodi et al. 2014).

Furthermore, the anti-tumor activity of atezolizumab was increased in combination with bevacizumab, which was associated with a further increase in intra-tumoral CD8⁺ T cells and increases in gene expression correlated with T-cell trafficking and tumor MHC-I

Appendix 18: Study Details Specific to Atezo + Bev Arm

expression and enhanced antigen-specific T-cell migration in metastatic RCC (Wallin et al. 2016).

The above-described data suggest that combined treatment with atezolizumab and bevacizumab may augment the anti-tumor immune response, resulting in improved and more durable clinical benefit for patients with non-squamous NSCLC.

A18–2.4 CLINICAL STUDIES OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB

Study GP28328 is an ongoing, Phase Ib, open-label, multicenter study combining atezolizumab (1200 mg Q3W) with bevacizumab (15 mg/kg Q3W) in patients with advanced solid tumors, with expansion arms for patients with RCC, metastatic CRC, gastric cancer, and ovarian cancer. Safety findings have been consistent with the known single-agent safety profiles for each drug; no new safety signals have been identified. The regimen has been well tolerated, and adverse events have been manageable. Another Phase Ib, open-label, multicenter study (GO30140) is investigating a similar dose of atezolizumab combined with bevacizumab in patients with HCC. In addition, this combination is being tested in a Phase II randomized study (WO29074) in which atezolizumab is administered as monotherapy or in combination with bevacizumab, compared with sunitinib, in patients with untreated advanced RCC.

In chemotherapy-naïve patients with Stage IV NSCLC, results from Phase III Study GO29436 (IMpower150) have shown that atezolizumab in combination with carboplatin+paclitaxel and bevacizumab results in significantly longer OS compared with carboplatin+paclitaxel and bevacizumab alone (Socinski et al. 2018). For inoperable, locally advanced, or metastatic RCC, Phase III Study WO29637 (IMmotion151) demonstrated improved PFS after treatment with the combination of atezolizumab plus bevacizumab compared with sunitinib treatment in treatment-naïve patients (Motzer et al. 2018). Phase Ib Study GO30140 in HCC *first-line treatment* found an ORR of 65% in 23 evaluable patients, across etiology, geography, baseline α -fetoprotein levels, and extrahepatic spread. The combination is currently being explored in a randomized Phase III study YO40245 (IMbrave150) versus sorafenib in first-line treatment for HCC (Stein et al. 2018). These are examples of clear synergy between atezolizumab and bevacizumab in different tumor types, which support further exploration of the combination in NSCLC.

Detailed clinical study results for atezolizumab and bevacizumab can be found in the Atezolizumab Investigator's Brochure and the Bevacizumab Investigator's Brochure, respectively.

A18–2.5 BENEFIT–RISK ASSESSMENT

Metastatic NSCLC remains an incurable disease with a high unmet medical need, especially in the CPI-pretreated patient population. Because of the potentially synergistic mechanisms of action of atezolizumab and bevacizumab, as well as their manageable and tolerable safety profiles (see Section [A18–5](#)), combination treatment with these two agents appears to have promising therapeutic potential in solid tumors and may augment the anti-tumor immune response, potentially resulting in improved and more durable clinical benefit for patients with non-squamous NSCLC.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section [1.4](#).

A18–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+BEV ARM

A18–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab (Tecentriq® U.S. *Prescribing Information*).

A18–3.2 RATIONALE FOR BEVACIZUMAB DOSE AND SCHEDULE

Bevacizumab will be administered by infusion at a fixed dose of 15 mg/kg Q3W (15 mg/kg on Day 1 of each 21-day cycle), *which is an approved dosage for bevacizumab (Avastin® U.S. Prescribing Information)*.

A18–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+BEV ARM

A18–4.1 TREATMENT IN ATEZO+BEV ARM

A18–4.1.1 Formulation, Packaging, and Handling

A18–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the atezolizumab formulation, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A18–4.1.1.2 Bevacizumab

The bevacizumab drug product will be supplied by the Sponsor as a sterile solution in a single-use, 4-mL or 16-mL, preservative-free glass vial. The 4-mL vial contains 100 mg of bevacizumab (25 mg/mL), and the 16-mL vial contains 400 mg of bevacizumab (25 mg/mL).

Appendix 18: Study Details Specific to Atezo + Bev Arm

For information on the *bevacizumab* formulation, *see* the pharmacy manual and the Bevacizumab Investigator's Brochure

A18–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus bevacizumab (Atezo + Bev) arm will receive treatment as outlined in [Table A18-1](#) until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see [Section 3.1.1](#) for details). It is recommended that treatment be initiated no later than 7 days after randomization; *however, the first dose of study treatment should not occur within 3 days after a core biopsy or other surgical procedure.*

Table A18-1 Treatment Regimen for Atezo + Bev Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none">• Atezolizumab 1200 mg by IV infusion on Day 1 <i>of each cycle</i>• Bevacizumab 15 mg/kg by IV infusion on Day 1 <i>of each cycle</i>

Atezo + Bev = atezolizumab plus bevacizumab.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in [Section 5.3.5.12](#). No safety data related to overdosing of atezolizumab or bevacizumab are available.

A18–4.1.2.1 Bevacizumab Administration

Bevacizumab will be administered by IV infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle. *On Day 1 of each cycle, bevacizumab will be administered at least 5 minutes after completion of the atezolizumab infusion.*

Administration of bevacizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#). Bevacizumab infusions will be administered per the instructions outlined in [Table A18-2](#).

Table A18-2 Administration of First and Subsequent Bevacizumab Infusions

First Infusion	Subsequent Infusions
<ul style="list-style-type: none"> No premedication is permitted prior to the bevacizumab infusion. Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) should be measured within 60 minutes prior to the infusion. Bevacizumab should be infused over 90 (\pm 15) minutes. Vital signs should be measured at the end of infusion and 2 (\pm 1) hours after the infusion. Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. 	<ul style="list-style-type: none"> If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. Vital signs should be recorded within 60 minutes prior to the infusion. Bevacizumab should be infused over 60 (\pm 10) minutes if the previous 90-minute infusion was tolerated without an IRR, or 90 (\pm 15) minutes if the patient experienced an IRR with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (\pm 5) minutes thereafter. Vital signs should be measured within 30 minutes after completion of the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of infusion-related reactions (IRRs) for bevacizumab are provided in Section [A18-5.1.4](#).

No dose modification for bevacizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section [A18-5.1.4.2](#).

Bevacizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A18-4.1.2.2 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#). Atezolizumab infusions will be administered per the instructions outlined in [Table A18-3](#).

Table A18-3 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
<ul style="list-style-type: none"> No premedication is permitted prior to the atezolizumab infusion. Vital signs (pulse rate, respiratory rate, <i>pulse oximetry</i>, blood pressure, and temperature) should be <i>measured</i> within 60 minutes prior to the infusion. Atezolizumab should be infused over 60 (\pm 15) minutes. If clinically indicated, vital signs should be <i>measured</i> every 15 (\pm 5) minutes during <i>the infusion</i> and at 30 (\pm 10) minutes after the infusion. Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. 	<ul style="list-style-type: none"> If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic <i>medications</i>, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. Vital signs should be <i>measured</i> within 60 minutes prior to the infusion. Atezolizumab should be infused over 30 (\pm 10) minutes if the previous infusion was tolerated without an IRR or 60 (\pm 15) minutes if the patient experienced an IRR with the previous infusion. If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be <i>measured</i> during the infusion and at 30 (\pm 10) minutes after the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of IRRs for atezolizumab are provided in [Appendix 6](#).

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section [A18–5.1.4](#). Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A18–4.1.3 Stage 2 Treatment

Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section [3.1.1](#)) or unacceptable toxicity related to bevacizumab will be given the option of receiving a different treatment combination during Stage 2, as outlined in [Table A18-4](#), provided they meet eligibility criteria (see Section [4.1](#)) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or

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unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A18-4 Stage 2 Treatment Regimens Available for Atezo + Bev Arm

Study Treatment	Appendix
Atezo + Docetaxel	Appendix 16
Atezo + Lina	Appendix 17

Atezo = atezolizumab; Bev = bevacizumab; Lina = linagliptin.

Refer to [Appendix 16](#) and [Appendix 17](#) for details specific to the atezolizumab plus docetaxel arm and atezolizumab plus linagliptin arm, respectively.

A18-4.2 CONCOMITANT THERAPY FOR ATEZO + BEV ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A18-4.2.1 Permitted Therapy for Atezo + Bev Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Inactivated vaccines (such as influenza and COVID-19)
 - Live, attenuated vaccines are not permitted (see [A18-4.2.3](#)).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer

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- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy *with sufficient monitoring of hematologic parameters in place*.

- Radiotherapy to the brain as outlined below:

Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

- The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.
- The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

- Anti-convulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretic *medications*, and/or analgesics may be administered for the second and subsequent atezolizumab and bevacizumab infusions only, at the discretion of the investigator. *Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.*

Anti-emetic medications, anti-diarrheal medications, and hematopoietic growth factors are not to be administered prophylactically prior to the first doses of study treatment. However, at the discretion of the investigator, anti-emetic medications, anti-diarrheal medications, and hematopoietic growth factors may be administered prophylactically per standard local practice before the second and subsequent doses of study treatment.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections [A18–4.2.2](#) and [A18–4.2.3](#)) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension,

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wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 -adrenergic agonists; see [Appendix 5](#)).

At this time there is no evidence to suggest an interaction between the COVID-19 vaccines and bevacizumab. Based on the mechanism of action of bevacizumab, an interaction with the COVID-19 vaccines is unlikely. COVID-19 vaccines must be given in accordance with the approved/authorized vaccine label and official immunization guidance. The decision of administration of a COVID-19 vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

A18–4.2.2 Cautionary Therapy for Atezo + Bev Arm

A18–4.2.2.1 Corticosteroids and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may be administered at the discretion of the investigator. The Medical Monitor is available to advise as needed.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to [Appendix 6](#) for details).

The above list of cautionary medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor is available to advise as needed if questions arise regarding medications not listed above.

A18–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section [A18–4.2.3](#)) may be used during the study at the discretion of the investigator.

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A18–4.2.2.3 Bisphosphonates

Osteonecrosis of the jaw has been reported in patients receiving bevacizumab, mainly in combination with bisphosphonates. Thus, caution must be exercised in using bevacizumab in patients receiving concomitant bisphosphonates.

A18–4.2.3 Prohibited Therapy for Atezo + Bev Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A18–4.2.1.
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the *final* dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Antithrombotic treatment with aspirin (> 325 mg/day) or clopidogrel (> 75 mg/day) or equivalent is prohibited.

A18–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + BEV ARM

Contraception requirements for women and men in the Atezo + Bev arm are outlined below.

- Women of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the *final* dose of atezolizumab and 6 months after the *final* dose of bevacizumab.

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A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

Hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below.

With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the *final* dose of bevacizumab to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A18–5 ASSESSMENT OF SAFETY FOR ATEZO+BEV ARM

A18–5.1 SAFETY PLAN FOR ATEZO+BEV ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and bevacizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections [A18–5.1.1](#), [A18–5.1.2](#), and [A18–5.1.3](#)). Guidelines for management of patients who experience specific adverse events are provided in Section [A18–5.1.4](#).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Adverse events will be reported as described in Sections [5.2–5.6](#).

A18–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis. Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A18–5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: GI perforations, hemorrhage, arterial thromboembolic events, fistulae, wound-healing complications, hypertension, venous thromboembolism, proteinuria, *congestive heart failure*, and *posterior reversible encephalopathy syndrome*.

Refer to Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for bevacizumab.

A18–5.1.3 Risks Associated with Combination Use of Atezolizumab and Bevacizumab

On the basis of the frequency of adverse events associated with either atezolizumab or bevacizumab, the following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and bevacizumab: cardiovascular, gastrointestinal, renal, and pulmonary toxicity.

A18–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo+Bev Arm

A18–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab or bevacizumab in this study.

A18–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see [Table A18-5](#)). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to *the equivalent of* ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on *the investigator's benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 non-serious adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤ 1 , bevacizumab may be restarted at the same dose level. If bevacizumab is delayed due to toxicity for > 42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab. Bevacizumab can be resumed after being withheld for > 42 days if the patient is likely to derive clinical benefit. The decision to re-challenge patients with bevacizumab should be based on *the investigator's benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

If either study drug is discontinued, the other study drug can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section [A18–4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A18–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in [Table A18-5](#). These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm

Event	Action to Be Taken
Pulmonary events including pneumonitis	
General guidance	<ul style="list-style-type: none"> • All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia <i>or other</i> infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.
Pulmonary event, Grade 1	<ul style="list-style-type: none"> • Continue atezolizumab and bevacizumab, <i>and monitor closely.</i> • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab. <ul style="list-style-type: none"> – <i>Consider resuming on radiographic evidence of improvement.</i>
Pulmonary event, Grade 2	<ul style="list-style-type: none"> • Withhold atezolizumab <i>for up to 12 weeks after event onset.</i> ^a Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL <i>with or without transbronchial biopsy.</i> • Initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.</i> • If event resolves to Grade 1 or better, resume atezolizumab. ^c • <i>If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab, and contact the Medical Monitor.</i> ^{d, e} • For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Pulmonary events (cont.)	
Pulmonary event, Grade 3 or 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^{d, e} Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b • <i>Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment.</i> • <i>Bronchoscopy or BAL with or without transbronchial biopsy is recommended.</i> • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Hepatic events	
Hepatic event, Grade 1	<ul style="list-style-type: none"> • Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values. • Continue bevacizumab.
Hepatic event, Grade 2	<p>All events:</p> <ul style="list-style-type: none"> • Monitor LFTs more frequently until return to baseline values. • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b <p>Events of >5 days' duration:</p> <ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset. ^a • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. ^c • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. ^d

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Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Hepatic events (cont.)	
<i>Hepatic event, Grade 3 or 4</i>	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact the Medical Monitor. ^d • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b
Gastrointestinal events	
General guidance	<ul style="list-style-type: none"> • All events of diarrhea or colitis should be thoroughly evaluated for more common etiologies other than drug-induced effects. • For events of significant duration or magnitude or associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis. • Administer anti-diarrheal agents and other supportive care per institutional guidelines or per suggested supportive care outlined below: <ul style="list-style-type: none"> <u>Medication</u> – Initiate loperamide (4 mg) every 6 hours around the clock, alternating with diphenoxylate hydrochloride (5 mg)/atropine sulfate (0.5 mg) every 6 hours around the clock, until no loose stools for 24 hours. – If Grade ≥2 diarrhea persists after 48 hours of treatment with loperamide and diphenoxylate/atropine, consider initiating second-line agents (e.g., octreotide, budesonide, tincture of opium).

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events (cont.)	
General guidance (cont.)	<p><u>Oral Supplementation</u></p> <ul style="list-style-type: none"> – Initiate potassium and/or magnesium if serum levels are less than the lower limit of normal. – Consider rehydration therapy with oral electrolyte solution for Grade ≥ 1 diarrhea or vomiting. <p><u>Dietary Modifications</u></p> <ul style="list-style-type: none"> – Instruct patient to eat small meals and eliminate lactose-containing products from diet. – Suggest diet of bananas, rice, apples, and toast, while avoiding fiber from vegetables and other fruits. – Encourage adequate hydration with salt-containing liquids (e.g., broth, sports drinks such as Gatorade).
Diarrhea, Grade 1 or 2 (tolerable)	<ul style="list-style-type: none"> • Continue atezolizumab and bevacizumab. • Initiate supportive care and monitor patient closely. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis if appropriate.
Diarrhea, Grade 2 (intolerable) or Grade 3	<ul style="list-style-type: none"> • Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. ^{a, c, d}

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Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events (cont.)	
Diarrhea, Grade 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^d Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Rule out bowel perforation. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.
Colitis, Grade 1	<ul style="list-style-type: none"> • Continue atezolizumab and bevacizumab. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy if symptoms persist for > 7 days.
Colitis, Grade 2	<ul style="list-style-type: none"> • Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. ^{a, c, d}

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events (cont.)	
Colitis, Grade 3	<ul style="list-style-type: none"> • Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. ^{a, c, d}
Colitis, Grade 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^d Bevacizumab may continue at the discretion of the investigator per medical judgment. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Gastrointestinal perforation, any grade	<ul style="list-style-type: none"> • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. • Discontinue bevacizumab. • Initiate treatment per institutional guidelines.

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Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Endocrine <i>events</i>	
Asymptomatic hypothyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab.
Symptomatic hypothyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab.
Asymptomatic hyperthyroidism	<p>TSH ≥ 0.1 mU/L and < 0.5 mU/L:</p> <ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab. <p>TSH < 0.1 mU/L:</p> <ul style="list-style-type: none"> Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b
Symptomatic adrenal insufficiency, Grade 2–4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b
Hyperglycemia, any grade	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab.
Hypophysitis (pan-hypopituitarism), Grade 2–4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Ocular events	
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 1	<ul style="list-style-type: none"> Continue atezolizumab and bevacizumab. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If symptoms persist, treat as a Grade 2 event.
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 2	<ul style="list-style-type: none"> Withhold atezolizumab. ^a Continue bevacizumab. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor. ^{a, c, d}
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 3 or 4	<ul style="list-style-type: none"> Permanently discontinue atezolizumab and contact Medical Monitor. ^d Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b
Cardiac events	
<i>Immune-mediated cardiac events</i>	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b
<i>Congestive heart failure, Grade 3 or 4</i>	<ul style="list-style-type: none"> Atezolizumab may be continued at the discretion of the investigator. Permanently discontinue bevacizumab.
IRRs, CRS, anaphylaxis, and hypersensitivity reaction	
General guidance	<ul style="list-style-type: none"> Guidelines for management of IRRs and CRS for atezolizumab are provided in Appendix 6. For anaphylaxis precautions, see Appendix 5. For severe hypersensitivity reactions, permanently discontinue atezolizumab and bevacizumab.
IRR to bevacizumab, Grade 1	<ul style="list-style-type: none"> Continue bevacizumab. Systemic intervention is not indicated.

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reaction (cont.)	
IRR to bevacizumab, Grade 2	<ul style="list-style-type: none"> • Reduce infusion rate to $\leq 50\%$ or interrupt infusion at the discretion of the investigator per medical judgment. • If the infusion is interrupted, it may be resumed at $\leq 50\%$ of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.
IRR to bevacizumab, Grade 3 or 4	<ul style="list-style-type: none"> • Stop infusion <i>and permanently discontinue bevacizumab</i>. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen) if clinically indicated.
<i>Hemophagocytic lymphohistiocytosis or macrophage activation syndrome</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Withhold all treatment. The Medical Monitor is available to advise as needed.
Pancreatic events	
Amylase and/or lipase elevation, Grade 3 or 4	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b
Pancreatitis, Grade 2–4	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b
Dermatologic events	
General guidance	<ul style="list-style-type: none"> • A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Dermatologic events (cont.)	
Dermatologic event, Grade 1 or 2	<ul style="list-style-type: none"> Continue atezolizumab and bevacizumab. Initiate supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids. For Grade 2 rash, consider referral to dermatologist. <p>Acneiform rash:</p> <ul style="list-style-type: none"> Consider initiating treatment with topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.
Dermatologic event, Grade 3	<ul style="list-style-type: none"> Withhold atezolizumab. ^a Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b Refer patient to dermatologist. A biopsy should be performed if appropriate. Consider initiating treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. If event resolves to Grade 2 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. ^{a, c, d}
Dermatologic event, Grade 4	<ul style="list-style-type: none"> Permanently discontinue atezolizumab and contact Medical Monitor. ^d Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b
Stevens-Johnson syndrome or toxic epidermal necrolysis, any grade	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold bevacizumab. ^b If event resolves to Grade 1 or better, resume bevacizumab. Permanently discontinue bevacizumab if withheld for >42 days or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed.

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Neurologic disorders	
Immune-mediated neuropathy, Grade 1	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab. Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, including facial paresis, Grade 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold bevacizumab. ^b
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Permanently discontinue bevacizumab.
Myasthenia gravis or Guillain-Barré syndrome, all grades	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Permanently discontinue bevacizumab.
Immune-mediated myelitis, Grade 1	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab.
Immune-mediated myelitis, Grade 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Permanently discontinue bevacizumab.
Immune-mediated myelitis, Grade 3 or 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Permanently discontinue bevacizumab.
Immune-related meningoencephalitis, any grade	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold bevacizumab. ^b If patient stabilizes within 42 days, resume bevacizumab. <i>If not, permanently discontinue bevacizumab.</i> ^b

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Hypertension	
General guidance	<ul style="list-style-type: none"> • <i>Treat with antihypertensive medication as needed.</i>
Hypertension, Grade 1	<ul style="list-style-type: none"> • <i>Continue atezolizumab and bevacizumab.</i> • <i>Consider increased blood pressure monitoring.</i>
Hypertension, Grade 2	<ul style="list-style-type: none"> • <i>Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.^a</i> • <i>If asymptomatic, begin or modify baseline antihypertensive therapy and continue bevacizumab.</i> • <i>If symptomatic, start or adjust antihypertensive therapy.</i>
Hypertension, Grade 3	<ul style="list-style-type: none"> • <i>Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.^a</i> • <i>Modify existing antihypertensive therapy (more than one drug or more intensive therapy than previously indicated).</i> • <i>Withhold bevacizumab until symptoms resolve to Grade 1 or better <u>and</u> blood pressure < 160/90 mmHg.</i>
Hypertension, Grade 4	<ul style="list-style-type: none"> • <i>Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.^a</i> • <i>Discontinue bevacizumab.</i>

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Hemorrhage	
<i>Hemorrhage, Grade 3 or 4 (excluding cerebral hemorrhage)</i>	<ul style="list-style-type: none"> • Continue atezolizumab. • Permanently discontinue bevacizumab.
<i>Cerebral hemorrhage, any grade</i>	<ul style="list-style-type: none"> • Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
<i>Grade ≥ 2 hemoptysis (≥ 2.5 mL of bright red blood per episode)</i>	<ul style="list-style-type: none"> • Continue atezolizumab. • Permanently discontinue bevacizumab.
<i>Bleeding in patients on full-dose anticoagulant therapy</i>	<ul style="list-style-type: none"> • Continue atezolizumab. • Permanently discontinue bevacizumab.
Venous thromboembolic events	
<i>Venous thromboembolic event, Grade 3</i>	<ul style="list-style-type: none"> • Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be withheld until the full-dose anticoagulation period is over. The use of direct oral anticoagulants is not recommended. • If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed during full-dose anticoagulation <u>if</u> all of the criteria below are met: <ul style="list-style-type: none"> – The patient must not have pathological conditions that carry high risk of bleeding (e.g., tumor involving major vessels or other conditions). – The patient must not have had Grade > 2 hemorrhagic events while in the study. – The patient must be on stable dose of heparin, low-molecular-weight heparin, or have an in-range INR (usually 2 to 3) on a stable dose of warfarin prior to restarting bevacizumab. • If thromboemboli worsen or recur upon resumption of study therapy, discontinue bevacizumab.
<i>Venous thromboembolic event, Grade 4</i>	<ul style="list-style-type: none"> • Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.

Appendix 18: Study Details Specific to Atezo+Bev Arm

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev Arm (cont.)

Event	Action to Be Taken
Arterial thromboembolic events	
Arterial thromboembolic event, any grade	<ul style="list-style-type: none"> • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. • <i>Permanently</i> discontinue bevacizumab.
Proteinuria	
Proteinuria, Grade 1 (1+ by dipstick; urinary protein < 1.0 g/24 hr)	<ul style="list-style-type: none"> • Continue atezolizumab and bevacizumab.
Proteinuria, Grade 2 (2+ and 3+ by dipstick; urinary protein 1.0–3.4 g/24 hr)	<ul style="list-style-type: none"> • Continue atezolizumab. • For 2+ dipstick: Continue bevacizumab and collect 24-hour urine protein prior to subsequent bevacizumab administration. • For 3+ dipstick: Obtain 24-hour urine prior to administering bevacizumab. • Withhold bevacizumab for urinary protein ≥ 2 g/24 hr. • If bevacizumab is withheld and urine protein improves to < 2 g/24 hr within 42 days after event onset, resume bevacizumab. If not, <i>permanently</i> discontinue bevacizumab.
Proteinuria, Grade 3 (4+ by dipstick; urinary protein ≥ 3.5 g/24 hr) with no diagnosis of nephrotic syndrome	<ul style="list-style-type: none"> • Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab. • If urine protein improves to < 2 g/24 hr within 42 days after event onset, resume bevacizumab. If not, <i>permanently</i> discontinue bevacizumab.
Nephrotic syndrome, Grade 3 or 4	<ul style="list-style-type: none"> • Atezolizumab may be continued at the discretion of the investigator. • <i>Permanently</i> discontinue bevacizumab.

Appendix 18: Study Details Specific to Atezo+Bev Arm

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev Arm (cont.)

Event	Action to Be Taken
Fistula	
<i>Tracheoesophageal fistula, any grade</i>	<ul style="list-style-type: none"> • Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. ^a
<i>Fistula (non-tracheoesophageal), Grade □4</i>	<ul style="list-style-type: none"> • Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. ^a
Wound dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	<ul style="list-style-type: none"> • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. • Permanently discontinue bevacizumab.
Posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome	
PRES/RPLS, any grade confirmed by MRI	<ul style="list-style-type: none"> • Withhold atezolizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. • Permanently discontinue bevacizumab.
<i>Atezolizumab-related events not described above</i>	
<i>Grade 1 or 2</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue bevacizumab.
<i>Grade 3 or 4</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Withhold bevacizumab. • If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. ^b

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
<i>Bevacizumab-related events not described above</i>	
Grade 1 or 2	<ul style="list-style-type: none"> Continue atezolizumab and bevacizumab at investigator's discretion.
Grade 3	<ul style="list-style-type: none"> Continue atezolizumab. Withhold bevacizumab. If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab.^b
Grade 4	<ul style="list-style-type: none"> Withhold atezolizumab and bevacizumab. If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab.^d If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab.^b

BAL = bronchoscopic alveolar lavage; CRP = C-reactive protein; CRS = cytokine release syndrome; GI = gastrointestinal; IRR = infusion-related reaction; MRI = magnetic resonance imaging; NSAID = non-steroidal anti-inflammatory drug; PRES = posterior reversible encephalopathy syndrome; RPLS = reversible posterior leukoencephalopathy syndrome.

^a Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^b If bevacizumab is delayed due to toxicity for ≥ 42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab.

^c If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

^d Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the investigator's benefit–risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

^e In case of pneumonitis, atezolizumab and bevacizumab should not be resumed after permanent discontinuation.

A18–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + BEV ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

- Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Bev arm are as follows:
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

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- Grade ≥ 3 hypertension
- Grade ≥ 3 proteinuria
- Any grade GI perforation, abscesses, or GI fistulae
- Grade ≥ 2 non-GI fistula or abscess
- Grade ≥ 3 wound-healing complication
- Any grade CNS bleeding
- Grade ≥ 2 hemoptysis
- Other Grade ≥ 3 hemorrhagic event
- Any grade arterial thromboembolic event
- Grade ≥ 3 venous thromboembolic event
- Any grade posterior reversible encephalopathy syndrome (PRES)
- Grade ≥ 3 congestive heart failure
- Myelitis
- Facial paresis

A18–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+BEV ARM

A18–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the *final* dose of atezolizumab or 6 months after the *final* dose of bevacizumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A18–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within

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6 months after the *final* dose of bevacizumab. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A18–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A18–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

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A18–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+BEV ARM

Table A18-6 Schedule of Activities for Atezo + Bev Arm

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) ^a		Stage 2 Screen. (see Appendix 2) ^c or Treatment Discontinuation ^d (see below)	Follow-Up ^d	
	Days –28 to –1	Cycle 1 ^b	Cycles ≥ 2		Every 3 Months (± 7 days)	
		Day 1	Day 1 (± 3 days)			
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available				
Vital signs ^e		x	x	x		
Weight ^f		x	x	x		
Complete physical examination ^g				x		
Limited physical examination ^{f, h}		x	x			
ECOG Performance Status ^f		x	x	x		
ECG ^{f, i}		Perform as clinically indicated				
Hematology ^j		x ^{k, l}	x ^k	x		
Chemistry ^m		x ^{k, l}	x ^k	x		
Coagulation (INR and aPTT)		x ^k				
TSH, free T3 (or total T3), and free T4 ⁿ		x ^l			x	
Pregnancy test ^o		x	x	x		
Urinalysis ^p		x	x ^q	x		
Blood sample for blood-based NGS ctDNA test ^r				x		
Serum autoantibody sample ^s		Perform if a patient experiences a suspected immune-mediated adverse event				

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Table A18-6 Schedule of Activities for Atezo + Bev Arm (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) ^a		Stage 2 Screen. (see Appendix 2) ^c or Treatment Discontinuation ^d (see below)	Follow-Up ^d
	Days –28 to –1	Cycle 1 ^b	Cycles ≥ 2		Every 3 Months (± 7 days)
		Day 1	Day 1 (± 3 days)		
PK samples	See Appendix 2	Refer to Table A18-22 .			
ADA samples		Refer to Table A18-22 .			
Biomarker samples		Refer to Table A18-22 .			
Blood sample for RBR (optional) ^t		x			
Tumor biopsy		x ^{u, v}			
Tumor biopsy (optional)		x ^{v, w}			
Tumor response assessments		x ^{x, y, z}			
Concomitant medications ^{aa}		x	x	x	
Adverse events ^{bb}		x	x	x ^{bb}	x ^{bb}
Atezolizumab administration ^{cc, dd}		x	x		
Bevacizumab administration ^{dd, ee}		x	x		
Survival follow-up and anti-cancer treatment					x ^{ff}

ADA=anti-drug antibody; Atezo + Bev = atezolizumab plus bevacizumab; CT=computed tomography; ctDNA=circulating tumor DNA; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; NGS=next-generation sequencing; PK=pharmacokinetic; RBR=Research Biosample Repository; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen.=screening; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

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Table A18-6 Schedule of Activities for Atezo + Bev Arm (cont.)

- ^a If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. The Medical Monitor is available to advise as needed.
- ^b It is recommended that treatment be initiated no later than 7 days after randomization.
- ^c Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.4) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.
- ^d Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the *final* dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments.
- ^e Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (\pm 5) minutes during and 30 (\pm 10) minutes after the infusion. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (\pm 10) minutes after the infusion. For the first infusion of bevacizumab, vital signs should be measured within 60 minutes prior to the infusion, at the end of the infusion, and 2 (\pm 1) hours after the infusion. For subsequent bevacizumab infusions, vital signs should be measured within 60 minutes prior to the infusion and within 30 minutes after completion of the infusion.
- ^f Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^g Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^h Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ⁱ It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.
- ^j Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).
- ^k Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-6 Schedule of Activities for Atezo + Bev Arm (cont.)

- ^l If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.
- ^m Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included on Day 1 of each treatment cycle.
- ⁿ TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).
- ^o All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum pregnancy tests will be performed at specified subsequent visits and at 3 months and 6 months after the *final* dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^p Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ^q Urinalysis may be performed up to 72 hours prior to Day 1 of each cycle, as results must be available prior to treatment administration. See [Table A18-5](#) for management guidelines for proteinuria.
- ^r Blood samples for blood-based NGS ctDNA test will not be collected from Protocol Version 19 *onward*.
- ^s Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Serum samples collected for the assessment of PK, ADAs, or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment, may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.
- ^t Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.
- ^u Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section [3.1.1](#) for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see Section [3.1.2](#)) will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible). See Section [4.5.6](#) for tissue sample requirements.
- ^v On-treatment biopsies must be performed at least 7 days after the previous bevacizumab dose. Bevacizumab must be administered ≥ 3 days after any on-treatment biopsy, but only after adequate wound healing has been demonstrated. The biopsy should not be performed in an anatomic location at risk for excessive bleeding, as determined by the investigator.

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-6 Schedule of Activities for Atezo + Bev Arm (cont.)

- ^w Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.
- ^x Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (± 1 week) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 6 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.
- ^y All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).
- ^z For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).
- ^{aa} Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.
- ^{bb} After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the *final* dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.
- ^{cc} Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.
- ^{dd} Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-6 Schedule of Activities for Atezo + Bev Arm (cont.)

^{ee} Bevacizumab will be administered by IV infusion at a dose of 15mg/kg on Day 1 of each 21-day cycle. The initial dose of bevacizumab will be delivered over 90 (\pm 15) minutes. If the first bevacizumab infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (\pm 10) minutes. If the 60 (\pm 10) minute infusion was tolerated without infusion-associated adverse events, the third infusion may be delivered over 30 (\pm 15) minutes. If the 30-minute bevacizumab infusion is well tolerated, all subsequent infusions may be delivered over 30 (\pm 10) minutes. Bevacizumab will be administered after completion of the atezolizumab infusion. Bevacizumab must be administered \geq 3 days after any on-treatment biopsy, but only after adequate wound healing has been demonstrated.

^{ff} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Appendix 18: Study Details Specific to Atezo + Bev Arm

Table A18-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Bev Arm

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, PBMC)
	30 (\pm 10) minutes after atezolizumab infusion	<ul style="list-style-type: none"> • Atezolizumab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum), PBMC)
Day 1 of Cycle 3	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycle 8	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (\leq 30 days after <i>final</i> dose)	At visit	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)

ADA = anti-drug antibody; Atezo + Bev = atezolizumab plus bevacizumab; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

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Appendix 19

Study Details Specific to Atezo + Bev + RTx Arm

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A19–1 BACKGROUND ON ATEZO+BEV+RTX ARM

A19–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, *myocarditis*, and *nephritis*, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma (in the European Union), non-small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer (in the European Union), hepatocellular carcinoma (HCC), melanoma (in the United States), and alveolar soft part sarcoma (in the United States).

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A19–1.2 BACKGROUND ON BEVACIZUMAB

Bevacizumab is a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF) that recognizes all isoforms of VEGF. It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor environment. Additional anti-tumor activity may be on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).

Appendix 19: Study Details Specific to Atezo + Bev + RTx Arm

Bevacizumab has been tested in Phase II and III studies in a variety of solid tumors in combination with chemotherapy. Bevacizumab is registered in over 40 countries worldwide for the first-line treatment of metastatic colorectal cancer (mCRC) in combination with chemotherapy, as second-line colorectal cancer (CRC) treatment, and first-line treatment of advanced NSCLC, metastatic breast cancer, advanced renal cell carcinoma (RCC), ovarian cancer, and glioblastoma (Reck and Crinò 2009).

In NSCLC, the Phase II/III Study E4599 showed that the addition of bevacizumab (15 mg/kg every 3 weeks [Q3W]) to the paclitaxel and carboplatin regimen led to a clinically relevant and statistically significant prolongation of overall survival ([OS] primary endpoint) compared with patients who were treated with paclitaxel and carboplatin alone (hazard ratio [HR]=0.80; 95% CI: 0.69 to 0.93; p=0.003; Kaplan-Meier [KM]-estimated median: 12.3 vs. 10.3 months). The OS benefit was supported by the results of progression-free survival (PFS) (HR=0.65; 95% CI: 0.56 to 0.76; KM-estimated median: 6.4 vs. 4.8 months) and response rate (29.0% vs. 12.9%).

In addition, data from the protocol-defined final PFS (primary efficacy parameter) analysis of Study BO17704 (AVAIL; Roche Report No. 1023798) showed that the addition of bevacizumab (7.5 or 15 mg/kg Q3W) to cisplatin/gemcitabine chemotherapy resulted in a clinically relevant and statistically significant improvement in PFS (bevacizumab 7.5 mg/kg: HR=0.75; 95% CI: 0.62 to 0.91; p=0.0026; KM-estimated median PFS: 6.7 vs. 8.1 months) (bevacizumab 15 mg/kg: HR=0.82; 95% CI: 0.68 to 0.98; p=0.0301; KM-estimated median PFS: 6.5 vs. 6.1 months). Objective response rate (ORR) was also significantly increased in both bevacizumab-containing arms (7.5 mg/kg: 34.1% vs. 20.1%; bevacizumab 15 mg/kg: 30.4% vs. 20.1%).

Bevacizumab is currently being tested in combination with atezolizumab across different indications in Phase I, II, and III clinical studies. *Atezolizumab plus bevacizumab has been approved as the first-line standard of care for patients with metastatic HCC.*

Refer to the Bevacizumab Investigator's Brochure for details on nonclinical and clinical studies.

A19–1.3 BACKGROUND ON RADIOTHERAPY AND OLIGOMETASTATIC DISEASE

A19–1.3.1 Nonclinical Evidence of Immune Re-Invigoration by Radiotherapy

A19–1.3.1.1 Radiotherapy in Checkpoint Inhibitor-Resistant Tumors

In tumors resistant to checkpoint inhibition, which is a rapidly growing segment clinically across disease sites, there is evidence that short bursts of radiation may modify the tumor microenvironment in nonclinical models. To this end, Wang et al. 2017, generated a nonclinical tumor model to study anti-PD-1 resistance by in vivo passaging of

Kras-mutated, p53-deficient murine lung cancer cells (p53^{R172HΔg/+}K-ras^{LA1/+}) in a syngeneic host dosed repetitively with anti-mouse PD-1 antibodies leading to a highly resistant lung model. Interestingly, PD-L1 (CD274) expression did not differ between the resistant and parental tumor cells. In contrast, major histocompatibility complex (MHC) class I and II, as well as β2-microglobulin, were significantly downregulated in the anti-PD-1-resistant tumors compared with parental tumors. Resistant tumors also contained fewer CD8⁺ (CD8α) and CD4⁺ tumor-infiltrating lymphocytes and reduced production of interferon (IFN)-γ. Localized flank radiotherapy induced IFN-β production, thereby elevating MHC class I expression on both parental and resistant tumor cells and restoring the responsiveness of resistant tumors to anti-PD-1 therapy.

A19–1.3.1.2 Role of Radiotherapy in (Oligo)Metastatic Disease

The definition of an oligometastatic state is in flux but essentially refers to a patient with a modest disease burden outside of the primary site. This state may consist of anywhere from 1–5 metastasis although some are willing to consider additional metastatic lesions as part of the oligometastatic state (Hellman and Weichselbaum 1995). The International Association for the Study of Lung Cancer recently published a consensus statement on the definition of oligometastatic disease in NSCLC. This expert panel agreed that the maximum number of metastases and organs involved depends on the possibility of offering a radical intent treatment strategy and thus, on the basis of the systematic review, a maximum of five metastases and three organs was agreed on. Importantly, the presence of diffuse serosal metastases or bone marrow involvement excludes cases from this definition (Dingemans et al. 2019).

In patients with a limited oligometastatic burden, emerging evidence suggests that treatment of all sites of disease with ablative therapies (such as surgery or stereotactic radiation) can improve patient outcomes, including OS and PFS.

Historically, evidence to support the oligometastatic state has consisted of single-arm, non-randomized studies without controls. One classic study reported on over 5000 patients with lung metastases from a variety of primary tumors. In patients who achieved a complete resection of their lung metastases, 5-year OS was 36%, better than might be expected for a cohort of patients with metastatic disease (Pastorino et al. 1997). Similarly, after radiation, a recent pooled analysis of 361 patients with oligometastatic lesions treated with radiation demonstrated a 3-year OS of 56% (Hong et al. 2018). The argument against the potential benefits of local therapies for this group of patients is based on selection of very fit patients with slow growing tumors, since randomized evidence to support the oligometastatic paradigm has been lacking (Primrose et al. 2010; Palma et al. 2014).

However, at least four recent randomized Phase II studies now provide some supporting evidence for the use of radiotherapy in an (oligo)metastatic state across various cancers

offering a potential to support and improve drug development. Specifically, patients who have already progressed through current accepted checkpoint inhibitors (CPIs) face a grim prognosis with modest options available to them (please refer to Section [A19–2.8](#)).

A19–2 RATIONALE FOR ATEZO+BEV+RTX ARM

A19–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses by binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, RCC, melanoma, CRC, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune CPIs, have had a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active *as monotherapy* for many patients.

A19–2.2 ANTI-VEGF CANCER TREATMENT

In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggested that VEGF may

reduce lymphocyte adhesion to vessel walls in the tumor microenvironment, thus contributing to decreased immune cell recruitment to the tumor site (Bouzin et al. 2007). Mice exposed to pathophysiologic levels of VEGF exhibited impaired dendritic cell (DC) function, which could be restored by blockade of VEGF receptor 2 (Huang et al. 2007). In addition, VEGF recruits macrophages into the tumor microenvironment that have an M2 polarization state, which is typically involved in wound healing. These M2 tumor-associated macrophages ultimately help establish and maintain an immunosuppressive microenvironment (Chen and Mellman 2013). In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). Synergistic effects have also been observed in a clinical study combining an immune-modulatory antibody (anti-cytotoxic T lymphocyte-associated protein 4; ipilimumab) and bevacizumab: Hodi et al. (2010) described increased T-cell trafficking in post-treatment biopsies, as well as marked increases in central memory cells in peripheral blood in the majority of patients.

A19–2.3 RADIOTHERAPY

A growing body of nonclinical work describes the immunogenic effects of radiation on the tumor microenvironment. Radiation can induce immunogenic cell death, local release of inflammatory cytokines, and damage associated molecular patterns (DAMPs) resulting in local effects on endothelial cell expression of adhesion receptors, increased immune cell trafficking, and immune cell activation (Rodriguez-Ruiz et al. 2017; Waldmann 2018).

However, radiation can also trigger effect within the tumor microenvironment that may be detrimental with regards to the development of anti-tumor immunity, including delayed increases in tumor infiltration by suppressive regulatory T cells as well as increased infiltration and activation of inhibitory macrophage and myeloid-derived suppressor cell lineages (Tsai et al. 2007; Fridlender et al. 2009; Tanaka et al. 2010; Kachikwu et al. 2011; Xu et al. 2013).

Dose, fractionation, and volume of radiation can influence immunologic effects in the tumor microenvironment. Nonclinical studies suggest that despite an initial local depletion of lymphocytes, hypofractionated regimens of radiation may be immune activating (Dewan et al. 2009). Additionally, recent work suggests that standard fractionation and hypofractionation induce expansion of unique immune populations with standard fractionation favoring a myeloid response and hypofractionation driving a lymphoid response that may be more favorable to adaptive anti-tumor immunity (Grapin et al. 2019).

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Compared to high doses of radiation, which induce immunogenic cell death, dose-dependent increases of MHC-I and death receptors, for example, Fas (Reits et al. 2006; Werner et al. 2017), moderate fractional doses of 3-10 Gy may be optimal for activating a type I IFN response in tumor cells via a dose-dependent increase in the cytoplasmic leakage of DNA from micronuclei, which activates the cyclic GMP-AMP synthase/stimulator of interferon genes (cGAS/STING) pathway (Harding et al. 2017; Vanpouille-Box et al. 2017).

The activation of the cGAS/STING pathway is critical for the priming of tumor-specific CD8 T cells in the draining lymph nodes, but their expansion and effector function that is responsible for the rejection of the irradiated and non-irradiated metastases requires the addition of antibodies blocking cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or PD-(L)1 (Vanpouille-Box et al. 2017).

At higher doses, radiation-induced STING activation may decline in part due to induced expression of Trex1 exonuclease, reducing the accumulation of cytoplasmic DNA resulting in negative feedback inhibition (Vanpouille-Box et al. 2017).

Another effect of low dose radiation (1–3 Gy), typically used in the clinic on a daily basis over 5-7 weeks, may be the modulation of the tumor microenvironment by ablating radiation-sensitive immune populations including suppressive and effector lymphocytes (Nakamura et al. 1990; Liu et al. 2010; Balogh et al. 2013; Liu et al. 2015). Both effects may create a window of opportunity to enhance response to immunotherapeutic agents, for example, by locally and temporarily depleting exhausted and suppressive T cells from the tumor microenvironment and allowing reconstitution with a more favorable infiltrate using immunotherapies, and abscopal or systemic responses have been reported when radiotherapy has been combined with immunotherapy to produce or re-invigorate T cells that reject not only the irradiated tumor but also the metastases outside of the field of radiation (Demaria et al. 2015; Vanpouille-Box et al. 2015; Ngwa et al. 2018).

Thus, with regards to dose, the optimal fraction and number of fractions that provide the optimal milieu for induction of IFN-I, and the consequent activation of anti-tumor T cells, appears to range between 6 to 10 Gy per fraction, for most cancer cells, as below 6 Gy in some cancer cells the accumulation of DNA in the cytosol is suboptimal, while above a threshold of approximately 10 Gy the Trex1 exonuclease is induced with the above mentioned consequences. Moreover, it has been described recently that multi-fraction approaches may be superior to single fraction doses to further enhance the amplification of the IFN-I pathway and IFN-I production (Vanpouille-Box et al. 2017).

Besides dose and number of fractions, scheduling of radiotherapy also plays an important role. Dovidio et al. (2014) demonstrated that dose scheduling is critical to the

synergistic effect of combination therapy, with systemic CPI treatment administered within ≤ 7 days or less of the completion of radiotherapy generating effective anti-tumor immunity and long-term tumor control.

A19–2.4 RATIONALE FOR COMBINING ATEZOLIZUMAB WITH BEVACIZUMAB

VEGF-A is a pro-angiogenic molecule produced by endothelium, tumors, and tumor-associated macrophages. The VEGF pathway also plays a crucial role in exerting and maintaining an immunosuppressive tumor microenvironment through several mechanisms. For example, VEGF-A inhibits the maturation of DCs (Gabrilovich et al. 1996), promotes the expression of inhibitory immune checkpoint molecules on intratumoral CD8⁺ T-cells that express VEGF-R2 (Voron et al. 2015), and induces Fas ligand (FasL) expression on endothelial cells, which acquired the ability to kill effector CD8⁺ T cells, but not regulatory T cells (Motz et al. 2014). Anti-VEGF agents such as bevacizumab are well known to promote the normalization of tumor vasculature and thereby increase access of therapeutic agents (Jain 2001). Furthermore, bevacizumab can restore and/or maintain the antigen-presentation capacity of DCs, leading to enhanced T-cell infiltration in tumors (Oelkrug and Ramage 2014; Wallin et al. 2016). Administration of anti-VEGF-A has been shown to attenuate tumor endothelial FasL expression and produce a significant increase in the influx of tumor-rejecting CD8⁺ T cells, leading to tumor growth suppression (Motz et al. 2014). In addition, anti-VEGF therapies can reduce the frequency of myeloid-derived suppressor cells, decrease production of suppressive cytokines, and lower expression of inhibitory checkpoints on CD8⁺ T cells in tumors (Roland et al. 2009; Voron et al. 2015). The immunomodulatory effect of bevacizumab is expected to increase CD8⁺ T-cell recruitment and relieve intratumoral immunosuppression, thereby boosting the effects of atezolizumab.

There is precedence for a beneficial effect of anti-angiogenesis in the context of immunotherapy. In a murine melanoma model, VEGF blockade was shown to synergize with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). High pretreatment serum VEGF was associated with poor survival following ipilimumab (anti-CTLA-4) monotherapy (Yuan et al. 2014), and synergistic effects were observed in a clinical study combining ipilimumab and bevacizumab, as shown by increased T-cell frequency in post-treatment biopsies, as well as marked increases in central memory cells in peripheral blood in the majority of patients (Hodi et al. 2014).

Furthermore, the anti-tumor activity of atezolizumab was increased in combination with bevacizumab, which was associated with a further increase in intra-tumoral CD8⁺ T cells and increases in gene expression correlated with T-cell trafficking and tumor MHC-I

expression and enhanced antigen-specific T-cell migration in metastatic RCC (Wallin et al. 2016).

The above-described data suggest that combined treatment with atezolizumab and bevacizumab may augment the anti-tumor immune response, resulting in improved and more durable clinical benefit for patients with non-squamous NSCLC.

A19–2.5 RATIONALE FOR COMBINING CANCER IMMUNE THERAPY WITH RADIOTHERAPY

Besides the immunogenic effects of radiation on the tumor microenvironment, that is, the induction of immunogenic cell death, local release of inflammatory cytokines and DAMPs, which can result in increased immune cell trafficking and immune cell activation and thus potentially enhance the efficacy of immune-CPIs, it has been demonstrated that radiotherapy has the potential to convert the cancer into an in situ, individualized vaccine (Demaria et al. 2005; Formenti and Demaria 2012).

However, in established tumors, similarly to most cancer vaccines, radiotherapy by itself is insufficient to generate therapeutically effective anti-tumor immunity (Klebanoff et al. 2011), because of the established immunosuppressive micro-environment tumors have achieved at the time of detection and treatment (Vesely et al. 2011). Extensive experimental evidence indicates that radiotherapy can work in synergy with immunotherapy to generate T cells that reject not only the irradiated tumor but also the metastases outside of the field of radiation (Vanpouille-Box et al. 2015), which offers a rationale for utilizing radiation to enhance response to radiotherapy-immune CPIs in situations where tumors are unlikely to respond to immune-CPIs alone.

A19–2.6 RATIONALE FOR COMBINING ANTI-ANGIOGENIC THERAPY WITH RADIOTHERAPY

The enhanced effect of a combinatorial approach using radiotherapy and anti-angiogenic treatment has been demonstrated in multiple clinical studies (Teicher et al. 1994; Teicher et al. 1995; Mauceri et al. 1998), with vessel normalization induced by anti-angiogenic drugs being one of the potential explanations for enhanced efficacy of the combination. However, the beneficial effects of combining radiotherapy with anti-angiogenic agents could also be demonstrated when radiotherapy was administered before the systemic treatment with anti-angiogenic agents (Kleibeuker et al. 2015). This could be in part explained by the stimulation of angiogenesis by irradiation by inducing the expression of pro-angiogenetic growth factors like VEGF by cancer cells or other cells that reside in the tumor microenvironment (Chuang et al. 2002; Solberg et al. 2008; Feng et al. 2015; Kleibeuker et al. 2016). Sofia Vala et al. (2010) demonstrated that low dose irradiation induces VEGF signaling in endothelial cells, while Meng et al. (2010) demonstrated increased VEGF expression of macrophages in the stromal tissue after irradiation.

These findings suggest that ionizing radiation can enhance tumor perfusion by induction of a pro-angiogenic response which can be counteracted by anti-angiogenesis treatment (Kleibeuker et al. 2016).

A19–2.7 CLINICAL STUDIES OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB

Study GP28328 is an ongoing, Phase Ib, open-label, multicenter study combining atezolizumab (1200 mg Q3W) with bevacizumab (15 mg/kg Q3W) in patients with advanced solid tumors, with expansion arms for patients with RCC, mCRC, gastric cancer, and ovarian cancer. Safety findings have been consistent with the known single-agent safety profiles for each drug; no new safety signals have been identified. The regimen has been well tolerated, and adverse events have been manageable. Another Phase Ib, open-label, multicenter study (GO30140) is investigating a similar dose of atezolizumab combined with bevacizumab in patients with HCC. In addition, this combination is being tested in a Phase II randomized study (WO29074) in which atezolizumab is administered as monotherapy or in combination with bevacizumab, compared with sunitinib, in patients with untreated advanced RCC.

In chemotherapy-naïve patients with Stage IV NSCLC, results from Phase III Study GO29436 (IMpower150) have shown that atezolizumab in combination with carboplatin+paclitaxel and bevacizumab results in significantly longer OS compared with carboplatin+paclitaxel and bevacizumab alone (Socinski et al. 2018). For inoperable, locally advanced, or metastatic RCC, Phase III Study WO29637 (IMmotion151) demonstrated improved PFS after treatment with the combination of atezolizumab plus bevacizumab compared with sunitinib treatment in treatment-naïve patients (Motzer et al. 2018). Phase Ib Study GO30140 in HCC front line found an ORR of 65% in 23 evaluable patients, across etiology, geography, baseline α -fetoprotein levels, and extrahepatic spread. The combination is currently being explored in a randomized Phase III study YO40245 (IMbrave150) versus sorafenib in first-line treatment for HCC (Stein et al. 2018). These are examples of clear synergy between atezolizumab and bevacizumab in different tumor types, which support further exploration of the combination in NSCLC.

Detailed clinical study results for atezolizumab and bevacizumab can be found in the Atezolizumab Investigator's Brochure and the Bevacizumab Investigator's Brochure, respectively.

A19–2.8 CLINICAL EVIDENCE SUPPORTING LOCAL RADIOTHERAPY IN METASTATIC DISEASE

A multitude of trials have explored the utility and effectiveness of local therapy, two of which were performed in the setting of metastatic NSCLC. In both, patients presented with a primary lung tumor and a limited number of metastatic lesions (1–3 in one study,

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1–5 in the other study), and after initial systemic therapy, patients were randomly assigned to standard palliative treatments versus consolidative ablative treatments to all sites of disease. Both studies were halted early due to evidence of efficacy, with the ablative treatments achieving an approximate 3-fold improvement in PFS (Gomez et al. 2016; Iyengar et al. 2018). Follow-up results with longer follow-up continued to demonstrate the benefits of local consolidative therapy in this oligometastatic setting (Gomez et al. 2019). Based on these results, the Phase III NRG LU-002 study is assessing the impact of consolidative ablative therapies on OS.

Finally, Palma et al. (2019), reported the results of a multi-institutional prospective study in patients with oligometastatic disease (up to five metastases) testing stereotactic body radiotherapy (SBRT): long term follow-up reported a statistically significant improvement in PFS and OS. The study used ablative radiotherapy with different doses and fractionations, but with the exception of the doses used when the spinal cord is in the field (7GyX5, 35 GY total dose), all fractionation schemas used achieved a biologically equivalent dose ≥ 100 Gy. Toxicities overall were modest; however, there were approximately 4% Grade 5 toxicity reported. Additional reviews of the safety of combined ablative SBRT and immunotherapy further confirm the overall safety of this combination (Verma et al. 2018).

Recently, Theelen et al. (2019) reported the results of a multicenter, Phase II randomized clinical study, assessing safety and efficacy of pembrolizumab (200 mg/kg Q3W) either alone (control arm) or after radiotherapy (3 doses of 8 Gy) in 92 patients with advanced NSCLC, not limited to patients with oligometastatic disease. A total of 76 patients were randomized to the control arm (n=40) or the experimental arm (n=36). The ORR at 12 weeks was 18% in the control arm versus 36% in the experimental arm (p=0.07). Median PFS was 1.9 months (95% CI: 1.7 to 6.9 months) versus 6.6 months (95% CI: 4.0 to 14.6 months) (HR=0.71; 95% CI: 0.42 to 1.18; p=0.19), and median OS was 7.6 months (95% CI: 6.0 to 13.9 months) versus 15.9 months (95% CI: 7.1 months to not reached) (HR=0.66; 95% CI: 0.37 to 1.18; p=0.16). In this study, the safety profile observed was consistent with previous studies of pembrolizumab treatment for advanced NSCLC (Garon et al. 2015; Herbst et al. 2016; Reck et al. 2016). Most immune-mediated events were Grade 1 or 2 and no significant differences were seen with regards to safety between arms. The investigators reported that 1 patient experienced an immune-related adverse event that may have been augmented by SBRT: This patient developed nephritis after the administration of SBRT on a retroperitoneal lesion and the third course of pembrolizumab, resulting in discontinuation of treatment.

Furthermore, Luke et al. (2018) reported data on 73 patients with solid tumors from a Phase I study treated with pembrolizumab monotherapy after ablative SBRT to 2 to

4 tumor lesions. While the timing of SBRT was similar to the study conducted by Theelen et al. (2019), doses varied from 30 to 50 Gy in 3 to 5 fractions, depending on the tumor site. In this study, Response Evaluation Criteria in Solid Tumors (RECIST)-based ORR was 13.2% in a population of heavily pretreated patients. Of note, the population was unselected for PD-L1 expression, consisted of 27 cancer types, and was enriched in histologies not associated with significant responses to pembrolizumab. The most common treatment related adverse events were general disorders and administration site conditions (n=7), followed by gastrointestinal (GI) disorders (n=6). The authors also concluded that the administration of SBRT before pembrolizumab treatment was well tolerated.

A19–2.9 BENEFIT–RISK ASSESSMENT

Metastatic NSCLC remains an incurable disease with a high unmet medical need, especially in the CPI-pretreated patient population. Because of the reinvigoration of an anti-tumor immune response by immune-modulating SBRT (I-SBRT) and the potential synergism with immune-CPI treatment, the potentially synergistic mechanisms of action of atezolizumab and bevacizumab, as well as their manageable and tolerable safety profiles (see Section A19–5), combination treatment with these two treatment modalities appears to have promising therapeutic potential in solid tumors and may reinvigorate and augment the anti-tumor immune response, potentially resulting in improved and more durable clinical benefit for patients with NSCLC.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.4.

A19–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + BEV + RTX ARM

A19–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab (Tecentriq® U.S. *Prescribing Information*).

A19–3.2 RATIONALE FOR BEVACIZUMAB DOSE AND SCHEDULE

Bevacizumab will be administered by infusion at a fixed dose of 15 mg/kg Q3W (15 mg/kg on Day 1 of each 21-day cycle), *which is an approved dosage for bevacizumab (Avastin® U.S. Prescribing Information).*

A19–3.3 RATIONALE FOR RADIOTHERAPY DOSE AND SCHEDULE

A large number of clinical studies are ongoing to test the ability of radiotherapy to improve tumor immunogenicity and enhance responses to immune checkpoint blockade

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(Kang et al. 2016). As mentioned earlier, laboratory data and emerging clinical data support a rationale of both targeting multiple metastatic sites and administering radiotherapy regimens with single or fractionated non-ablative SBRT (I-SBRT) (Theelen et al. 2019). To minimize potential toxic effects caused by the addition of radiotherapy and yield optimal immunologic priming in this CPI-experienced patient population, based on emerging data on the relevance of dose per fraction to best induce IFN-I, a non-ablative dose of 8 Gy x 3 fractions, delivered approximately every other day to each metastatic site up to 5 sites has been chosen. To further reduce the possibility of toxic effects, I-SBRT has to be administered sequentially rather than concurrently with systemic therapy, with no longer than seven days between the last radiotherapy dose and the first dose of atezolizumab + bevacizumab to minimize delay of systemic treatment. Constraints to normal tissue will follow, based on the technical requirements in part defined by NRG-BR001, the first National Cancer Institute-sponsored study of SBRT for the treatment of multiple metastases (Al-Hallaq et al. 2016).

A19–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+BEV+RTX ARM

A19–4.1 SYSTEMIC TREATMENT IN ATEZO+BEV+RTX ARM

A19–4.1.1 Formulation, Packaging, and Handling

A19–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the atezolizumab formulation, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A19–4.1.1.2 Bevacizumab

The bevacizumab drug product will be supplied by the Sponsor as a sterile solution in a single-use, 4-mL or 16-mL, preservative-free glass vial. The 4-mL vial contains 100 mg of bevacizumab (25 mg/mL), and the 16-mL vial contains 400 mg of bevacizumab (25 mg/mL).

For information on the *bevacizumab* formulation, see the pharmacy manual and the Bevacizumab Investigator's Brochure.

A19–4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + Bev + RTx arm will receive systemic treatment as outlined in [Table A19-1](#) until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as

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pain secondary to disease) (see Section 3.1.1 for details). It is mandated that systemic treatment be initiated no later than 7 days after completion of radiotherapy.

Table A19-1 Treatment Regimen for Atezo + Bev + RTx Arm

Radiotherapy	
Treatment Duration	Dose and Fractionation
Up to 21 days (\pm 5 days, including simulation, contouring, and planning)	8Gy \times 3
Systemic Therapy	
Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	<ul style="list-style-type: none">• Atezolizumab 1200 mg by IV infusion on Day 1 of each cycle• Bevacizumab 15 mg/kg by IV infusion on Day 1 of each cycle

Atezo + Bev + RTx = atezolizumab plus bevacizumab plus radiotherapy.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

No safety data related to overdosing of atezolizumab or bevacizumab are available.

A19–4.1.2.1 Bevacizumab Administration

Bevacizumab will be administered by IV infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle. *On Day 1 of each cycle, bevacizumab will be administered at least 5 minutes after completion of the atezolizumab infusion.*

Administration of bevacizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#). Bevacizumab infusions will be administered per the instructions outlined in [Table A19-2](#).

Table A19-2 Administration of First and Subsequent Bevacizumab Infusions

First Infusion	Subsequent Infusions
<ul style="list-style-type: none"> No premedication is permitted prior to the bevacizumab infusion. Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) should be measured within 60 minutes prior to the infusion. Bevacizumab should be infused over 90 (\pm 15) minutes. Vital signs should be measured at the end of infusion and 2 (\pm 1) hours after the infusion. Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. 	<ul style="list-style-type: none"> If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic <i>medications</i>, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. Vital signs should be recorded within 60 minutes prior to the infusion. Bevacizumab should be infused over 60 (\pm 10) minutes if the previous 90-minute infusion was tolerated without an IRR, or 90 (\pm 15) minutes if the patient experienced an IRR with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (\pm 5) minutes thereafter. Vital signs should be measured within 30 minutes after completion of the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of IRRs for bevacizumab are provided in Section [A19-5.1.6](#).

No dose modification for bevacizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section [A19-5.1.6.2](#).

Bevacizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A19-4.1.2.2 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 5](#). Atezolizumab infusions will be administered per the instructions outlined in [Table A19-3](#).

Table A19-3 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
<ul style="list-style-type: none"> No premedication is permitted prior to the atezolizumab infusion. Vital signs (pulse rate, respiratory rate, <i>pulse oximetry</i>, blood pressure, and temperature) should be <i>measured</i> within 60 minutes prior to the infusion. Atezolizumab should be infused over 60 (\pm 15) minutes. If clinically indicated, vital signs should be <i>measured</i> every 15 (\pm 5) minutes during <i>the infusion</i> and at 30 (\pm 10) minutes after the infusion. Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. 	<ul style="list-style-type: none"> If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic <i>medications</i>, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. Vital signs should be <i>measured</i> within 60 minutes prior to the infusion. Atezolizumab should be infused over 30 (\pm 10) minutes if the previous infusion was tolerated without an IRR, or 60 (\pm 15) minutes if the patient experienced an IRR with the previous infusion. If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be <i>measured</i> during the infusion and at 30 (\pm 10) minutes after the infusion.

IRR = infusion-related reaction.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in [Appendix 6](#).

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section [A19–5.1.6](#). Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A19–4.1.3 Radiotherapy Administration

Patients in the Atezo + Bev + RTx arm will receive stereotactic radiotherapy as outlined in the technical radiotherapy manual. Radiotherapy phase starts once a patient is randomized to the Atezo + Bev + RTx Arm and signed the arm specific informed consent. It includes I-SBRT simulation, contouring, and planning followed by I-SBRT administration. If a patient is randomized to the Atezo + Bev + RTx arm but cannot start

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treatment with radiotherapy for clinical/technical reasons (e.g., contraindication for radiotherapy that is detected after randomization, e.g., during the radiotherapy planning process), this patient will be allowed to skip radiotherapy and start treatment with Atezo + Bev. The reason for skipping radiotherapy will be documented accordingly.

Radiotherapy will be delivered with four major guiding principles:

- The goal of the protocol is to use SBRT to optimize the response to immunotherapy.
- In order to minimize toxicity, non-ablative SBRT doses will be used and normal tissue tolerance doses will never be exceeded.
- In order to avoid delays in subsequent systemic therapy, all SBRT will be delivered over the course of 21 days (± 5 days).
- There are many techniques that facilitate the safe application of SBRT, each center will be able to continue to use their preferred technique.

Please refer to the technical radiotherapy manual for further details on the radiotherapy treatment regimen.

A19–4.1.4 Stage 2 Treatment

Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1) or unacceptable toxicity related to bevacizumab will be given the option of receiving a different treatment combination during Stage 2, as outlined in [Table A19-4](#), provided they meet eligibility criteria (see Section 4.1) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A19-4 Stage 2 Treatment Regimens Available for Atezo + Bev + RTx Arm

Study Treatment	Appendix
Atezo + Docetaxel	Appendix 16
Atezo + Lina	Appendix 17

Atezo + Bev + RTx = atezolizumab plus bevacizumab plus radiotherapy;
Atezo = atezolizumab; Lina = linagliptin.

Refer to [Appendix 16](#) and [Appendix 17](#) for details specific to the atezolizumab plus docetaxel arm and atezolizumab plus linagliptin arm, respectively.

A19–4.2 CONCOMITANT THERAPY FOR ATEZO + BEV + RTX ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of any study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A19–4.2.1 Permitted Therapy for Atezo + Bev + RTx Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Inactivated vaccines (such as influenza and COVID-19)
 - Live, attenuated vaccines are not permitted (see [A19–4.2.3](#)).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:
 - Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy *with sufficient monitoring of hematologic parameters in place*.
- Prophylactic treatment of asymptomatic metastasis, unless at risk for an impending clinical event such as cord compression or pathologic fractures, is not allowed in this arm.
- Radiotherapy to the brain as outlined below:

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Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

- The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.
- The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

- Anti-convulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretic *medications*, and/or analgesics may be administered for the second and subsequent atezolizumab and bevacizumab infusions only, at the discretion of the investigator. *Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.*

Anti-emetic medications, anti-diarrheal medications, and hematopoietic growth factors are not to be administered prophylactically prior to the first doses of systemic study treatment. However, at the discretion of the investigator, anti-emetic medications, anti-diarrheal medications, and hematopoietic growth factors may be administered prophylactically per standard local practice before the second and subsequent doses of systemic study treatment.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections [A19–4.2.2](#) and [A19–4.2.3](#)) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 -adrenergic agonists; see [Appendix 5](#)).

At this time there is no evidence to suggest an interaction between the COVID-19 vaccines and bevacizumab. Based on the mechanism of action of bevacizumab, an interaction with the COVID-19 vaccines is unlikely. COVID-19 vaccines must be given in accordance with the approved/authorized vaccine label and official immunization

guidance. The decision of administration of a COVID-19 vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

A19–4.2.2 Cautionary Therapy for Atezo + Bev + RTx Arm

A19–4.2.2.1 Corticosteroids and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may be administered at the discretion of the investigator. The Medical Monitor is available to advise as needed.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to [Appendix 6](#) for details).

The above list of cautionary medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor is available to advise as needed if questions arise regarding medications not listed above.

A19–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section [A19–4.2.3](#)) may be used during the study at the discretion of the investigator.

A19–4.2.2.3 Bisphosphonates

Osteonecrosis of the jaw has been reported in patients receiving bevacizumab, mainly in combination with bisphosphonates. Thus, caution must be exercised in using bevacizumab in patients receiving concomitant bisphosphonates.

A19–4.2.3 Prohibited Therapy for Atezo + Bev + RTx Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting any study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A19–4.2.1.
- Investigational therapy is prohibited within 28 days prior to initiation of any study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of systemic study treatment, during treatment with atezolizumab, and for 5 months after the *final* dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, IFNs and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of systemic study treatment and during systemic study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Antithrombotic treatment with aspirin (> 325 mg/day) or clopidogrel (> 75 mg/day) or equivalent is prohibited.

A19–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + BEV + RTX ARM

Contraception requirements for women and men in the Atezo + Bev + RTx arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 5 months after the *final* dose of atezolizumab, for 6 months after the *final* dose of bevacizumab, and for at least 6 months after the *final* dose of radiotherapy.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

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Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

Hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below.

With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the *final* dose of bevacizumab and for at least 6 months after the *final* dose of radiotherapy to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A19-4.4 QUALITY ASSURANCE

A19-4.4.1 Quality Assurance for Morpheus Sites

Prior to opening the arm, each participating site will be required to send a benchmark treatment plan to the Medical Monitor, to ensure that the treatment plans are designed in compliance with the protocol. The Sponsor will provide computed tomography (CT) datasets as a basis for the benchmark treatment plan. Furthermore, the Sponsor will collect anonymized radiotherapy treatment plans for each patient.

A19-5 ASSESSMENT OF SAFETY FOR ATEZO+BEV+RTX ARM

A19-5.1 SAFETY PLAN FOR ATEZO+BEV+RTX ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and bevacizumab as well as I-SBRT (Theelen et al. 2019) in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections [A19-5.1.1](#), [A19-5.1.2](#), [A19-5.1.3](#), [A19-5.1.4](#), and [A19-5.1.5](#)). Guidelines for management of patients who experience specific adverse events related to atezolizumab and/or bevacizumab are provided in Section [A19-5.1.6](#). The management of potential I-SBRT related adverse events will be performed as per institutional guidelines.

Appendix 19: Study Details Specific to Atezo + Bev + RTx Arm

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

To further reduce the possibility of toxic effects by the addition of radiotherapy, the treatments will be administered sequentially instead of concurrently, with I-SBRT preceding systemic treatment.

Adverse events will be reported as described in Sections [5.2–5.6](#).

A19–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial palsy, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis. Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A19–5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: GI perforations, hemorrhage, arterial thromboembolic events, fistulae, wound-healing complications, hypertension, venous thromboembolism, proteinuria, *congestive heart failure*, and *posterior reversible encephalopathy syndrome*.

Refer to Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for Bevacizumab.

A19–5.1.3 Risks Associated with Combination Use of Atezolizumab and Bevacizumab

On the basis of the frequency of adverse events associated with either atezolizumab or bevacizumab, the following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and bevacizumab: cardiovascular, gastrointestinal, renal, and pulmonary toxicity.

A19–5.1.4 Risks Associated with Combination Use of SBRT and Checkpoint Inhibitors

Recently, Theelen et al. (2019) reported the results of a multicenter, Phase II randomized clinical study, assessing safety and efficacy of pembrolizumab (200 mg/kg Q3W) either alone (control arm) or after radiotherapy (3 doses of 8 Gy) in 92 patients with advanced NSCLC. In this study, the safety profile observed was consistent with previous studies of pembrolizumab treatment for advanced NSCLC (Garon et al. 2015; Herbst et al. 2016; Reck et al. 2016). Most immune-mediated events were Grade 1 or 2, and the most common adverse events were fatigue (28 of 72 patients [39%]), flu-like symptoms (23 of 72 [32%]), and cough (20 of 72 [28%]). There were no significant differences between the arms at the $\alpha=0.1$ level, except fatigue (10 of 37 patients [27%] vs. 18 of 35 [51%]; $p=0.05$) and pneumonia (3 of 37 [8%] vs. 9 of 35 [26%]; $p=0.06$). However, after applying the Holms-Bonferroni correction to compensate for the number of different adverse events categories compared, no significance differences between arms remained. Grade 3 to 5 pembrolizumab-related toxic effects were reported in 12 patients (17%), with no significant differences between arms. The investigators reported that 1 patient experienced an immune-related adverse event that may have been augmented by I-SBRT:

This patient developed nephritis after the administration of SBRT on a retroperitoneal lesion and the third course of pembrolizumab, resulting in discontinuation of treatment.

A19–5.1.5 Risks Associated with Combination Use of Radiotherapy and Bevacizumab

Pulmonary hemorrhage/hemoptysis potentially related to bevacizumab has been observed primarily in studies in patients with NSCLC. Prior radiotherapy has been identified as a possible risk factor for this adverse event, while other risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs, treatment with anticoagulants, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location, and cavitation of tumors prior to or during therapy.

In Study AVF2119g in patients with metastatic breast cancer, there was a slight increase in the incidence of congestive heart failure or cardiomyopathy in the combination arm (3.1% vs. 0.9%). Prior anthracycline exposure and prior chest wall radiation may increase the risk of congestive heart failure in patients receiving bevacizumab (Miller et al. 2005).

Study AVF2941n (BRiTE) was a registry of 1953 patients with mCRC in the United States who were treated with a bevacizumab-containing regimen as their first-line therapy. The study evaluated the incidences of GI perforation, Grade ≥ 3 bleeding events; post-operative bleeding and wound healing complications, arterial thrombotic

events, and other bevacizumab-related serious adverse events. Subgroup analyses of this study showed that patients with primary tumor intact, recent prior history of sigmoidoscopy or colonoscopy, or prior adjuvant radiotherapy appeared to have a slightly higher incidence of GI perforation (Hedrick et al. 2006).

A19–5.1.6 Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm

A19–5.1.6.1 Dose Modifications for Systemic Treatment

There will be no dose modifications for atezolizumab or bevacizumab in this study.

A19–5.1.6.2 Systemic Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see [Table A19-5](#)). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to *the equivalent of* ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on *the investigator's benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's benefit–risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 non-serious adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤ 1 , bevacizumab may be restarted at the same dose level. If bevacizumab is delayed due to toxicity for > 42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab. Bevacizumab can be resumed after being withheld for > 42 days if the patient is likely to derive clinical benefit. The decision to re-challenge patients with bevacizumab should be based on *the investigator's benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

If either study drug is discontinued, the other study drug can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section [A19–4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A19–5.1.6.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in [Table A19-5](#). These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Of note, the management of potential I-SBRT related adverse events will be performed as per institutional guidelines.

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev + RTx Arm

Event	Action to Be Taken
Pulmonary events including pneumonitis	
General guidance	<ul style="list-style-type: none"> All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia <i>or other</i> infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.
Pulmonary event, Grade 1	<ul style="list-style-type: none"> Continue atezolizumab and bevacizumab, <i>and monitor closely.</i> Re-evaluate on serial imaging. Consider patient referral to pulmonary specialist. For Grade 1 pneumonitis, consider withholding atezolizumab. <ul style="list-style-type: none"> – <i>Consider resuming on radiographic evidence of improvement.</i>
Pulmonary event, Grade 2	<ul style="list-style-type: none"> Withhold atezolizumab <i>for up to 12 weeks after event onset.</i> ^a Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL <i>with or without transbronchial biopsy.</i> Initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.</i> If event resolves to Grade 1 or better, resume atezolizumab. ^c <i>If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab, and contact the Medical Monitor.</i> ^{d, e} For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be Taken
Pulmonary events (cont.)	
Pulmonary event, Grade 3 or 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^{d, e} Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b • <i>Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment.</i> • <i>Bronchoscopy or BAL with or without transbronchial biopsy is recommended.</i> • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Hepatic events	
Hepatic event, Grade 1	<ul style="list-style-type: none"> • Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values. • Continue bevacizumab.
Hepatic event, Grade 2	<p>All events:</p> <ul style="list-style-type: none"> • Monitor LFTs more frequently until return to baseline values. • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b <p>Events of >5 days' duration:</p> <ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset. ^a • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. ^c • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. ^d

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be Taken
Hepatic events (cont.)	
<i>Hepatic event, Grade 3 or 4</i>	<ul style="list-style-type: none"> • <i>Permanently discontinue atezolizumab and contact the Medical Monitor. ^d</i> • <i>Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury.</i> • <i>Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.</i> • <i>If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</i> • <i>If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.</i> • <i>Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b</i>
Gastrointestinal events	
General guidance	<ul style="list-style-type: none"> • All events of diarrhea or colitis should be thoroughly evaluated for more common etiologies other than drug-induced effects. • For events of significant duration or magnitude or associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis. • Administer anti-diarrheal agents and other supportive care per institutional guidelines or per suggested supportive care outlined below: <ul style="list-style-type: none"> <u>Medication</u> – Initiate loperamide (4 mg) every 6 hours around the clock, alternating with diphenoxylate hydrochloride (5 mg)/atropine sulfate (0.5 mg) every 6 hours around the clock, until no loose stools for 24 hours. – If Grade ≥2 diarrhea persists after 48 hours of treatment with loperamide and diphenoxylate/atropine, consider initiating second-line agents (e.g., octreotide, budesonide, tincture of opium).

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events (cont.)	
General guidance (cont.)	<p><u>Oral Supplementation</u></p> <ul style="list-style-type: none"> – Initiate potassium and/or magnesium if serum levels are less than the lower limit of normal. – Consider rehydration therapy with oral electrolyte solution for Grade ≥ 1 diarrhea or vomiting. <p><u>Dietary Modifications</u></p> <ul style="list-style-type: none"> – Instruct patient to eat small meals and eliminate lactose-containing products from diet. – Suggest diet of bananas, rice, apples, and toast, while avoiding fiber from vegetables and other fruits. – Encourage adequate hydration with salt-containing liquids (e.g., broth, sports drinks such as Gatorade).
Diarrhea, Grade 1 or 2 (tolerable)	<ul style="list-style-type: none"> • Continue atezolizumab and bevacizumab. • Initiate supportive care and monitor patient closely. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis if appropriate.
Diarrhea, Grade 2 (intolerable) or Grade 3	<ul style="list-style-type: none"> • Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment.^b • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor.^{a, c, d}

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events (cont.)	
Diarrhea, Grade 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^d Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Rule out bowel perforation. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.
Colitis, Grade 1	<ul style="list-style-type: none"> • Continue atezolizumab and bevacizumab. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy if symptoms persist for > 7 days.
Colitis, Grade 2	<ul style="list-style-type: none"> • Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. ^{a, c, d}

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be Taken
Gastrointestinal events (cont.)	
Colitis, Grade 3	<ul style="list-style-type: none"> • Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. ^{a, c, d}
Colitis, Grade 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^d Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Gastrointestinal perforation, any grade	<ul style="list-style-type: none"> • Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. • Initiate treatment per institutional guidelines.

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be Taken
Endocrine events	
Asymptomatic hypothyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab.
Symptomatic hypothyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab.
Asymptomatic hyperthyroidism	<p>TSH ≥ 0.1 mU/L and < 0.5 mU/L:</p> <ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab. <p>TSH < 0.1 mU/L:</p> <ul style="list-style-type: none"> Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b
Symptomatic adrenal insufficiency, Grade 2–4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b
Hyperglycemia, any grade	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab.
Hypophysitis (pan-hypopituitarism), Grade 2–4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be Taken
Ocular events	
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 1	<ul style="list-style-type: none"> Continue atezolizumab and bevacizumab. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If symptoms persist, treat as a Grade 2 event.
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 2	<ul style="list-style-type: none"> Withhold atezolizumab.^a Continue bevacizumab. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor.^{a, c, d}
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 3 or 4	<ul style="list-style-type: none"> Permanently discontinue atezolizumab and contact Medical Monitor.^d Bevacizumab may continue at the discretion of the investigator per medical judgment.^b
Cardiac events	
<i>Immune-mediated cardiac events</i>	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Bevacizumab may continue at the discretion of the investigator per medical judgment.^b
<i>Congestive heart failure, Grade 3 or 4</i>	<ul style="list-style-type: none"> Atezolizumab may be continued at the discretion of the investigator. Permanently discontinue bevacizumab.
IRRs, CRS, anaphylaxis, and hypersensitivity reaction	
General guidance	<ul style="list-style-type: none"> Guidelines for management of IRRs and CRS for atezolizumab are provided in Appendix 6. For anaphylaxis precautions, see Appendix 5. For severe hypersensitivity reactions, permanently discontinue atezolizumab and bevacizumab.
IRR to bevacizumab, Grade 1	<ul style="list-style-type: none"> Continue bevacizumab. System intervention is not indicated.

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be taken
IRRs, CRS, anaphylaxis, and hypersensitivity reaction (cont.)	
IRR to bevacizumab, Grade 3 or 4	<ul style="list-style-type: none"> • Stop infusion <i>and permanently discontinue bevacizumab</i>. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen) if clinically indicated.
Pancreatic events	
Amylase and/or lipase elevation, Grade 3 or 4	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b
Pancreatitis, Grade 2–4	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b
Dermatologic events	
General guidance	<ul style="list-style-type: none"> • A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.
Dermatologic event, Grade 1 or 2	<ul style="list-style-type: none"> • Continue atezolizumab and bevacizumab. • Initiate supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids. • For Grade 2 rash, consider referral to dermatologist. <p>Acneiform rash:</p> <ul style="list-style-type: none"> • Consider initiating treatment with topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be Taken
Dermatologic events (cont.)	
IRR to bevacizumab, Grade 2	<ul style="list-style-type: none"> • Reduce infusion rate to $\leq 50\%$ or interrupt infusion at the discretion of the investigator per medical judgment. • If the infusion is interrupted, it may be resumed at $\leq 50\%$ of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.
Dermatologic event, Grade 3	<ul style="list-style-type: none"> • Withhold atezolizumab. ^a Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b • Refer patient to dermatologist. A biopsy should be performed if appropriate. • Consider initiating treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 2 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. ^{a, c, d}
Dermatologic event, Grade 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^d • Bevacizumab may continue at the discretion of the investigator per medical judgment. ^b
Stevens-Johnson syndrome or toxic epidermal necrolysis, any grade	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Withhold bevacizumab. ^b • If event resolves to Grade 1 or better, resume bevacizumab. • Permanently discontinue bevacizumab if withheld for >42 days or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed.

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be Taken
Neurologic disorders	
Immune-mediated neuropathy, Grade 1	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab. Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, including facial paresis, Grade 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold bevacizumab. ^b
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Permanently discontinue bevacizumab.
Myasthenia gravis or Guillain-Barré syndrome, all grades	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Permanently discontinue bevacizumab.
Immune-mediated myelitis, Grade 1	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Continue bevacizumab.
Immune-mediated myelitis, Grade 2	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Permanently discontinue bevacizumab.
Immune-mediated myelitis, Grade 3 or 4	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Permanently discontinue bevacizumab.
Immune-related meningoencephalitis, any grade	<ul style="list-style-type: none"> Follow guidelines for atezolizumab in Appendix 6. Withhold bevacizumab. ^b If patient stabilizes within 42 days, resume bevacizumab. <i>If not, permanently discontinue bevacizumab.</i> ^b

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be Taken
Hypertension	
General guidance	<ul style="list-style-type: none"> • <i>Treat with antihypertensive medication as needed.</i>
Hypertension, Grade 1	<ul style="list-style-type: none"> • <i>Continue atezolizumab and bevacizumab.</i> • <i>Consider increased blood pressure monitoring.</i>
Hypertension, Grade 2	<ul style="list-style-type: none"> • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. ^a • <i>If asymptomatic, begin or modify baseline antihypertensive therapy and continue bevacizumab.</i> • <i>If symptomatic, start or adjust antihypertensive therapy.</i>
Hypertension, Grade 3	<ul style="list-style-type: none"> • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. ^a • <i>Modify existing antihypertensive therapy (more than one drug or more intensive therapy than previously indicated).</i> • <i>Withhold bevacizumab until symptoms resolve to Grade 1 or better <u>and</u> blood pressure <160/90 mmHg.</i>
Hypertension, Grade 4	<ul style="list-style-type: none"> • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. ^a • Discontinue bevacizumab.

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be Taken
Hemorrhage	
<i>Hemorrhage, Grade 3 or 4 (excluding cerebral hemorrhage)</i>	<ul style="list-style-type: none"> • Continue atezolizumab. • Permanently discontinue bevacizumab.
<i>Cerebral hemorrhage, any grade</i>	<ul style="list-style-type: none"> • Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
<i>Grade ≥2 hemoptysis (≥2.5 mL of bright red blood per episode)</i>	<ul style="list-style-type: none"> • Continue atezolizumab. • Permanently discontinue bevacizumab.
<i>Bleeding in patients on full-dose anticoagulant therapy</i>	<ul style="list-style-type: none"> • Continue atezolizumab. • Permanently discontinue bevacizumab.
Venous thromboembolic events	
<i>Venous thromboembolic event, Grade 3</i>	<ul style="list-style-type: none"> • Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be withheld until the full-dose anticoagulation period is over. The use of direct oral anticoagulants is not recommended. • If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during full-dose anticoagulation <u>if</u> all of the criteria below are met: <ul style="list-style-type: none"> – The patient must not have pathological conditions that carry high risk of bleeding (e.g., tumor involving major vessels or other conditions). – The patient must not have had Grade >2 hemorrhagic events while in the study. – The patient must be on stable dose of heparin, low-molecular-weight heparin, or have an in-range INR (usually 2 to 3) on a stable dose of warfarin prior to restarting bevacizumab. • If thromboemboli worsen or recur upon resumption of study therapy, discontinue bevacizumab.
<i>Venous thromboembolic event, Grade 4</i>	<ul style="list-style-type: none"> • Atezolizumab and camonsertib may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be Taken
Arterial thromboembolic events	
Arterial thromboembolic event, any grade	<ul style="list-style-type: none"> • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. • <i>Permanently</i> discontinue bevacizumab.
Proteinuria	
<i>Proteinuria, Grade 1 (1+ by dipstick; urinary protein \leq 1.0 g/24 hr)</i>	<ul style="list-style-type: none"> • <i>Continue atezolizumab and bevacizumab.</i>
<i>Proteinuria, Grade 2 (2+ and 3+ by dipstick; urinary protein 1.0–3.4 g/24 hr)</i>	<ul style="list-style-type: none"> • <i>Continue atezolizumab.</i> • <i>For 2+ dipstick: Continue bevacizumab and collect 24-hour urine protein prior to subsequent bevacizumab administration.</i> • <i>For 3+ dipstick: Obtain 24-hour urine prior to administering bevacizumab.</i> • <i>Withhold bevacizumab for urinary protein \geq 2 g/24 hr.</i> • <i>If bevacizumab is withheld and urine protein improves to <2 g/24 hr within 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab.</i>
<i>Proteinuria, Grade 3 (4+ by dipstick; urinary protein \geq 3.5 g/24 hr) with no diagnosis of nephrotic syndrome</i>	<ul style="list-style-type: none"> • <i>Atezolizumab may be continued at the discretion of the investigator.</i> • <i>Withhold bevacizumab.</i> • <i>If urine protein improves to <2 g/24 hr within 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab.</i>
<i>Nephrotic syndrome, Grade 3 or 4</i>	<ul style="list-style-type: none"> • <i>Atezolizumab may be continued at the discretion of the investigator.</i> • <i>Permanently discontinue bevacizumab.</i>

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be Taken
Fistula	
<i>Tracheoesophageal fistula, any grade</i>	<ul style="list-style-type: none"> • Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. ^a
<i>Fistula (non-tracheoesophageal), Grade □4</i>	<ul style="list-style-type: none"> • Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. ^a
Wound dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	<ul style="list-style-type: none"> • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. • Permanently discontinue bevacizumab.
Posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome	
PRES/RPLS, any grade confirmed by MRI	<ul style="list-style-type: none"> • Withhold atezolizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. • Permanently discontinue bevacizumab.
<i>Atezolizumab-related events not described above</i>	
<i>Grade 1 or 2</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Continue bevacizumab.
<i>Grade 3 or 4</i>	<ul style="list-style-type: none"> • Follow guidelines for atezolizumab in Appendix 6. • Withhold bevacizumab. • If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. ^b

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Bev+RTx Arm (cont.)

Event	Action to Be Taken
<i>Bevacizumab-related events not described above</i>	
Grade 1 or 2	<ul style="list-style-type: none"> Continue atezolizumab and bevacizumab at investigator's discretion.
Grade 3	<ul style="list-style-type: none"> Continue atezolizumab. Withhold bevacizumab. If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab.^b
Grade 4	<ul style="list-style-type: none"> Withhold atezolizumab and bevacizumab. If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab.^d If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab.^b

BAL=bronchoscopic alveolar lavage; CRP=C-reactive protein; CRS=cytokine release syndrome; GI=gastrointestinal; IRR=infusion-related reaction; MRI=magnetic resonance imaging; NSAID=non-steroidal anti-inflammatory drug; PRES=posterior reversible encephalopathy syndrome; RPLS=reversible posterior leukoencephalopathy syndrome.

^a Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's benefit-risk assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

^b If bevacizumab is delayed due to toxicity for ≥ 42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab.

^c If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

^d Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the investigator's benefit-risk assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

^e In case of pneumonitis, atezolizumab and bevacizumab should not be resumed after permanent discontinuation.

**A19–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR
ATEZO+BEV+RTX ARM (IMMEDIATELY REPORTABLE
TO THE SPONSOR)**

- Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo+Bev+RTx arm are as follows:
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10× upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, and hemophagocytic lymphohistiocytosis or macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia

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- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Grade ≥ 3 hypertension
- Grade ≥ 3 proteinuria
- Any grade gastrointestinal perforation, abscesses, or gastrointestinal fistulae
- Grade ≥ 2 non-gastrointestinal fistula or abscess
- Grade ≥ 3 wound-healing complication
- Any grade CNS bleeding
- Grade ≥ 2 hemoptysis
- Other grade ≥ 3 hemorrhagic event
- Any grade arterial thromboembolic event
- Grade ≥ 3 venous thromboembolic event
- Any grade posterior reversible encephalopathy syndrome (PRES)
- Grade ≥ 3 congestive heart failure
- Myelitis
- Facial paresis

A19–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+BEV+RTX ARM

A19–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the *final* dose of atezolizumab, 6 months after the *final* dose of bevacizumab, or 6 months after the *final* dose of radiotherapy. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A19–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the *final* dose of bevacizumab or within 6 months after the *final* dose of radiotherapy. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A19–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A19–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

A19–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+BEV+RTX ARM

Table A19-6 Schedule of Activities for Atezo + Bev + RTx Arm

Assessment/Procedure	Stage 1 Screening	Radiotherapy Phase	Treatment Cycles (21-Day Cycles) ^a		Stage 2 Screen. (see Appendix 2) ^c or Treatment Discontinuation ^d (see below)	Follow-Up ^d
	Days –28 to –1	Day 1 to 21 (±5 days)	Cycle 1 ^b	Cycles ≥2		Every 3 Months (±7 days)
Molecular profile of lung cancer (if available)	See Appendix 2		Whenever updated information becomes available			
Vital signs ^e			x	x	x	
Weight ^f			x	x	x	
Complete physical examination ^g					x	
Limited physical examination ^{f, h}			x	x		
ECOG Performance Status ^f			x	x	x	
ECG ^{f, i}			Perform as clinically indicated			
Hematology ^j			x ^{k, l}	x ^k	x	
Chemistry ^m			x ^{k, l}	x ^k	x	
Coagulation (INR and aPTT)			x ^k			
TSH, free T3 (or total T3), and free T4 ⁿ			x ^l		x	
Pregnancy test ^o			x	x	x	
Urinalysis ^p			x	x ^q	x	

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-6 Schedule of Activities for Atezo+Bev+RTx Arm (cont.)

Assessment/Procedure	Stage 1 Screening Days –28 to –1	Radiotherapy Phase Day 1 to 21 (±5 days)	Treatment Cycles (21-Day Cycles) ^a		Stage 2 Screen. (see Appendix 2) ^c or Treatment Discontinuation ^d (see below)	Follow-Up ^d Every 3 Months (±7 days)
			Cycle 1 ^b Day 1	Cycles ≥2 Day 1 (±3 days)		
Blood sample for blood-based NGS ctDNA test ^r	See Appendix 2				x	
Serum autoantibody sample ^s			Perform if a patient experiences a suspected immune-mediated adverse event			
PK samples			Refer to Table A19-7 .			
ADA samples			Refer to Table A19-7 .			
Biomarker samples			Refer to Table A19-7 .			
Blood sample for RBR (optional) ^t			x			
Tumor biopsy			x ^{u, v}			
Tumor biopsy (optional)			x ^{v, w}			
Tumor response assessments			x ^{x, y, z}			
Concomitant medications ^{aa}			x	x	x	
Adverse events ^{bb}			x	x	x ^{bb}	x ^{bb}
Atezolizumab administration ^{cc, dd}			x	x		
Bevacizumab administration ^{dd, ee}			x	x		
I-SBRT planning ^{ff}		x ^{gg}				

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-6 Schedule of Activities for Atezo+Bev+RTx Arm (cont.)

Assessment/Procedure	Stage 1 Screening Days –28 to –1	Radiotherapy Phase Day 1 to 21 (±5 days)	Treatment Cycles (21-Day Cycles) ^a		Stage 2 Screen. (see Appendix 2) ^c or Treatment Discontinuation ^d (see below)	Follow-Up ^d Every 3 Months (±7 days)
			Cycle 1 ^b Day 1	Cycles ≥2 Day 1 (±3 days)		
I-SBRT administration 3x8GY ^{ff}		x				
Survival follow-up and anti-cancer treatment						x ^{hh}

ADA=anti-drug antibody; Atezo+Bev+RTx=atezolizumab plus bevacizumab plus radiotherapy; CT=computed tomography; ctDNA=circulating tumor DNA; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; FDG=fluorodeoxyglucose; I-SBRT=immune-modulating stereotactic body radiotherapy; MRI=magnetic resonance imaging; NGS=next-generation sequencing; PET=positron emission tomography; PK=pharmacokinetic; RBR=Research Biosample Repository; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen=screening.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

- ^a If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. The Medical Monitor is available to advise as needed.
- ^b It is recommended that treatment be initiated no later than 7 days after completion of radiotherapy.
- ^c Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.4) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.
- ^d Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the *final* dose of systemic study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments.

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-6 Schedule of Activities for Atezo+Bev+RTx Arm (cont.)

- ^e Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (\pm 5) minutes during and 30 (\pm 10) minutes after the infusion. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (\pm 10) minutes after the infusion. For the first infusion of bevacizumab, vital signs should be measured within 60 minutes prior to the infusion, at the end of the infusion, and 2 (\pm 1) hours after the infusion. For subsequent bevacizumab infusions, vital signs should be measured within 60 minutes prior to the infusion and within 30 minutes after completion of the infusion.
- ^f Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^g Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^h Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ⁱ It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.
- ^j Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).
- ^k Laboratory tests must be performed within 96 hours prior to dosing during the treatment period
- ^l If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.
- ^m Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included on Day 1 of each treatment cycle.
- ⁿ TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).
- ^o All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum pregnancy tests will be performed at specified subsequent visits and at 3 months and 6 months after the *final* dose of systemic study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^p Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-6 Schedule of Activities for Atezo+Bev+RTx Arm (cont.)

- ^q Urinalysis may be performed up to 72 hours prior to Day 1 of each cycle, as results must be available prior to treatment administration. See [Table A19-5](#) for management guidelines for proteinuria.
- ^r Blood samples for blood-based NGS ctDNA test will not be collected from Protocol Version 19 *onward*.
- ^s Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Serum samples collected for the assessment of PK, ADAs, or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment, may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.
- ^t Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.
- ^u Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see [Section 3.1.1](#) for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see [Section 3.1.2](#)) will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible). See [Section 4.5.6](#) for tissue sample requirements.
- ^v On-treatment biopsies must be performed at least 7 days after the previous bevacizumab dose. Bevacizumab must be administered ≥ 3 days after any on-treatment biopsy, but only after adequate wound healing has been demonstrated. The biopsy should not be performed in an anatomic location at risk for excessive bleeding, as determined by the investigator.
- ^w Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.
- ^x Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (± 1 week) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 6 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see [Section 3.1.1](#) for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.
- ^y All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Appendix 19: Study Details Specific to Atezo+Bev + RTx Arm

Table A19-6 Schedule of Activities for Atezo+Bev+RTx Arm (cont.)

- ^z For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).
- ^{aa} Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of any study treatment until the treatment discontinuation visit.
- ^{bb} After informed consent has been obtained but prior to initiation of any study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the *final* dose of systemic study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the *final* dose of systemic study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.
- ^{cc} Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (\pm 15) minutes. Subsequent infusions will be delivered over 30 (\pm 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (\pm 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.
- ^{dd} Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).
- ^{ee} Bevacizumab will be administered by IV infusion at a dose of 15mg/kg on Day 1 of each 21-day cycle. The initial dose of bevacizumab will be delivered over 90 (\pm 15) minutes. If the first bevacizumab infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (\pm 10) minutes. If the 60 (\pm 10) minute infusion was tolerated without infusion-associated adverse events, the third infusion may be delivered over 30 (\pm 15) minutes. If the 30-minute bevacizumab infusion is well tolerated, all subsequent infusions may be delivered over 30 (\pm 10) minutes. Bevacizumab will be administered after completion of the atezolizumab infusion. Bevacizumab must be administered \geq 3 days after any on-treatment biopsy, but only after adequate wound healing has been demonstrated.
- ^{ff} For details on I-SBRT planning and administration please refer to the technical radiotherapy manual.

Appendix 19: Study Details Specific to Atezo+ Bev + RTx Arm

Table A19-6 Schedule of Activities for Atezo+ Bev+ RTx Arm (cont.)

- ^{gg} For patients with vertebral/paraspinal metastases that are planned to be irradiated, an MRI of this region should be considered to support the I-SBRT planning process. If an FDG-PET has been performed within 56 days of the start of the radiotherapy phase, it is strongly recommended to consider the results of the I-SBRT planning process.
- ^{hh} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Appendix 19: Study Details Specific to Atezo + Bev + RTx Arm

Table A19-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Bev + RTx Arm

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, PBMC)
	30 (\pm 10) minutes after atezolizumab infusion	<ul style="list-style-type: none"> • Atezolizumab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycle 8	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (\leq 30 days after <i>final</i> dose)	At visit	<ul style="list-style-type: none"> • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)

ADA=anti-drug antibody; Atezo + Bev + RTx=atezolizumab plus bevacizumab plus radiotherapy; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

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Appendix 20

Placeholder for Future Arm

The content of Appendix 20 Schedules of Activities for Screening has been moved to Appendix 2. Appendix 20 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 21

List of Drugs That Can Prolong QT Interval and Torsades de Pointes

This table has been adapted from Yap and Camm (2003). Please note that this list is not comprehensive.

Antiarrhythmic drugs	Type 1A (TdP reported in all) Quinidine (TdP reported) Procainamide (TdP reported) Disopyramide (TdP reported) Ajmaline (TdP reported) Type 1C (increase QT by prolonging QRS interval) Encainide Flecainide Type 3 (TdP reported in all) Amiodarone Sotalol d-Sotalol Bretylum Ibutilide Dofetilide Amakalant Semantilide
Calcium channel blockers	Prenylamine (TdP reported, withdrawn) Bepridil (TdP reported, withdrawn) Terodiline (TdP reported, withdrawn)
Psychiatric drugs	Thioridazine (TdP reported) Chlorpromazine (TdP reported) Haloperidol (TdP reported) Droperidol (TdP reported) Amitriptyline Nortriptyline Imipramine (TdP reported) Desipramine (TdP reported) Clomipramine Maprotiline (TdP reported) Doxepin (TdP reported)

Appendix 21: List of Drugs That Can Prolong QT Interval and Torsades De Pointes

Psychiatric drugs (cont.)	Lithium (TdP reported) Chloral hydrate Sertindole (TdP reported, withdrawn in the U.K.) Pimozide (TdP reported) Ziprasidone
Antihistamines	Terfenadine (TdP reported, withdrawn in the U.S.A.) Astemizole (TdP reported) Diphenhydramine (TdP reported) Hydroxyzine Ebastine Loratadine Mizolastine
Antimicrobial and antimalarial drugs	Erythromycin (TdP reported) Clarithromycin (TdP reported) Ketoconazole Fluconazole Pentamidine (TdP reported) Quinine Chloroquine (TdP reported) Halofantrine (TdP reported) Amantadine (TdP reported) Sparfloxacin Grepafloxacin (TdP reported, withdrawn in the U.K. and U.S.A.) Pentavalent antimonial meglumine
Serotonin agonists/antagonists	Ketanserin (TdP reported) Cisapride (TdP reported, withdrawn in the U.K. and U.S.A.)
Immunosuppressant	Tacrolimus (TdP reported)
Antidiuretic hormone	Vasopressin (TdP reported)
Other agents	Adenosine Organophosphates Probucol (TdP reported) Papaverine (TdP reported) Cocaine

TdP = torsades de pointes.

Appendix 21: List of Drugs That Can Prolong QT Interval and Torsades De Pointes

REFERENCE

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Appendix 22

Examples of Inhibitors or Inducers of CYP-Mediated Metabolism and Clinical Inhibitors for Transporters

Please note, the tables below represent examples of various inhibitors and inducers of CYP-mediated metabolism and transporters. These tables are not intended to be comprehensive lists.

Tables have been modified from: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>

Table A22-1 Examples of Inhibitors or Inducers of CYP-Mediated Metabolism and Clinical Inhibitors for Transporters

Transporter	Gene	Inhibitor
P-gp ^a	ABCB1	<ul style="list-style-type: none"> • Amiodarone • Clarithromycin^b • Cobicistat • Cyclosporine^{b, c} • Dronedarone • erythromycin • Itraconazole • Ketoconazole • Lapatinib^c • Lopinavir • Ritonavir • Quinidine • Ranolazine • Saquinavir • Verapamil
BCRP	ABCG2	<ul style="list-style-type: none"> • Curcumin • Cyclosporine A^{b, d} • Darolutamide^{b, e} • Eltrombopag^b • Febuxostat^e • Fostamatinib^d • Rolapitant^{d, f} • Teriflunomide^{b, e}

BCRP = breast cancer resistant protein; OAT = organic anion transporter; OATP = organic anion transporting polypeptide; P-gp = P-glycoprotein.

^a A number of P-gp inhibitors also inhibit CYP3A4.

^b Also an inhibitor of OATP1B1 and/or OATP1B3.

^c Also an inhibitor of BCRP.

^d Also an inhibitor of P-gp.

^e Also an inhibitor of OAT3.

^f Intravenously administered rolapitant does not inhibit BCRP.

Appendix 22: Examples of Inhibitors or Inducers of CYP-Mediated Metabolism and Clinical Inhibitors for Transporters

Table A22-2 Examples of Clinical Inhibitors for CYP-Mediated Metabolism

Enzyme	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYP1A2	Ciprofloxacin, enoxacin, fluvoxamine ^a	Methoxsalen, mexiletine, oral contraceptives, vemurafenib	Acyclovir, allopurinol, cimetidine, peginterferon alpha-2a, piperine, zileuton
CYP2B6			Clopidogrel ^b , tenofovir, ticlopidine ^c , voriconazole ^d
CYP2C8	Gemfibrozil ^e	Clopidogrel ^b , deferasirox, teriflunomide	Trimethoprim
CYP2C9		Amiodarone ^h , fluconazole ^f , miconazole, piperine	Ceritinib, diosmin, disulfiram, fluvastatin, fluvoxamine ^a , voriconazole ^d
P2C19	Fluconazole ^f , fluoxetine ^g , fluvoxamine ^a , ticlopidine ^c	Cenobamate, felbamate, voriconazole ^d	Omeprazole
CYP2D6	Bupropion, fluoxetine ^g , paroxetine, quinidine ^h , terbinafine	Abiraterone, cinacalcet, duloxetine, lorcaserin, mirabegron, rolapitant	Amiodarone ^h , celecoxib, cimetidine, clobazam, cobicistat, escitalopram, fluvoxamine ^a , labetalol, sertraline, vemurafenib
CYP3A4	The following inhibitors cause a ≥ 10 -fold increase in AUC of sensitive substrate(s): cobicistat ^h , danoprevir and ritonavir ^j , elvitegravir and ritonavir ^j , grapefruit juice ^k , indinavir and ritonavir ^j , itraconazole ^h , ketoconazole ^h , lopinavir and ritonavir ^{h,j} , paritaprevir and ritonavir and ombitasvir (and/or dasabuvir) ^j , posaconazole, ritonavir ^{h,i,j} , saquinavir and ritonavir ^{h,j} , tipranavir and ritonavir ^j , telithromycin, troleandomycin, voriconazole ^d	Aprepitant, ciprofloxacin, conivaptan ^l , crizotinib, cyclosporine, diltiazem ^m , dronedarone ^h , erythromycin ^h , fluconazole ^f , fluvoxamine ^a , grapefruit juice ^k , imatinib, isavuconazole, tofisopam, verapamil ^h	Chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine ^h , ticagrelor ^h

Appendix 22: Examples of Inhibitors or Inducers of CYP-Mediated Metabolism and Clinical Inhibitors for Transporters

Table A22-2 Examples of Clinical Inhibitors for CYP-Mediated Metabolism (cont.)

Enzyme	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYP3A4 (cont.)	The following inhibitors cause a 5- to 10-fold increase in the AUC of sensitive substrate(s): ceritinib, clarithromycin ^h , idelalisib, nefazodone, nelfinavir		

AUC=area under the concentration–time curve; C_{max}=maximum concentration observed;
HCV=hepatitis C virus; OAT=organic anion transporter; OATP=organic anion transporting polypeptide;
P-gp=P-glycoprotein.

Note: Strong, moderate, and weak inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥ 5 -fold, ≥ 2 to < 5 -fold, and ≥ 1.25 to < 2 -fold, respectively.

- ^a Strong inhibitor of CYP1A2 and CYP2C19, moderate inhibitor of CYP3A, and weak inhibitor of CYP2D6.
- ^b Moderate inhibitor of CYP2C8 and a weak inhibitor of CYP2B6.
- ^c Also Strong inhibitor of CYP2C19 and a weak inhibitor of CYP2B6. The classification as a CYP2B6 inhibitor is based on the AUC change of bupropion. The effect of ticlopidine on hydroxybupropion, which is primarily metabolized by CYP2B6, is larger.
- ^d Also Strong inhibitor of CYP3A, moderate inhibitor of CYP2C19, and weak inhibitor of CYP2B6 and CYP2C9.
- ^e Strong inhibitor of CYP2C8 and an inhibitor of OATP1B1 and OAT3.
- ^f Strong inhibitor of CYP2C19 and a moderate inhibitor of CYP2C9 and CYP3A.
- ^g Strong inhibitors of CYP2C19 and CYP2D6.
- ^h Inhibitor of P-gp (defined as those increasing AUC or C_{max} of digoxin, dabigatran, or edoxaban ≥ 1.5 -fold).
- ⁱ Strong inhibitor of CYP3A4 and weak inducer of CYP2B6, CYP2C9, and CYP2C19.
- ^j Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.
- ^k The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation is used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation is used (e.g., low dose, single strength). Also includes Seville oranges, star fruit, and Seville orange juice.
- ^l The classification is based on studies conducted with intravenously administered conivaptan.
- ^m Diltiazem increased the AUC of certain sensitive CYP3A substrates (e.g., buspirone) more than 5-fold.

Appendix 22: Examples of Inhibitors or Inducers of CYP-Mediated Metabolism and Clinical Inhibitors for Transporters

Table A22-3 Examples of Clinical Inducers for CYP-Mediated Metabolism

Enzyme	Strong Inducers	Moderate Inducers	Weak Inducers
CYP1A2		Phenytoin ^a , rifampin ^b , smoking, teriflunomide	
CYP2B6	Carbamazepine ^c	Efavirenz ^d , rifampin ^b	Isavuconazole, lemborexant, lorlatinib, nevirapine, ritonavir ^{e, f}
CYP2C8		Rifampin ^b	
CYP2C9		Enzalutamide ^g , rifampin ^b	Apalutamide ^h , aprepitant, carbamazepine ^c , dabrafenib, lorlatinib, ritonavir ^{e, f}
CYP2C19	Rifampin ^b	Apalutamide ^h , efavirenz ^d , enzalutamide ^g , phenytoin ^a	Ritonavir ^{e, f}
CYP3A	Apalutamide ^h , carbamazepine ^c , enzalutamide ^g , ivosidenib ⁱ , lumacaftor, mitotane, phenytoin ^a , rifampin ^b , St. John's wort ^j	Bosentan, cenobamate ^k , dabrafenib, efavirenz ^d , etravirine, lorlatinib, pexidartinib, phenobarbital, primidone, sotorasib	Armodafinil, elagolix, mobocertinib, modafinil ^l , rufinamide, vemurafenib, zanubrutinib

AUC = area under the concentration–time curve.

Note: Strong, moderate, and weak inducers are drugs that decrease the AUC of sensitive index substrates of a given metabolic pathway $\geq 80\%$, ≥ 50 to $<80\%$, and ≥ 20 to $<50\%$, respectively.

^a Strong inducer of CYP3A and a moderate inducer of CYP1A2 and CYP2C19.

^b Strong inducer of CYP2C19 and CYP3A and a moderate inducer of CYP1A2, CYP2B6, CYP2C8, and CYP2C9.

^c Strong inducer of CYP2B6 and CYP3A and weak inducer of CYP2C9.

^d Moderate inducer of CYP2B6, CYP2C19, and CYP3A.

^e Weak inducer of CYP2B6, CYP2C9, and CYP2C19. Classification is based on studies conducted with ritonavir itself (not with other anti-HIV drugs) at doses of 100–200 mg/day, although larger effects have been reported in literature for high doses of ritonavir.

^f Moderate inducer of CYP1A2 with a dose of 800 mg/day ritonavir (not with other anti-HIV drugs). The effect on CYP1A2 at lower doses of ritonavir is unknown.

^g Strong inducer of CYP3A and moderate inducer of CYP2C9 and CYP2C19.

^h Strong inducer of CYP3A, moderate inducer of CYP2C19, and weak inducer of CYP2C9.

ⁱ The effect was based on prediction using physiologically based pharmacokinetic modeling.

^j The effect of St. John's wort varies widely and is preparation dependent.

^k The classification is based on a 200 mg daily dose of cenobamate. Its effect potentially could be stronger at 400 mg/day.

^l The classification is based on effect of 200 mg/day modafinil. A higher dose (400 mg/day) modafinil had a larger induction effect on CYP3A.

Appendix 23

Investigational Medicinal Product, *Auxiliary*, and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

**Table A23-1 Investigational, Authorized Auxiliary, and Unauthorized
Auxiliary Medicinal Product Designations for the European
Economic Area**

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product) ^a	Authorized	No ^b
Tiragolumab (RO7092284)	IMP (test product) ^a	Unauthorized	Not applicable
XL092	IMP (test product)	Unauthorized	Not applicable
Docetaxel	IMP (test product) ^a	Authorized	No ^c
Bevacizumab (RO4876646)	IMP (test product)	Authorized	No ^d
Sacituzumab govitecan	IMP (test product)	Authorized	No ^e
Evolocumab	IMP (test product)	Authorized	No ^e
Camonsertib (RO7616992)	IMP (test product)	Unauthorized	Not applicable
Linagliptin	IMP (test product)	Authorized	No ^e
Prednisone	AxMP (rescue medication)	Authorized	Yes
Methylprednisolone	AxMP (rescue medication)	Authorized	Yes
Dexamethasone	AxMP (rescue medication)	Authorized	Yes
Thyroid replacement hormone	AxMP (rescue medication)	Authorized	Yes
Methimazole/ Carbimazole	AxMP (rescue medication)	Authorized	Yes
Loperamide	AxMP (rescue medication)	Authorized	Yes

Appendix 23: Investigational Medicinal Product, *Auxiliary*, and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table A23-1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for the European Economic Area (cont.)

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Diphenoxylate-atropine	AxMP (rescue medication)	Authorized	Yes
Metformin/Insulin	AxMP (rescue medication)	Authorized	Yes
Ondansetron/Palonosetron	AxMP (rescue medication)	Authorized	Yes
Fosaprepitant/Aprepitant	AxMP (rescue medication)	Authorized	Yes
Olanzapine	uAxMP (rescue medication)	Authorized	No ^f
G-CSF	AxMP (rescue medication)	Not applicable ^g	Not applicable ^g

AxMP = auxiliary medicinal product; EEA = European Economic Area; G-CSF = granulocyte colony-stimulating factor; IMP = investigational medicinal product; NSCLC = non–small cell lung cancer; uAxMP = unauthorized auxiliary medicinal product.

^a Atezolizumab, tiragolumab, and docetaxel are each considered to be an IMP test product as well as an IMP comparator.

^b Atezolizumab is approved for the treatment of metastatic NSCLC but not in combination with the other IMPs tested in the study.

^c Docetaxel is approved for the treatment of NSCLC but not in combination with atezolizumab.

^d Bevacizumab is approved for the treatment of NSCLC but not in combination with atezolizumab and radiotherapy.

^e Not indicated for use in NSCLC.

^f Olanzapine is not authorized in the treatment of anticipatory nausea.

^g G-CSF is a class of medicine and not an individual product. Therefore, this field is not applicable. The sponsor expects that appropriate G-CSF is given as standard treatment per local practice.

Appendix 23: Investigational Medicinal Product, *Auxiliary*, and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table A23-2 Investigational and Non-Investigational Medicinal Product Designations for the United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in U.K.	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product) ^a	Authorized	No ^b
Tiragolumab (RO7092284)	IMP (test product) ^a	Unauthorized	Not applicable
XL092	IMP (test product)	Unauthorized	Not applicable
Docetaxel	IMP (test product) ^a	Authorized	No ^c
Bevacizumab (RO4876646)	IMP (test product)	Authorized	No ^d
Sacituzumab govitecan	IMP (test product)	Authorized	No ^e
Evolocumab	IMP (test product)	Authorized	No ^e
Camonsertib (RO7616992)	IMP (test product)	Unauthorized	Not applicable
Linagliptin	IMP (test product)	Authorized	No ^e
Prednisone	NIMP (rescue medication)	Authorized	Yes
Methylprednisolone	NIMP (rescue medication)	Authorized	Yes
Dexamethasone	NIMP (rescue medication)	Authorized	Yes
Thyroid replacement hormone	NIMP (rescue medication)	Authorized	Yes
Methimazole/ Carbimazole	NIMP (rescue medication)	Authorized	Yes
Loperamide	NIMP (rescue medication)	Authorized	Yes
Diphenoxylate-atropine	NIMP (rescue medication)	Authorized	Yes
Metformin/ Insulin	NIMP (rescue medication)	Authorized	Yes

Appendix 23: Investigational Medicinal Product, *Auxiliary*, and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table A23-2 Investigational and Non-Investigational Medicinal Product Designations for the United Kingdom (cont.)

Product Name	IMP/NIMP Designation	Marketing Authorization Status in U.K.	Used within Marketing Authorization
Ondansetron/ Palonosetron	NIMP (rescue medication)	Authorized	Yes
Fosaprepitant/ Aprepitant	NIMP (rescue medication)	Authorized	Yes
Olanzapine	NIMP (rescue medication)	Authorized	No ^f
G-CSF	NIMP (rescue medication)	Not applicable ^g	Not applicable ^g

G-CSF = granulocyte colony-stimulating factor; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; NSCLC = non–small cell lung cancer.

- ^a Atezolizumab, tiragolumab and docetaxel are each considered to be an IMP test product as well as an IMP comparator.
- ^b Atezolizumab is approved for the treatment of metastatic NSCLC but not in combination with the other IMPs tested in the study.
- ^c Docetaxel is approved for the treatment of NSCLC but not in combination with atezolizumab.
- ^d Bevacizumab is approved for the treatment of NSCLC but not in combination with atezolizumab and radiotherapy.
- ^e Not indicated for use in NSCLC.
- ^f Olanzapine is not authorized in the treatment of anticipatory nausea.
- ^g G-CSF is a class of medicine and not an individual product. Therefore, this field is not applicable. The sponsor expects that appropriate G-CSF is given as standard treatment per local practice.

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