Official Title: A Phase Ib Dose-Escalation and Dose-Expansion Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Venetoclax in Combination With Atezolizumab, Carboplatin, and Etoposide in Patients With Untreated Extensive-Stage Small Cell Lung Cancer

NCT Number: NCT04422210

Document Date: Protocol Version 2: 11-March-2020

PROTOCOL

TITLE:	**A PHASE Ib DOSE-ESCALATION AND DOSE-EXPANSION STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF VENETOCLAX IN COMBINATION WITH ATEZOLIZUMAB, CARBOPLATIN, AND ETOPOSIDE IN PATIENTS WITH UNTREATED EXTENSIVE-STAGE SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO41864
VERSION NUMBER:	2
EUDRACT NUMBER:	2019-004487-22
IND NUMBER:	146772
NCT NUMBER:	To be determined
TEST PRODUCT:	Venetoclax (RO5537382) Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	16 January 2020
DATE AMENDED:	See electronic date stamp below.

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
11-Mar-2020 19:10:30	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
1	16 January 2020

PROTOCOL AMENDMENT, VERSION 2:
RATIONALE

Protocol GO41864 has been amended to incorporate feedback from the U.S. Food and Drug Administration. Changes to the protocol, along with a rationale for each change, are summarized below:

- The overview of the study design has been modified to only allow the use of atezolizumab instead of a variety of single-agent checkpoint inhibitors (anti-PD-1/PD-L1) (Section 3.1.1).
- Additional modifications in study design include a reduction in the number of cycles of induction therapy from a total number of 6 to 4 in Arm B (Section 3.1.1 and Section 3.1.2.2).
- The protocol inclusion criteria (Section 4.1.1) has been amended to allow patients who have completed 3 cycles of atezolizumab in combination with 4 cycles of carboplatin and etoposide induction chemotherapy compared with 2 cycles of atezolizumab in combination with 4 cycles of carboplatin and etoposide induction chemotherapy to be eligible for the maintenance arm of the study (Section 3.1.5).
- Clarification regarding the assessment period for dose-limiting toxicities (DLT) has been provided, and new definitions of DLTs have been included in Section 3.1.3.
- Exact parameters that would trigger the requirement for primary growth-colony stimulating factor prophylaxis in Arm B have been clarified in Section 3.1.2.2.
- Term “NC” (non-continuous) dose levels have been replaced with “lower” dose level in Section 3.1.4.
- The clarification for patients who continue treatment beyond radiographic disease progression has been added to Section 4.5.5:
- Venetoclax dose reduction levels have been clarified in Section 5.1.5.1.
- The language describing reporting requirements and the duration of reproductive risk as female patients or as partners of male patients has been updated in Sections 5.4.3.1 and 5.4.3.2.
- Protocol language has been updated with additional details regarding the potential dose expansion cohort to evaluate maintenance therapy with venetoclax and atezolizumab only (Arm A), including ORR values, in Section 6.1.
- Appendix 1 (Schedule of Activities for Dose-Escalation Arm A and Dose-Expansion Maintenance Only (Arm A) and Dose-Expansion Maintenance Only) has been updated to reflect tumor assessment schedule after radiographic disease progression as outlined in Section 4.5.5.
- Appendix 2 (Schedule of Activities for Dose-Escalation Induction + Maintenance [Arm B] and Dose-Expansion Induction + Maintenance) has been updated to reflect tumor assessment schedule after radiographic disease progression as outlined in Section 4.5.5.
- Appendix 3 (Schedule of Pharmacokinetic and Immunogenicity Sampling) has been updated with further clarification of sample collection at Treatment Discontinuation.

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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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE Ib DOSE-ESCALATION AND DOSE-EXPANSION STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF VENETOCLAX IN COMBINATION WITH ATEZOLIZUMAB, CARBOPLATIN, AND ETOPOSIDE IN PATIENTS WITH UNTREATED EXTENSIVE-STAGE SMALL CELL LUNG CANCER**
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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 of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE Ib DOSE-ESCALATION AND DOSE-EXPANSION STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF VENETOCLAX IN COMBINATION WITH ATEZOLIZUMAB, CARBOPLATIN, AND ETOPOSIDE IN PATIENTS WITH UNTREATED EXTENSIVE-STAGE SMALL CELL LUNG CANCER**
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PHASE:	Ib
INDICATION:	Small cell lung cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This is a Phase Ib, open-label, multicenter, two-stage study, consisting of a dose-escalation phase and a dose-expansion phase, to evaluate the safety, tolerability, pharmacokinetics, and efficacy of venetoclax in combination with atezolizumab, carboplatin, and etoposide as induction therapy and venetoclax in combination with atezolizumab as maintenance therapy following induction, for patients with extensive-stage small cell lung cancer (ES-SCLC) who are chemotherapy-naïve for their extensive-stage disease.

The objectives for the dose-escalation phase of this study are to assess safety and tolerability as well as to determine the maximum tolerated dose (MTD) and the recommended Phase II dose (RP2D) for venetoclax in both induction (Arm B) and maintenance (Arm A) therapies.

The objectives of the dose-expansion phase are to evaluate the safety, tolerability, pharmacokinetics, and efficacy of venetoclax at the RP2D in induction followed by maintenance therapies or in maintenance therapy only, as determined in the dose-escalation phase of the study.

Specific objectives and corresponding endpoints for the study are outlined in the protocol.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., venetoclax plus atezolizumab, carboplatin, and etoposide in the induction setting or venetoclax plus atezolizumab in the maintenance setting).

Objectives and Endpoints for Dose-Escalation Phase

Safety Objective (Primary Objective)

The safety objective for the dose-escalation phase is to evaluate the safety and tolerability of venetoclax plus atezolizumab as maintenance therapy (Arm A) and venetoclax in combination with atezolizumab, carboplatin, and etoposide as induction therapy followed by venetoclax plus atezolizumab as maintenance therapy (Arm B) —including estimation of the MTD, determination

of the RP2D, and characterization of DLTs (refer to full protocol)—on the basis of the following endpoints:

- The incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Technology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted laboratory test results

Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives for the dose-escalation phase are the following:

- To characterize the pharmacokinetics of venetoclax and atezolizumab when given in combination as part of the maintenance therapy on the basis of the following endpoints:
  - Plasma concentrations of venetoclax at specified timepoints
  - Serum concentrations of atezolizumab at specified timepoints
- To characterize the pharmacokinetics of venetoclax and atezolizumab when given in combination with carboplatin and etoposide as part of the induction therapy on the basis of the following endpoints:
  - Plasma concentrations of venetoclax at specified timepoints
  - Serum concentrations of atezolizumab at specified timepoints

Immunogenicity Objectives

The exploratory immunogenicity objective for the dose-escalation phase is to evaluate the immune response to atezolizumab on the basis of the following endpoints:

- Incidence of anti-drug antibodies (ADAs) to atezolizumab in the presence of venetoclax
- Incidence of ADAs to atezolizumab in the presence of venetoclax, carboplatin, and etoposide

Biomarker Objectives

The exploratory biomarker objectives for the dose-escalation phase are to identify and evaluate biomarkers that are predictive of response to venetoclax (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to venetoclax, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of venetoclax activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- Relationship between biomarkers in tumor tissue and blood (listed in the protocol) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Objectives and Endpoints for Dose-Expansion Phase

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for the dose-expansion phase is to evaluate the preliminary efficacy of venetoclax in combination with atezolizumab as maintenance therapy or venetoclax in combination with atezolizumab, carboplatin, and etoposide as induction therapy followed by venetoclax plus atezolizumab as maintenance therapy on the basis of the following endpoint:

- Overall response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions $\geq$ 28 days apart, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Secondary Efficacy Objective

The secondary efficacy objective for the dose-expansion phase is to evaluate the preliminary efficacy of venetoclax in combination with atezolizumab as maintenance therapy or venetoclax in combination with atezolizumab, carboplatin, and etoposide as induction therapy followed by venetoclax plus atezolizumab as maintenance therapy on the basis of the following endpoints:

- Duration of response (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, as determined by the investigator according to RECIST v1.1
- Progression-free survival (PFS) after enrollment, defined as the time from enrollment to the first occurrence of disease progression or relapse or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
- Overall survival (OS) after enrollment, defined as the time from enrollment to death from any cause
- PFS rate at 6 months, defined as the proportion of patients who have not experienced disease progression, relapse, or death from any cause at 6 months, as determined by the investigator according to RECIST v1.1
- OS rate at 1 year, defined as the proportion of patients who have not experienced death from any cause at 1 year

Safety Objectives

The safety objective for the dose-expansion phase are to evaluate the safety and tolerability of venetoclax in combination with atezolizumab, carboplatin, and etoposide as induction therapy or venetoclax in combination with atezolizumab, carboplatin, and etoposide as induction therapy followed by venetoclax plus atezolizumab as maintenance therapy on the basis of the following endpoints:

- To determine the incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted laboratory test results

Pharmacokinetic Objectives

The PK objectives for the dose-expansion phase are the following:

- To characterize the pharmacokinetics of venetoclax and atezolizumab when given in combination as part of the maintenance therapy on the basis of the following endpoints:
  - Plasma concentrations of venetoclax at specified timepoints
  - Serum concentrations of atezolizumab at specified timepoints
- To characterize the pharmacokinetics of venetoclax, atezolizumab, carboplatin, and etoposide when given in combination as part of the induction therapy on the basis of the following endpoints:
  - Plasma concentrations of venetoclax at specified timepoints
  - Serum concentrations of atezolizumab at specified timepoints
  - Plasma concentrations of carboplatin at specified timepoints
  - Plasma concentrations of etoposide at specified timepoints

Immunogenicity Objective

The exploratory immunogenicity objective for the dose-expansion phase are the same as those described for the dose-escalation phase and are described in the protocol.

Biomarker Objectives

The exploratory biomarker objectives for the dose-expansion phase are the same as those described for the dose-escalation phase and are described in protocol.

Study Design

Description of the Study

This is a Phase Ib, multicenter, open-label, two-stage study consisting of a dose-escalation phase and a dose-expansion phase to evaluate the safety, tolerability, pharmacokinetics, and efficacy of venetoclax in combination with atezolizumab, carboplatin, and etoposide.

Overview of the Study Design

In the dose-escalation stage, venetoclax will be tested first in the maintenance setting (Arm A) followed by testing in both the induction and maintenance settings (Arm B).

- Arm A: Venetoclax and atezolizumab as maintenance therapy for patients with ES-SCLC who have completed 4-6 cycles of carboplatin and etoposide first-line induction chemotherapy, with or without *atezolizumab*
- Arm B: Venetoclax, atezolizumab, carboplatin, and etoposide as induction therapy (4 cycles) followed by venetoclax plus atezolizumab as maintenance therapy for patients with previously untreated ES-SCLC

The dose-escalation stage will then be followed by the dose-expansion portion of the study to evaluate the safety and efficacy of adding venetoclax to induction and/or maintenance therapy at the RP2D and schedule as determined during dose-escalation.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 30 days after previously signing the consent form. The investigator will record reasons for screen failure within the interactive voice or web-based response system (IxRS) and electronic Case Report Form (eCRF).

Dose-Escalation Phase

The purpose of the dose-escalation phase of the study is to determine the RP2D and maximum tolerated dose (MTD) for venetoclax when given in combination with atezolizumab in the maintenance setting and in combination with atezolizumab, carboplatin, and etoposide in the induction setting (followed by venetoclax in combination with atezolizumab as maintenance therapy) in patients with ES-SCLC.

The dose-escalation cohort will use a standard 3 + 3 design (refer to the protocol) to assess the safety, tolerability, and pharmacokinetics of study treatment. Venetoclax will be tested sequentially in the maintenance setting first (Arm A). Once the MTD and the RP2D are identified for maintenance treatment, the RP2D identified in Arm A will be applied to the maintenance portion of the induction plus maintenance setting (Arm B). The MTD and RP2D of venetoclax will be determined separately for maintenance and induction settings.

Within each arm, dose-escalation cohorts will be run sequentially (e.g., 200 mg followed by 400 mg, etc.; see the protocol).

Maintenance Only (Arm A)

In the maintenance-only arm, venetoclax will be explored on a continuous dosing schedule at doses ranging from 400 mg QD to 800 mg/QD in the following dose-escalation treatment cohorts using a standard 3 + 3 design:

- **Maintenance Cohort A1 (Dose Level 1):**
  Venetoclax: 400 mg QD continuous on Days 1–21
  Atezolizumab: 1200 mg every 3 weeks (Q3W) on Day 1
- **Maintenance Cohort A2 (Dose Level 2):**
  Venetoclax: 800 mg QD continuous on Days 1–21
  Atezolizumab: 1200 mg Q3W on Day 1

Dose-escalation to 200 mg QD continuous on Days 1–21 may be explored if dose-limiting toxicities (DLTs) are experienced and adverse events are thought to be potentially mitigated with a lower dose of venetoclax (refer to the protocol).

Once tolerability and dose are established in the maintenance-only arm (Arm A), the induction followed by maintenance arm (Arm B) will be opened, based on thorough review led by the Medical Monitor in consultation with the Principal Investigators and a committee composed of, at a minimum, the following Sponsor representatives: statistician, safety scientist, PK scientist, and clinical scientist. Patients on maintenance therapy who do not experience unacceptable toxicity and have evidence of clinical benefit (as defined in the protocol) may continue to receive maintenance study treatment every 21 days until documented disease progression determined by investigator or unacceptable toxicity, whichever occurs first.

Induction Plus Maintenance (Arm B)

In the induction plus maintenance arm (Arm B; see protocol), venetoclax will be explored on a non-continuous (NC) dosing schedule in the following dose-escalation treatment cohorts using a standard 3 +3 design:

- **Induction Cohort B1 (Dose Level 1):**

  Venetoclax: 200 mg/QD NC on Days 1–7

  Atezolizumab: 1200 mg Q3W on Day 1

  Carboplatin: AUC 5 mg/mL min (Calvert formula) on Day 1

  Etoposide: 100 mg/m^2 on Days 1–3

- **Induction Cohort B2 (Dose Level 2):**

  Venetoclax: 400 mg/QD NC on Days 1–7

  Atezolizumab: 1200 mg Q3W on Day 1

  Carboplatin: AUC 5 mg/mL min (Calvert formula) on Day 1

  Etoposide: 100 mg/m^2 on Days 1–3

- **Induction Cohort B3 (Dose Level 3):**

  Venetoclax: 800 mg/QD NC on Days 1–7

  Atezolizumab: 1200 mg Q3W on Day 1

  Carboplatin: AUC 5 mg/mL min (Calvert formula) on Day 1

  Etoposide: 100 mg/m^2 on Days 1–3

- **Induction Cohort B4 (Dose Level 4**):

  Venetoclax: 800 mg/QD NC on Days 1–14

  Atezolizumab: 1200 mg Q3W on Day 1

  Carboplatin: AUC 5 mg/mL min (Calvert formula) on Day 1

  Etoposide: 100 mg/m^2 on Days 1-3

Patients may be treated in up to five NC dosing cohorts (i.e., venetoclax 200 mg Days 1–7 NC, 400 mg Days 1–7 NC, 800 mg Days 1–7 NC, 800 mg Days 1–14 NC, and any of the dose levels integrating primary prophylactic growth factor support). Specifically, at the initiation of the induction phase of dose-escalation Arm B, cohorts will be treated without primary prophylactic growth-colony stimulating factor (G-CSF). If, after review of available data, the MTD is exceeded in a specific cohort due to DLTs associated with a high frequency of febrile neutropenia, severe neutropenia or prolonged neutropenia, then that cohort level will be tested again at the same dose with primary prophylactic growth factor support (see protocol for additional details). Of note, primary G-CSF prophylaxis is only mandated during induction and not during maintenance therapy. Such cohorts will be designated with "-P" to denote the primary G-CSF prophylactic requirement (e.g., Cohort B1-P). Subsequent dose-escalation cohorts will then be required to incorporate primary G-CSF prophylaxis.

Patients will be treated for a total of 4 cycles of study treatment for induction. Each cycle will consist of 21 days. Dose-escalation will continue until DLTs are observed. If there is excessive

toxicity and DLTs at the lowest tested venetoclax dose in induction, then venetoclax will be subsequently expanded in the maintenance setting only.

Patients initially treated in the induction arm who tolerate study treatment without excessive toxicity, and have not undergone disease progression, will then proceed to maintenance treatment with venetoclax plus atezolizumab. The venetoclax dose for the maintenance setting in Arm B will be the dose that has been cleared in the maintenance-only arm (Arm A) of the study (maintenance RP2D, RP2D-M). The venetoclax RP2D for the induction setting (induction RP2D, RP2D-I) will be based on the MTD of venetoclax in combination with atezolizumab, carboplatin and etoposide.

During the maintenance phase in either Arm A or Arm B, prophylactic cranial irradiation (PCI) is permitted (though not mandated) prior to the commencement of maintenance therapy per local standard of care. Due to the lack of data with concurrent use of PCI with either atezolizumab or venetoclax, concurrent administration of PCI during maintenance therapy is not permitted. PCI will be reported on the Prophylactic Cranial Irradiation electronic Case Report Form (eCRF). Consolidative thoracic radiation with curative intent or the intent to eliminate residual disease is not permitted. Palliative radiation for symptomatic management is allowed (refer to protocol for further details).

Definition of Dose-Limiting Toxicity

Patients will be closely monitored for adverse events during a DLT assessment period, which starts on Day 1 of Cycle 1 and continues through Day 1 of Cycle 2. Adverse events meeting criteria for DLT within the assessment period must be reported to the Sponsor within 24 hours. The expected start of Cycle 2 would be on Day 22 if there are no treatment delays. The same DLT criteria will be used in the maintenance and induction settings.

Determination of whether a patient is evaluable for DLT assessment will be made in accordance with the following rules:

- Patients who receive study treatment and remain on study through the DLT assessment period will be considered DLT-evaluable.
- Patients who discontinue from treatment with venetoclax prior to completing the DLT assessment period for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD determination, and will be replaced by an additional patient at that same dose level.
- Patients who receive less than 50% of planned venetoclax doses during the DLT assessment period will be considered non-evaluable for dose-escalation decisions and will be replaced by another patient in that cohort.

A DLT is defined in this trial as any one of the following events occurring during the DLT assessment period and is assessed by the investigator as possibly being related to study treatment.

The following events will be considered DLTs only if they are associated with treatment delay beyond 14 days in initiating Cycle 2, Day 1:

- Grade 4 thrombocytopenia (platelet count <25,000/mm^3)
- Grade 3 thrombocytopenia with severe bleeding
- Grade 4 anemia
- Grade 4 neutropenia (absolute neutrophil count [ANC] $<$ 500/μL)

The following events will be considered DLTs regardless of whether they result in a treatment delay:

- Any treatment-related death
- Grade 3 febrile neutropenia lasting for more than 7 days with growth factor support and supportive care
- Grade 4 febrile neutropenia of any duration
- Grade $\geq$ 3 diarrhea, nausea, or vomiting lasting for $\geq$ 72 hours despite adequate treatment and supportive care (e.g., anti-emetics, anti-diarrheals, etc.)

- Laboratory tumor lysis syndrome (TLS) lasting for ≥ 7 days with best supportive care or clinical TLS according to the Howard criteria (Howard et al. 2011)
- Treatment related Grade ≥ 3 non-hematologic, non-hepatic toxicities lasting for ≥72 hours-
- *Laboratory abnormalities consistent with Hy's Law will be considered a DLT. Hy's Law is defined as AST and/or ALT elevation >3 ×ULN, in conjunction with an elevation in total bilirubin to >2 × ULN, without findings of cholestasis (ALP within normal limits), in patients for whom no other cause of hepatotoxicity is evident.*
- *All study treatment-related adverse events requiring permanent discontinuation of any of the study drugs*

Dose-Escalation Rules, Determination of Dose-Limiting Toxicities, and Recommended Phase II Dose

Dose-escalation for venetoclax in the maintenance only (Arm A) as well as in the induction and maintenance (Arm B) settings will occur in accordance with the rules listed below.

Arm A (Refer to protocol):

A minimum of 3 DLT-evaluable patients will initially be enrolled into each cohort.

If none of the first 3 DLT-evaluable patients experiences a DLT, enrollment of the next cohort at the next dose level may proceed.

If 1 of the first 3 DLT-evaluable patients experiences a DLT, the cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, enrollment of the next cohort at the next dose level may proceed.

If 2 or more of the first 6 DLT-evaluable patients in the cohort experience a DLT, an additional 3 patients will be evaluated for DLTs at a lower NC dose level. If none of the first 3 DLT-evaluable patients experiences a DLT, the MTD in maintenance will have been reached.

If 1 of the first 3 DLT-evaluable patients experiences a DLT, the NC dose level cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, the MTD in maintenance will have been reached.

If 2 or more of the first 6 DLT-evaluable patients in the NC dose-escalation cohort experience a DLT, the MTD will have been exceeded and dose-escalation in maintenance will stop.

If the MTD is exceeded at any dose level, the highest dose at which fewer than 2 of 6 DLT-evaluable patients (i.e., ≥ 33%) experience a DLT will be declared the MTD.

If the MTD is not exceeded at any dose level, the highest dose of venetoclax (800 mg) administered in maintenance will be declared the MTD for the maintenance setting.

Arm B (Refer to protocol):

A minimum of 3 DLT-evaluable patients will initially be enrolled into each cohort.

If none of the first 3 DLT-evaluable patients experiences a DLT, enrollment of the next cohort at the next dose level may proceed.

If 1 of the first 3 DLT-evaluable patients experiences a DLT, the cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, enrollment of the next cohort at the next dose level may proceed.

If 2 or more of the first 6 DLT-evaluable patients in the next cohort at the next dose level experience a DLT, the MTD in induction will have been exceeded and dose-escalation will stop.

If the MTD is exceeded at any dose level, the highest dose at which fewer than 2 of 6 DLT-evaluable patients (i.e., ≥ 33%) experience a DLT will be declared the MTD.

If the MTD is not exceeded at any dose level, the highest dose of venetoclax (800 mg NC Day 1–7) administered in induction will be declared the MTD for the induction setting.

If a particular cohort in induction dose-escalation (Arm B) exceeds MTD due to DLTs associated with neutropenia or febrile neutropenia without primary prophylactic growth factor support, then that cohort level will be tested again with primary prophylactic growth factor support. For example, if venetoclax 400 mg Day 1–7 exceeds the MTD due to DLTs associated with neutropenia or febrile neutropenia without primary prophylactic growth factor support, then primary prophylactic growth factor support will be implemented in the study and that dose level cohort will be tested again with another 3 + 3 cohort. Of note, primary G-CSF prophylaxis is only mandated during induction and not during maintenance therapy. Once prophylactic growth factor support is instituted, then this will be required for further escalation cohorts during all induction cycles. For guidance on *the* use of prophylactic growth factor support*, please refer to the protocol*.

Patients exhibiting acceptable safety and evidence of clinical benefit (as determined by the investigator) may continue to receive study treatment until confirmed objective disease progression or unacceptable toxicity, whichever occurs first.

The Sponsor will review cumulative safety data and make recommendations regarding dose escalation and overall study conduct on the basis of trial safety data to ensure patient safety while receiving study treatment. These include recommendations to open or suspend patient enrollment in a given dose-escalation cohort based on the overall benefit–risk profile of venetoclax in combination with atezolizumab, carboplatin, and etoposide.

Relevant demographic, adverse event, laboratory, dose administration, and PK data (if available) will be reviewed prior to the selection of a RP2D in the maintenance (RP2D-M) and RP2D in the induction setting (RP2D-I). The RP2D-I will be based on the MTD of venetoclax when combined with standard doses of atezolizumab, carboplatin, plus etoposide and the RP2D-M will be based on the MTD of venetoclax when combined with standard dose of atezolizumab. Both RP2D-I and RP2D-M will integrate aggregate safety data during treatment. Decision making will be led by the Medical Monitor in consultation with the Principal Investigators and a committee composed of at a minimum the following Sponsor representatives: statistician, safety scientist, PK scientist, and clinical scientist.

Dose-Expansion Cohort

Once the MTD in the induction and in the maintenance settings has been established from the dose-escalation cohorts, additional patients will be enrolled in the dose-expansion cohort to further assess the safety and efficacy of venetoclax in combination with carboplatin, etoposide and/or atezolizumab. If an MTD for venetoclax during induction was established, then the dose-expansion cohort will continue to test venetoclax in both induction and maintenance. If significant toxicity and DLTs in induction preclude identification of an MTD for venetoclax in induction treatment, then the safety and efficacy of venetoclax will only be investigated in a dose-expansion cohort in the maintenance setting. If the maintenance-only cohort is expanded, then prior *induction* treatment of carboplatin and etoposide *for 4 cycles in combination with atezolizumab for* at least *3* cycles will be required. If there are concerns about the tolerability of venetoclax during the dose-expansion stage, then a lower dose or alternative dosing schedule may be explored based on the severity and timing of DLTs as well as the specific adverse events encountered. For example, consideration may be given to enrolling an expansion cohort at the next lower dose level (as defined in dose-escalation stage; see protocol). Decision making will integrate cumulative safety and efficacy data during treatment and will be led by the Medical Monitor in consultation with the Principal Investigators and a committee composed of at a minimum the following Sponsor representatives: statistician, safety scientist, PK scientist, and clinical scientist.

Treatment after Disease Progression

During the study, patients who meet criteria for disease progression per RECIST v1.1 and show evidence of clinical benefit may continue treatment at the investigator's discretion, provided that the patients meet all of the following criteria:

Evidence of clinical benefit, as assessed by the investigator

Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease

No decline in Eastern Cooperative Oncology Group (ECOG) performance status that can be attributed to disease progression

Absence of tumor progression at critical anatomical sites (e.g., CNS, leptomeningeal disease, etc.) that cannot be managed by protocol-allowed medical interventions

Investigator assessment of overall tumor response at all timepoints will be based only on RECIST v1.1.

Number of Patients

Approximately 18–42 patients will be enrolled in the dose-escalation cohorts. An additional estimated 20 patients will be enrolled in the dose-expansion cohort of this study.

Target Population

Inclusion Criteria

Dose-Escalation, Maintenance Arm A

- Patients with ES-SCLC who have completed 4-6 cycles of carboplatin and etoposide induction chemotherapy, with or without *atezolizumab*, as their first-line therapy for extensive-stage disease and have responded (CR or PR) or have stable disease (SD) are eligible for the maintenance arm of the study.
- All side effects attributed to prior anti-cancer therapy must have resolved to Grade 1 or baseline.
- A maximum of 8 weeks (56 days) is allowed between last chemotherapy dose (Cycle 4, Day 3) given in induction and the start of maintenance therapy.

Dose-Escalation, Induction Arm B

- Patients with no prior systemic treatment for ES-SCLC are eligible for this study.
- ANC $\geq$ 1,500 cells/μL without granulocyte colony-stimulating factor support

Dose-Expansion, Maintenance Only

- Patients with ES-SCLC who have completed 4 cycles of carboplatin and etoposide induction chemotherapy and at least *3* cycles of *atezolizumab* as their first-line therapy for extensive-stage disease and have *responded (CR or PR) or have* SD are eligible for the maintenance arm of the study.

Dose-Escalation (Arms A and B) and Dose-Expansion

- Signed Informed Consent Form
- Age $\geq$ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- ECOG performance status of 0 or 1
- Patients must be able to swallow pills
- Histologically or cytologically confirmed diagnosis of ES-SCLC per the Veterans Administration Lung Study Group (VALG) staging system

- Patients who received prior chemoradiotherapy for limited-stage SCLC must have been treated with curative intent and experienced a treatment-free interval of at least 6 months since last chemotherapy, radiotherapy, or chemoradiotherapy cycle prior to diagnosis of ES-SCLC
- Patients with a history of treated CNS metastases that are currently asymptomatic are eligible, provided they meet all of the following criteria:
  - Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)
  - No ongoing requirement for corticosteroids as therapy for CNS disease
  - No evidence of interim progression between the completion of CNS-directed therapy and enrollment
  - Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to enrollment, if all other criteria are met.
- Measurable disease, as defined by RECIST v1.1. Baseline measurements and evaluation of all sites of disease must be obtained ≤ 4 weeks prior to enrollment.
  - Previously irradiated lesions can only be considered as measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of disease.
- Eligible to receive a carboplatin-based chemotherapy regimen
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to enrollment:
  - ANC ≥ 1500 cells/μL (without granulocyte-colony stimulating factor support within 7 days prior to Cycle 1, Day 1)
  - Lymphocyte count ≥ 500 cells/μL
  - Platelet count ≥ 100,000 cells/μL without transfusion
  - Hemoglobin ≥ 9.0 g/dL

    Patients may be transfused to meet this criterion.
  - INR or aPTT ≤ 1.5 × ULN

    This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose and with INR ≤ 3.5 × ULN.
  - AST (SGOT), ALT (SGPT), and alkaline phosphatase ≤ 2.5 × ULN with the following exceptions:

    Patients with documented liver metastases: AST and/or ALT ≤ 5 × ULN

    Patients with documented bone or liver metastases: alkaline phosphatase ≤ 5 × ULN
  - Serum total bilirubin ≤ 1.5 × ULN

    Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.
  - *Albumin ≥ 25 g/L (2.5 g/dL)*

– Creatinine clearance (CRCL) ≥ 50 mL/min calculated with the use of the 24-hour CRCL or modified Cockcroft-Gault equation (i.e., estimation of creatinine clearance rate [eCCr]) with the use of ideal body mass (IBM) instead of mass:

$$eCCr = \frac{(140 - age) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$

Or, if serum creatinine is in μmol/L:

$$eCCr = \frac{(140 - age) \times IBM\ (kg) \times (1.04 \text{ if female})}{\text{serum creatinine } (\mu mol/L)}$$

- Patients must submit a pre-treatment tumor tissue sample. Any available tumor tissue sample can be submitted (fresh, paraffin-embedded tissue block, or serial cut slides [15 preferred]). The tissue sample should be submitted before or within 4 weeks after enrollment; however, patients may be enrolled into the study before the pre-treatment tumor tissue sample is submitted. If tissue is not available, approval from the Medical Monitor is required before enrolling.
- Patients must submit a blood sample for exploratory biomarker research before treatment, on-study, and following progression of disease.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use non-hormonal contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 30 days after the final dose of venetoclax, 5 months after the final dose of atezolizumab, or 6 months after the final dose of carboplatin or etoposide, whichever is longer. Women must refrain from donating eggs during this same period.

  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.
- Women who are not postmenopausal (≥12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.

  If a serum pregnancy test has not been performed 14 days prior to dosing, a urine pregnancy test must be performed 7 days prior to dosing. If the test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.

- 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 partners, 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 treatment with chemotherapy (i.e., carboplatin and etoposide) and for at least 6 months after the final dose of carboplatin or etoposide 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, sympotothermal, or postovulation methods) 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.

Exclusion Criteria

- Use of non–protocol-specified anti-cancer therapies or other combination partners with carboplatin/etoposide during induction
- Symptomatic or actively progressing CNS metastases

  Note: Asymptomatic patients with treated (i.e., local CNS-directed therapy) or untreated CNS lesions 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 from CNS disease.
  - Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
  - The patient has no symptoms caused by CNS disease (i.e., no headache, nausea, vomiting, convulsion, paralysis, etc.).
  - The patient has no ongoing requirement for anticonvulsants for CNS disease.
  - The patient has no ongoing requirement for dexamethasone/corticosteroids for CNS disease (previously untreated patients must also not have any history of requiring or receiving dexamethasone/corticosteroids for CNS disease).
  - For patients with previously treated CNS metastases, there is no evidence of interim CNS progression between the completion of CNS-directed therapy and enrollment.
  - For previously untreated patients, there is no evidence of brain edema related to CNS disease (e.g., vasogenic edema).
  - For previously untreated patients, a brain magnetic resonance imaging (MRI) scan with contrast is required at screening and is the preferred modality for all subsequent scheduled follow-up tumor assessments.

    Note: Computed tomography (CT) scan with contrast may be acceptable for all subsequent scheduled follow-up tumor assessments if the following criteria are met.

    - Both brain MRI and CT scan with contrast must be performed at screening to assess untreated CNS disease.
    - The CT scan with contrast can be used to reliably evaluate lesions identified on the screening MRI with contrast.

If CT scan with contrast cannot be used to reliably evaluate lesions identified on the screening MRI with contrast, then MRI scan with contrast must be used at all subsequent scheduled follow-up tumor assessments.
The same modality must be used at every tumor assessment.

- Pregnant or breastfeeding, or intending to become pregnant during the study
  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 1 week prior to enrollment
- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once a month or more frequently)
  Patients with indwelling catheters (e.g., PleurX®) are allowed regardless of drainage frequency.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, total serum calcium > 12 mg/dL, or corrected calcium > ULN)
- History of malignancy other than SCLC within 5 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell cancer of the skin, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis
  Patients with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.
  Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen are eligible for this study.
  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., no psoriatic arthritis) are permitted provided that they meet the following conditions:
  - Rash must cover less than 10% of body surface area.
  - Disease is well-controlled at baseline and only requiring low potency topical steroids.
  - No acute exacerbations of underlying condition within the last 12 months requiring treatment with either psoralen plus ultraviolet A radiation (PUVA), methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral topical steroids
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive test result for HIV

All patients must be tested for HIV; patients who test positive for HIV will be excluded.

- Active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test result at screening) or hepatitis C virus (HCV)

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. HBV DNA should be obtained in these patients prior to enrollment and should be undetectable. These patients must be willing to undergo monthly DNA testing. Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Active tuberculosis
- Known infection with human T-cell leukemia virus 1
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within the previous 3 months, unstable arrhythmias, or unstable angina

  Patients with known coronary disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
- Major surgical procedure within 28 days prior to enrollment or anticipation of need for major surgical procedure during the course of the study
- Prior allogenic bone marrow transplantation or solid organ transplant
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk for treatment complications
- Illnesses or conditions that interfere with their capacity to understand, follow, and/or comply with study procedures
- Treatment with investigational therapy with therapeutic intent within 28 days prior to enrollment
- Administration of a live, attenuated vaccine within 4 weeks before enrollment or anticipation that such a live attenuated vaccine will be required during the study

  Patients must not receive live, attenuated influenza vaccines (e.g. FluMist®) within 4 weeks prior to enrollment, during treatment, and for 5 months following the last dose of atezolizumab or chemotherapy.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1, and anti-PD-L1 therapeutic antibodies
- Treatment with systemic immunosuppressive medications (including, but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 1 week prior to enrollment

  Patients who have received acute systemic immunosuppressant medications (e.g., use of corticosteroids for nausea, vomiting, or management of or premedication for allergic reactions) may be enrolled in the study after discussion with and approval by the

Medical Monitor. In those patients, the need and length of the washout period prior to enrollment will also be established in conjunction with the Medical Monitor.
The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of allergic reactions to carboplatin or etoposide or to any of its excipients (etoposide)
- Known hypersensitivity to venetoclax or to any of its excipients
- Administration of the following agents within 7 days prior to the first dose of study drug:
  - Steroid therapy for anti-neoplastic intent (stable steroid mediation not more than 10 mg prednisolone per day or an equivalent dose of other corticosteroids for controlling CNS metastases is acceptable)
  - Strong or moderate CYP3A inhibitors (see protocol for examples)
  - Strong or moderate CYP3A inducers (see protocol for examples)

  Additional restrictions for on-study use of CYP3A inhibitors/inducers are outlined in the protocol.
- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade-containing Seville oranges), or starfruit (carambola) within 3 days before within 3 days prior to the first dose of study drug
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Inability or unwillingness to swallow a large number of tablets
- History of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)

End of Study
The end of this study is defined as 6 months after the last patient's radiographic last assessment. The end of the study is expected to occur 24 months after the last patient is enrolled. In addition, the Sponsor may decide to terminate the study at any time.

Length of Study
The total length of the study, from screening of the first patient to the end of the study, is expected to be 31 to 49 months.

Investigational Medicinal Products
The investigational medicinal products (IMP) for this study are atezolizumab and venetoclax. Carboplatin and etoposide are background treatments and are thus considered non-investigational medicinal products (NIMPs) in this study.

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.

Venetoclax
Patients will self-administer venetoclax tablets by mouth daily. Venetoclax is formulated as 100-mg tablets; patients may take up to eight 100-mg tablets daily to receive an 800-mg continual dose. Each dose of venetoclax will be taken with approximately 240 mL of water within 30

minutes after the patient's first meal of the day (e.g., breakfast). For continuous venetoclax dose (Days 1–21), patients should continue taking venetoclax without a break between cycles.

Carboplatin and Etoposide

Carboplatin and etoposide will be used in the commercially available formulation.

Dosage, Administration, Sequence, and Compliance

Atezolizumab will be given at fixed dose of 1200 mg by IV infusion every 21 [±2] days in both induction and maintenance. For more information on the formulation, packaging, and handling of atezolizumab, please refer to the prescribing information.

Carboplatin and etoposide induction therapy will be administered as follows:

During induction, patients will be treated with carboplatin and etoposide chemotherapy. For information on the formulation, packaging, and handling of these therapies, please see the prescribing information for each drug.

Standard doses of each agent will be administered for a total of four 21-day cycles during induction.

- Carboplatin AUC 5 mg/mL min (Calvert formula dosing) IV infusion over 30–60 minutes on Day 1 of each cycle after completion of atezolizumab IV infusion with standard anti-emetics per local practice guidelines.
- Etoposide 100 mg/m^2 IV on Days 1–3 of each cycle. On Day 1 of each cycle, etoposide should be administered intravenously over 60 minutes following carboplatin administration. On Days 2 and 3 of each cycle, etoposide (100 mg/m2) should be administered intravenously over 60 minutes. Premedication should be administered according to local standard of care.

On Day 1 of each cycle, all eligible patients will receive treatment in the following order:

Induction: atezolizumab → carboplatin → etoposide→ venetoclax

Maintenance: atezolizumab → venetoclax

On Days 2 and 3, patients will receive etoposide infusions.

Because the effects of corticosteroids on T-cell proliferation have the potential to attenuate atezolizumab-mediated anti-tumor immune activity, premedication with corticosteroids should be minimized to the extent that is clinically feasible. Secondly, at the initiation of the induction phase of dose-escalation Arm B, cohorts will be treated without primary prophylactic G-CSF. The administration of secondary prophylactic G-CSF for high-frequency febrile neutropenia, severe neutropenia, or prolonged neutropenia must be discussed and agreed upon between the investigator and the Medical Monitor. Please refer to protocol administration details, which are in accordance with institutional standards and American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), or ESMO guidelines. Of note, if and once primary prophylactic G-CSF is deemed to be necessary as determined in the dose-escalation phase (see the protocol), then this requirement will be implemented during induction therapy for all subsequent patients.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

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 the protocol. Atezolizumab infusions will be administered per the instructions outlined in the protocol.

Cycles in which no chemotherapy is given do not count toward the total number of induction chemotherapy cycles.

After the induction phase, patients will begin maintenance therapy with atezolizumab plus venetoclax.

The suggested infusion times for carboplatin and etoposide may be adapted in accordance with local standard of care.

Any dose modification should be noted on the Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in the protocol.

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 the protocol.

Guidelines for dose modification and treatment interruption or discontinuation for carboplatin and etoposide are provided in the protocol.

Statistical Methods

Primary Analysis

The analysis population for the efficacy analyses will consist of all enrolled patients in the dose-expansion cohort, with patients grouped according to their assigned dose levels and treatment schedules.

The primary efficacy objective for the Phase Ib dose-expansion cohort is to evaluate the preliminary efficacy of venetoclax in combination with atezolizumab as maintenance therapy or venetoclax in combination with atezolizumab, carboplatin, and etoposide as induction therapy followed by venetoclax plus atezolizumab as maintenance therapy on the basis of the following endpoint:

- ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions $\geq$ 4 weeks apart, as determined by the investigator according to RECIST v1.1 criteria.

Patients with no disease assessments for any reason will be classified as non-responders. An estimate of ORR with 90% exact confidence interval (CI) will be presented using the method of Pearson Clopper.

Interim Analyses

Planned Interim Analyses

None planned.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody, also called anti-therapeutic antibody
AML	acute myeloid leukemia
Bcl-2	B-cell lymphoma 2
CBR	clinical benefit rate
CE	carboplatin and etoposide
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CRCL	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DDI	drug-drug interaction
DLTs	dose-limiting toxicities
DOR	duration of response
EBV	Epstein-Barr virus
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
ER	estrogen receptor
ES-SCLC	extended stage small cell lung cancer
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
G-CSF	growth-colony stimulating factor
GFR	glomerular filtration rate
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
IBM	ideal body mass
ICH	International Council for Harmonisation

Abbreviation	Definition
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reactions
IV	intravenous
IxRS	interactive voice or web-based response system
LS-SCLC	limited stage small cell lung cancer
MM	multiple myeloma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NC	non-continuous (dosing schedule)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NIMPs	non-investigational medicinal products
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
Q3W	every 3 weeks
QD	daily
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
R-ICE	rituximab, ifosfamide, carboplatin, etoposide
RP2D	recommended Phase II dose
R/R	relapsed and refractory
SCLC	small cell lung cancer
SD	stable disease
SLL	small lymphocytic lymphoma
T3	triiodothyronine
TLS	tumor lysis syndrome
ULN	upper limit of normal

Abbreviation	Definition
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON LUNG CANCER

Lung cancer is the leading cause of cancer deaths worldwide. It is the second most common cancer in both men and women, accounting for approximately 13% of all new cancers (Surveillance, Epidemiology, and End Results [SEER] 2019). In 2018, it was estimated that there were 470,039 new cases of lung cancer and 387,913 lung cancer deaths in Europe (Bray et al. 2018). In the United States, an estimated 228,150 new cases of lung cancer and 142,670 lung cancer deaths are projected in 2019 (Siegel et al. 2019; SEER 2019).

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer (Molina et al. 2008; Howlader et al. 2014). Small cell lung cancer (SCLC) accounts for approximately 13% of all lung cancer cases, and is distinguished from NSCLC by its rapid growth time and early development of metastatic disease (Govindan et al. 2006). Nearly all cases of SCLC are attributable to cigarette smoking (Pesch et al. 2012). SCLC has a simple staging system that divides patients into 2 groups: limited stage (LS-SCLC) and extended stage (ES-SCLC). LS-SCLC is defined as Stage I to III (T any, N any, M0) that can be safely treated with definitive radiation therapy, excluding T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume too large to be encompassed in a tolerable radiation plan. ES-SCLC is defined as Stage IV (T any, N any, M1a/b) and represents tumors beyond the boundaries of LS-SCLC, including distant metastases, malignant pericardial or pleural effusions, and contralateral supraclavicular and contralateral hilar involvement.

Poor prognostic factors for survival in patients with SCLC include extensive-stage disease, poor performance status, weight loss, number of organs involved, and markers associated with excessive bulk of disease (e.g., lactate dehydrogenase) (Yip et al. 2000; Foster et al. 2009). Central nervous system, bone marrow, and liver metastases; as well as endocrinologic paraneoplastic syndromes, are also generally associated with worse outcomes. Smoking cessation should be strongly encouraged in SCLC patients because patients who smoke have an increased toxicity during treatment and shorter survival (Videtic et al. 2003; National Comprehensive Cancer Network [NCCN] 2019).

Patients with LS-SCLC can be treated with chemotherapy and radiation with the potential for long-term survival (Stinchcombe et al. 2008). However, the majority (approximately 70%) of patients with SCLC are diagnosed with ES-SCLC, which has poor survival prospects (median overall survival [OS] approximately 10 months) (Socinski et al. 2009). The aggressiveness of ES-SCLC, which may result in the development of symptomatic disease between annual scans, limits the potential effect of screening on mortality. Chest pain, dyspnea, and cough are among the most frequent disease-related symptoms experienced by patients with SCLC. Less commonly, SCLC can present with an endocrinologic or neurologic paraneoplastic syndrome. Of note, SCLC is the most common malignancy associated with neurologic paraneoplastic

syndromes (e.g., cerebellar degenerative syndromes or the Lambert Eaton myasthenic syndrome). Chemotherapy alone can palliate symptoms and prolong survival for patients with ES-SCLC; however, long-term survival is rare (Johnson et al. 2004; Demedts et al. 2010).

1.2 FIRST-LINE TREATMENT FOR EXTENSIVE-STAGE SMALL CELL LUNG CANCER

A PD-L1 inhibitor (atezolizumab or durvalumab) given in combination with platinum-based chemotherapy consisting of carboplatin and etoposide (CE) or cisplatin and etoposide as induction therapy for 4 cycles, followed by atezolizumab or durvalumab maintenance therapy, is the current standard first-line treatment for patients with ES-SCLC in the United States (NCCN 2019). The regimen with atezolizumab has also recently gained European Commission approval (Roche Media Release, 2019) based on the results of the randomized Phase III Study GO30081 (IMpower133). A total of 403 patients were randomized in IMpower133, with 201 patients randomly assigned to the atezolizumab plus CE group and 202 patients assigned to the placebo plus CE group. With a median follow-up of 13.9 months, the hazard ratio (HR) for death was 0.70 (95% confidence interval [CI]: 0.54, 0.91; $p=0.007$) with a median OS of 12.3 months in the atezolizumab plus CE group and 10.3 months in the placebo plus CE group. The HR for progression-free survival (PFS) was 0.77 (95% CI: 0.62, 0.96; $p=0.02$), with a median PFS of 5.2 months and 4.3 months for atezolizumab plus CE and placebo plus CE, respectively (Horn et al. 2018). Response rates were similar in both arms, with an overall response rate (ORR) of 60% in the atezolizumab arm and 64% in the placebo arm.

The safety profile of atezolizumab plus CE was consistent with the previously reported safety profile of the individual agents, with no new findings observed. Specifically, adverse events related to any component of the trial regimen occurred in 188 patients (94.9%) in the atezolizumab group and in 181 patients (92.3%) in the placebo group. The most common Grade 3 or 4 adverse events related to the trial regimen were neutropenia and anemia. The number of deaths related to the trial regimen was the same in both arms: 3 patients (1.5%) in the atezolizumab group (death was due to neutropenia in 1 patient, pneumonia in 1 patient, and an unspecified cause in 1 patient) and in 3 patients (1.5%) in the placebo group (death was due to pneumonia in 1 patient, septic shock in 1 patient, and cardiopulmonary failure in 1 patient). Immune-related adverse events occurred in 79 patients (39.9%) in the atezolizumab group and in 48 patients (24.5%) in the placebo group, with rash and hypothyroidism being the most common (Horn et al. 2018).

Results from the CASPIAN study with another PD-L1 inhibitor, durvalumab, in the same patient population were published showing consistent results with the IMpower133 trial (Paz-Ares et al. 2019). The randomized, open-label, Phase III CASPIAN study randomized 805 patients: 268 were assigned to durvalumab plus platinum–etoposide,

268 to durvalumab plus tremelimumab plus platinum–etoposide, and 269 to platinum–etoposide alone. The results of the tremelimumab containing arm will be reported at the time of the final OS analysis. Durvalumab plus platinum–etoposide was associated with a significant improvement in OS, with a HR of 0.73 (95% CI 0.59–0.91; p=0.0047]); median OS was 13.0 months (95% CI 11.5–14.8) in the durvalumab plus platinum–etoposide group versus 10.3 months (9.3–11.2) in the platinum–etoposide group. Although PFS was not formally tested for statistical significance, the HR was 0.78 (95% CI: 0.65, 0.94), with a median PFS of 5.1 months for durvalumab plus platinum–etoposide and 5.4 months for platinum–etoposide. Grade 3 or 4 adverse events of any cause occurred in 163 (62%) of 265 treated patients in the durvalumab plus platinum–etoposide group and 166 (62%) of 266 in the platinum–etoposide group; adverse events leading to death occurred in 13 (5%) and 15 (6%) patients in each group.

Prior to the approval of the IMpower133 regimen, the standard of care for nearly 30 years was platinum-based chemotherapy with etoposide, a topoisomerase II inhibitor (Fruh et al. 2013). Clinical studies with the combination of cisplatin and etoposide as first-line treatment in patients with ES-SCLC showed complete response (CR) rates exceeding 40% and median survival time of approximately 9 months (Evans et al. 1985). Subsequently, small randomized studies have suggested similar efficacy of cisplatin and carboplatin in patients with SCLC (Skarlos et al. 1994; Okamoto et al. 2007). A meta-analysis of four randomized studies compared cisplatin-based versus carboplatin-based regimens in patients with SCLC (Rossi et al. 2012). Of the 663 patients included in this meta-analysis, 68% had extensive-stage disease. In patients receiving cisplatin- versus carboplatin-containing regimens, there was no significant difference observed in response rate (67% vs. 66%), PFS (5.5 vs. 5.3 months; HR: 1.10; 95% CI: 0.94, 1.29), or OS (9.6 vs. 9.4 months; HR: 1.08; 95% CI: 0.92, 1.27), suggesting equivalent efficacy in patients with SCLC. Several studies using cisplatin or carboplatin with etoposide (at various doses) have shown consistent outcomes (see Table 1).

Table 1 Results from Randomized Studies using Platinum-Based Chemotherapy for ES-SCLC

	Platinum Dosing	Etoposide Dosing	ORR (%)	Median PFS (mo)	Median OS (mo)
Roth et al. 1992	Cisplatin 20 mg/m^2 Days 1–5	80 mg/m^2 Days 1–5	61%	4.3	8.6
Pujol et al. 2001	Cisplatin 100 mg/m^2 Day 2	100 mg/m^2 Days 1–3	61%	6.3	9.3
Noda et al. 2002	Cisplatin 80 mg/m^2 Day 1	100 mg/m^2 Days 1–3	68%	4.8	9.4
Eckardt et al. 2006	Cisplatin 80 mg/m^2 Day 1	100 mg/m^2 Days 1–3	69%	6.3	10.1
Hanna et al. 2006	Cisplatin 60 mg/m^2 Day 1	120 mg/m^2 Days 1–3	44%	4.6	10.2
Okamoto et al. 2007	Cisplatin 25 mg/m^2 Days 1–3	80 mg/m^2 Days 1–3	73%	4.7	9.9
Okamoto et al. 2007	Carboplatin AUC 5 Day 1	80 mg/m^2 Days 1–3	73%	5.2	10.6
Rudin et al. 2008	Carboplatin AUC 5 Day 1	100 mg/m^2 Days 1–3	52%	5.4	10.6
Socinski et al. 2009	Carboplatin AUC 5 Day 1	80 mg/m^2 Days 1–3	60%	7.6	10.6
Nagel et al. 2011	Carboplatin AUC 6 Day 1	120 mg/m^2 Days 1–3	67%	7.0	11.0
Schmittel et al. 2011	Carboplatin AUC 5 Day 1	140 mg/m^2 Days 1–3	52%	6.0	9.0

AUC = area under the concentration-time curve; ES-SCLC = extensive-stage small cell lung cancer; mo = months; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Despite the impressive initial response rates observed with first-line chemotherapy regimens, most patients with ES-SCLC develop resistance and their prognosis is poor. PFS is approximately 6 months and median survival is approximately 1 year. Unlike NSCLC, SCLC is devoid of kinase vulnerabilities such as EGFR, ROS, and ALK. Instead, SCLC survival and proliferation are largely reliant on the currently undruggable MYC family of transcription factors, and through the loss of tumor suppressors p53 and Rb (George et al. 2015), underlining a significant need for improved novel treatment options for patients with ES-SCLC. With this consideration, combining a pro-apoptotic molecule such as venetoclax with chemotherapeutic and immunotherapeutic agents, such as antibodies that modulate immune cell activity, offer an alternative treatment approach that could potentially improve the prognosis of patients with this disease.

1.3 BCL-2 SIGNALING PATHWAY AND SMALL CELL LUNG CANCER

Cancer cells are characterized by their capacity for relentless growth, survival, and evasion of cell death (Adams and Cory 2007; Strasser et al. 2011). Apoptosis is the dominant mode of programmed cell death with two distinct pathways: the intrinsic mitochondrial pathway and the extrinsic death receptor pathway (Strasser et al. 2011). Intrinsic apoptosis is regulated by a balance between pro-apoptotic proteins and the B-cell lymphoma 2 (Bcl-2) family of anti-apoptotic proteins, of which key members are Bcl-2, Bcl-X_L, Bcl-w, A1, and MCL-1 (Cory et al. 2003). Cancer cells often overexpress anti-apoptotic Bcl-2 family proteins to promote survival (Korsmeyer 1992; Thomas et al.

2013). Many cytotoxic cancer therapies ultimately induce apoptosis and altered expression of pro- and anti-apoptotic proteins and can promote therapy resistance (Longley and Johnston 2005; Thomas et al. 2013; Delbridge and Strasser 2015). Therefore, Bcl-2 family members have emerged as attractive targets for therapeutic development. Small-molecule inhibitors of the Bcl-2 family have been studied, including the dual Bcl-2/Bcl-X_L inhibitor ABT-737 (Oltersdorf et al. 2005) and its orally bioavailable analog ABT-263 (navitoclax; Tse et al. 2008), as well as ABT-199 (venetoclax or GDC-0199), a platelet-sparing, selective Bcl-2 inhibitor (Souers et al. 2013).

Elevated Bcl-2 expression in SCLC tumors was first described nearly 25 years ago, with a reported 65% to 76% of patients having Bcl-2-positive tumor samples by immunohistochemistry (IHC) analysis (Ben-Ezra et al. 1994; Kaiser et al. 1996). Recent internal analysis of procured SCLC tumor samples confirmed this earlier data by demonstrating that 77% of samples were Bcl-2 positive by IHC, and further revealed that 35% of the samples were Bcl-2-high based on a cutoff of $\geq$50% of tumor cells stained with an intensity of 2+ or 3+ (Genentech internal data, unpublished).

Nonclinical studies have also demonstrated that SCLC cell lines are sensitive to the dual Bcl-2/Bcl-X_L inhibitors ABT-737 and navitoclax (Oltersdorf et al. 2005; Tse et al. 2008; Inoue-Yamauchi et al. 2017). Through the development of the Bcl-2 specific inhibitor venetoclax, the dependence of SCLC cell lines on Bcl-2 has been more thoroughly described. Utilizing a panel of SCLC cell lines, Lochmann et al. demonstrated positive correlation between BCL2 mRNA expression and venetoclax sensitivity in vitro (Lochmann et al. 2018). Importantly, this sensitivity was maintained in vivo and oral daily (QD) dosing of venetoclax at 100 mg/kg QD was sufficient to induce tumor stasis or tumor regressions in several xenograft models of SCLC, including chemorefractory patient-derived xenograft models. These studies suggest that Bcl-2 is an important mediator of survival in nonclinical SCLC models.

Activity of Bcl-2 family inhibitors have also been tested in the clinic in patients with ES-SCLC. Despite nonclinical data showing activity of navitoclax in that setting, its activity in the clinic as a single agent seems to be limited. In a phase I trial of single-agent navitoclax in 20 pretreated ES-SCLC evaluable patients, 1 patient had partial response (PR) and 5 patients had stable disease (SD) (Gandhi et al. 2011). In a Phase II open-label trial for recurrent SCLC (Rudin et al. 2012), of 39 enrolled patients, 1 had PR and 9 SD, with the most common adverse event being thrombocytopenia, an on-target result of BCL-X_L inhibition in platelets. Moreover, 1 PR was observed out of 19 patients treated in a phase I study evaluating navitoclax in combination with paclitaxel in untreated ES-SCLC (Vlahovic et al. 2014).

Another agent, obatoclax, a pan-Bcl-2 family antagonist, was tested in a randomized Phase II study and was shown to be relatively well tolerated when added to CE in first-line treatment of ES-SCLC, but failed to significantly improve ORR, PFS, or OS (Langer et al. 2014). The ORR was 62% with obatoclax plus CE versus 53% with CE (1-sided p

= 0.143). The median PFS was 5.8 months (95% CI: 5.3–6.5) with obatoclax plus CE and 5.2 months (95% CI: 4.1–5.7) with CE. Median OS was 10.5 months (95% CI: 8.9–13.8) and 9.8 months (7.2–11.2) with a non−statistically significant HR for OS, 0.823; 1-sided p = 0.121. Grade 3/4 adverse events were primarily hematologic and similar in frequency between treatment arms. Because nonclinical data indicate that obatoclax has weaker potency against Bcl-2 and Bcl-X_L compared to ABT-737/navitoclax (Zhai et al. 2006) and weaker potency against Bcl-2 compared to venetoclax, there may have been insufficient inhibition of Bcl-2 family members in this trial. Furthermore, the relative dose intensity could have been affected by neurotoxicity, which was dose-limiting in this study. Some OS improvement was observed in patients who completed 6 cycles (14.2 months vs. 11.6 months).

As described above, the non-selective Bcl-2 inhibitors navitoclax and obatoclax have shown a mixed benefit/toxicity profile in SCLC, where thrombocytopenia hindered the management of these patients. Therefore, selective and potent Bcl-2 inhibition with venetoclax is hypothesized to have improved efficacy and to be more tolerable compared with the non-selective inhibitors.

1.4 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 cancer patients 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.

Safety findings of single-agent atezolizumab across multiple tumor types are consistent with the known mechanism of action of atezolizumab and the underlying disease. Overall, treatment with atezolizumab is well tolerated with a manageable adverse event profile. Currently, the most commonly reported adverse events (≥10%) include fatigue, decreased appetite, cough, nausea, dyspnea, constipation, diarrhea, pyrexia, vomiting, arthralgia, back pain, asthenia, anemia, pruritus, rash, headache, and peripheral edema.

The adverse events observed with atezolizumab in combination with chemotherapy and/or targeted therapies are consistent with the known risks of the individual study treatment. Systemic immune activation, characterized by an excessive immune

response, is a potential risk associated with atezolizumab when used in combination with another immunomodulating compound. There are no atezolizumab-related adverse events that are exacerbated when used in combination with other agents.

Immune-related adverse events are consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-related adverse events are expected. Immune-related adverse events associated with atezolizumab include pneumonitis, hepatitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, meningoencephalitis, myocarditis, and nephritis.

Atezolizumab is approved for the treatment of urothelial carcinoma, NSCLC, SCLC, and triple-negative breast cancer.

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

1.5 BACKGROUND ON VENETOCLAX

Venetoclax (also referred to as GDC-0199, RO5537382, ABT-199, A-1195425.0, Venclexta®, and Venclyxto®) is an orally bioavailable, selective small-molecule inhibitor of Bcl-2 in the biaryl acylsulfonamide chemical class. Venetoclax binds with high affinity ($Ki < 0.01$ nM) to the anti-apoptotic protein Bcl-2 and with lower affinity to other anti-apoptotic Bcl-2 family proteins such as Bcl-X_L and Bcl-w ($> 4{,}000$-fold and $> 2{,}000$- to $> 20{,}000$-fold lower affinity than to Bcl-2, respectively; Souers et al. 2013). Survival of platelets depends on BCL-X_L, and thrombocytopenia is therefore a major DLT caused by inhibition of BCL-X_L in the clinic. Venetoclax has an improved therapeutic index by maintaining efficacy against tumor cells while avoiding dose-limiting thrombocytopenia.

Venetoclax has been extensively studied in oncology, particularly in hematological malignancies but also in some solid tumors. Efficacy data indicate that venetoclax, both as a monotherapy and in combination with other therapeutic agents, shows promising safety, tolerability, pharmacokinetics, and efficacy. This includes combinations with rituximab, obinutuzumab, bendamustine plus rituximab, O6-benzylguanine, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), obinutuzumab plus CHOP (G-CHOP), bortezomib plus dexamethasone, azacitidine or decitabine, and cytarabine in patients with hematologic malignancies including chronic lymphocytic leukemia (CLL]/small lymphocytic lymphoma (SLL), non-Hodgkin lymphoma (NHL), multiple myeloma (MM), myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML).

In the United States, venetoclax is currently indicated for the treatment of adult patients with CLL or SLL. In addition, it is also approved in combination with azacitidine or

decitabine or low-dose cytarabine (LDAC) for the treatment of newly diagnosed AML in adults aged 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. This indication is approved under accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

In the EU, venetoclax in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least 1 prior therapy. Monotherapy is indicated for the treatment of CLL in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

Moreover, data with venetoclax in solid tumors such as ER-positive, Bcl-2 positive metastatic breast cancer (Lok et al. 2019) show promising activity. In a Phase Ib dose-escalation study, venetoclax dosed at 200, 400, 600, or 800 mg/daily in combination with tamoxifen 20 mg/daily, was shown to be well tolerated with no dose-limiting toxicities (DLTs) being observed in any of the cohorts and the maximum tolerated dose (MTD) not being reached. Efficacy was promising, with an observed ORR of 54% and clinical benefit rate (CBR) of 75% for the 800-mg cohort, comparing favorably with historical studies of patients treated with tamoxifen in first-line relapse (e.g., ORR 17%–33% and CBR 38%–56%).

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

1.6 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

SCLC is a very aggressive disease characterized by poor survival, with little progress being made in developing novel treatments in more than two decades. However, advances with immunotherapies have opened new therapeutic avenues. Recently, regulatory approval has been granted for atezolizumab plus CE in the United States and European Union, based on the IMpower133 study (see Section 1.2), for the first-line treatment of patients with ES-SCLC. Moreover, results from the randomized, open-label, Phase III CASPIAN study with another PD-L1 inhibitor, durvalumab, in the same patient population demonstrated consistent results with the IMpower133 trial (Paz-Ares et al. 2019).

However, despite the survival benefit observed with this regimen, median survival remains at approximately 1 year, leaving considerable room for improvement in outcomes. Bcl-2 is highly expressed in SCLC, and Bcl-2 inhibition with venetoclax has been shown to be active and well tolerated both as a monotherapy as well as in combination with various chemotherapy backbones in different (mostly hematological) malignancies. In light of these observations, this study (Study GO41864) is designed to evaluate whether the anti-tumor effect of the standard combination of atezolizumab plus

CE can be enhanced by adding venetoclax in treating patients with chemotherapy-naive ES-SCLC.

1.6.1 Study Rationale

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 metastatic cancer, including SCLC. Recent approvals in the United States and European Union of atezolizumab plus chemotherapy in metastatic SCLC based on the IMpower133 study in the first-line setting as well as the results of the CASPIAN phase III study validate the inhibition of the PD-L1/PD-1 pathway for achieving clinical benefit in these patients. Furthermore, the safety profile of atezolizumab or durvalumab plus chemotherapy appears to be as tolerable as chemotherapy doublet combinations in the front-line setting. Despite this advancement, patient outcomes in ES-SCLC continue to be very poor and a need remains for effective therapeutics that can be added to the approved regimen of atezolizumab, carboplatin, and etoposide.

The high levels of Bcl-2 expressed in SCLC and the single-agent activity of venetoclax in nonclinical SCLC models suggest that the combination of a Bcl-2 inhibitor, such as venetoclax, and the atezolizumab plus chemotherapy standard of care treatment may improve the therapeutic outcome of SCLC through enhanced tumor killing. In nonclinical studies, cisplatin and etoposide have been shown to synergistically combine with ABT-737 (dual Bcl-2/Bcl-X_L inhibitor) in vitro (Li et al. 2009), where cisplatin and etoposide were both shown to downregulate the anti-apoptotic protein MCL-1, which is a known to be a resistance factor for venetoclax. Additionally, upregulation of Bcl-2 protein has been identified as a mechanism of drug resistance in vitro in SCLC cell lines that were generated to be etoposide resistant and showed cross-resistance to cisplatin and doxorubicin (Sartorius and Krammer 2002). Together, these data provide a mechanistic rationale for combining Bcl-2 inhibition with etoposide and platinum to enhance tumor cell killing.

Tumor-cell killing by cytotoxic chemotherapy, augmented by pro-apoptotic activity of venetoclax, can reasonably be expected to expose the immune system to high levels of tumor antigens. Importantly, recent studies have shown that venetoclax does not inhibit T-cell activation in vitro and does not antagonize anti-PD-1/PD-L1 efficacy in vivo (Lasater et al. 2018; Matthew et al. 2018). Therefore, invigorating tumor-specific T-cell immunity by inhibiting PD-L1/PD-1 signaling and combining with pro-apoptotic therapy such as venetoclax may result in deeper and more durable responses compared with standard treatment alone. This approach has a strong scientific rationale, and the evaluation of its safety and efficacy is warranted and could open new doors for the future treatment of patients with SCLC.

Venetoclax has been evaluated in a variety of oncological indications, particularly in hematological malignancies. Many of those evaluations have translated into regulatory

approvals in many indications within CLL and AML. From a safety perspective, venetoclax has been generally well tolerated as a single agent as well as in combination with targeted therapies and chemotherapy (refer to the Venetoclax Investigator's Brochure for more details). Adverse events commonly observed with venetoclax include nausea, vomiting, diarrhea, myelotoxicity (including neutropenia, febrile neutropenia, anemia, thrombocytopenia, and leukopenia), and infections. To date, the majority of these adverse events have been manageable without requiring treatment discontinuation. Important identified risks for venetoclax include tumor lysis syndrome (TLS), particularly in CLL and mantle cell lymphoma, and neutropenia. Serious infection is also an identified risk. Of note, cytopenias and TLS are commonly observed in hematologic malignances in some cases independently of treatment, and their prevalence in solid tumors remains to be elucidated.

Therefore, the current Phase Ib study is designed to identify a safe and tolerable dose of venetoclax in the context of atezolizumab plus chemotherapy, as well as to explore whether the anti-tumor effects of atezolizumab plus chemotherapy can be improved with the addition of the pro-apoptotic small molecule venetoclax to atezolizumab and chemotherapy in patients with ES-SCLC.

1.6.2 Benefit–Risk Assessment

This study will enroll patients with ES-SCLC with no prior systemic treatment, and all patients will receive an approved regimen that will include atezolizumab plus standard chemotherapy (CE). Atezolizumab plus CE was well tolerated in the pivotal IMpower133 study, with a safety profile consistent with the known risks of individual treatment and comparable to treatment with chemotherapy alone. Overall, the toxicity profile is considered to be tolerable and manageable.

The addition of venetoclax to chemotherapy and immunotherapy is believed to enhance apoptosis and to improve tumor growth inhibition. Moreover, tumor-cell killing by cytotoxic chemotherapy and augmented by the pro-apoptotic activity of venetoclax may bolster the immune-mediated mechanism of action of atezolizumab. Therefore, this study will offer an opportunity to evaluate the safety and activity of a promising novel approach combining venetoclax with chemotherapy and immunotherapy for the treatment of SCLC in the clinical setting.

Although the combination is expected to have limited overlapping toxicities, which include neutropenia, febrile neutropenia and thrombocytopenia, there remains the potential for unexpected toxicities. To minimize this risk, stringent inclusion and exclusion criteria (Sections 4.1.1 and 4.1.2), close safety monitoring (Section 5.1), together with rules for dose modifications and safety management guidelines (Section 5.1.5) for known risks of single-agent atezolizumab and venetoclax have been implemented. The addition of venetoclax to atezolizumab and chemotherapy, based on the manageable safety profile and potential for augmented efficacy, can represent a

potential valuable treatment option and offer a favorable benefit–risk balance for patients in this study.

2. OBJECTIVES AND ENDPOINTS

This is a Phase Ib, open-label, multicenter, two-stage study, consisting of a dose-escalation phase and dose-expansion phase, to evaluate the safety, tolerability, pharmacokinetics, and efficacy of venetoclax in combination with atezolizumab, carboplatin, and etoposide as induction therapy and venetoclax in combination with atezolizumab as maintenance therapy following induction, for patients with ES-SCLC who are chemotherapy-naïve for their extensive-stage disease.

The objectives for the dose-escalation phase of this study are to assess safety and tolerability as well as to determine the maximum tolerated dose (MTD) and the recommended Phase II dose (RP2D) for venetoclax in both induction (Arm B) and maintenance (Arm A) therapies.

The objectives of the dose-expansion phase are to evaluate the safety, tolerability, pharmacokinetics, and efficacy of venetoclax at the RP2D in induction followed by maintenance therapies or in maintenance therapy only, as determined in the dose-escalation phase of the study.

Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., venetoclax plus atezolizumab, carboplatin, and etoposide in the induction setting or venetoclax plus atezolizumab in the maintenance setting.

2.1 OBJECTIVES AND ENDPOINTS FOR DOSE-ESCALATION PHASE

2.1.1 Safety Objective (Primary Objective)

The safety objective for the dose-escalation phase is to evaluate the safety and tolerability of venetoclax plus atezolizumab as maintenance therapy (Arm A) and venetoclax in combination with atezolizumab, carboplatin, and etoposide as induction therapy followed by venetoclax plus atezolizumab as maintenance therapy (Arm B) —including estimation of the MTD, determination of the RP2D, and characterization of DLTs (see Section 3.1.3)—on the basis of the following endpoints:

- The incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Technology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted laboratory test results

2.1.2 Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives for the dose-escalation phase are the following:

- To characterize the pharmacokinetics of venetoclax and atezolizumab when given in combination as part of the maintenance therapy on the basis of the following endpoints:
  - Plasma concentrations of venetoclax at specified timepoints
  - Serum concentrations of atezolizumab at specified timepoints
- To characterize the pharmacokinetics of venetoclax and atezolizumab when given in combination with carboplatin and etoposide as part of the induction therapy on the basis of the following endpoints:
  - Plasma concentrations of venetoclax at specified timepoints
  - Serum concentrations of atezolizumab at specified timepoints

2.1.3 Immunogenicity Objective

The exploratory immunogenicity objective for the dose-escalation phase is to evaluate the immune response to atezolizumab on the basis of the following endpoints:

- Incidence of anti-drug antibodies (ADAs) to atezolizumab in the presence of venetoclax
- Incidence of ADAs to atezolizumab in the presence of venetoclax, carboplatin, and etoposide

2.1.4 Biomarker Objectives

The exploratory biomarker objectives for the dose-escalation phase are to identify and evaluate biomarkers that are predictive of response to venetoclax (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to venetoclax, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of venetoclax activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- Relationship between biomarkers in tumor tissue and blood (listed in Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

2.2 OBJECTIVES AND ENDPOINTS FOR DOSE-EXPANSION PHASE

2.2.1 Efficacy Objectives

2.2.1.1 Primary Efficacy Objective

The primary efficacy objective for the dose-expansion phase is to evaluate the preliminary efficacy of venetoclax in combination with atezolizumab as maintenance therapy or venetoclax in combination with atezolizumab, carboplatin, and etoposide as

induction therapy followed by venetoclax plus atezolizumab as maintenance therapy on the basis of the following endpoint:

- ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions $\geq$28 days apart, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

2.2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for the dose-expansion phase is to evaluate the preliminary efficacy of venetoclax in combination with atezolizumab as maintenance therapy or venetoclax in combination with atezolizumab, carboplatin, and etoposide as induction therapy followed by venetoclax plus atezolizumab as maintenance therapy on the basis of the following endpoints:

- Duration of response (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, as determined by the investigator according to RECIST v1.1
- PFS after enrollment, defined as the time from enrollment to the first occurrence of disease progression or relapse or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
- OS after enrollment, defined as the time from enrollment to death from any cause
- PFS rate at 6 months, defined as the proportion of patients who have not experienced disease progression, relapse, or death from any cause at 6 months, as determined by the investigator according to RECIST v1.1
- OS rate at 1 year, defined as the proportion of patients who have not experienced death from any cause at 1 year

2.2.2 Safety Objective

The safety objective for the dose-expansion phase are to evaluate the safety and tolerability of venetoclax in combination with atezolizumab, carboplatin, and etoposide as induction therapy or venetoclax in combination with atezolizumab, carboplatin, and etoposide as induction therapy followed by venetoclax plus atezolizumab as maintenance therapy on the basis of the following endpoints:

- To determine the incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted laboratory test results

2.2.3 Pharmacokinetic Objectives

The PK objectives for the dose-expansion phase are the following:

- To characterize the pharmacokinetics of venetoclax and atezolizumab when given in combination as part of the maintenance therapy on the basis of the following endpoints:
  - Plasma concentrations of venetoclax at specified timepoints
  - Serum concentrations of atezolizumab at specified timepoints
- To characterize the pharmacokinetics of venetoclax, atezolizumab, carboplatin, and etoposide when given in combination as part of the induction therapy on the basis of the following endpoints:
  - Plasma concentrations of venetoclax at specified timepoints
  - Serum concentrations of atezolizumab at specified timepoints
  - Plasma concentrations of carboplatin at specified timepoints
  - Plasma concentrations of etoposide at specified timepoints

2.2.4 Immunogenicity Objective

The exploratory immunogenicity objective for the dose-expansion phase are the same as those described for the dose-escalation phase and are described in Section 2.1.3.

2.2.5 Biomarker Objectives

The exploratory biomarker objectives for the dose-expansion phase are the same as those described for the dose-escalation phase and are described in Section 2.1.4.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase Ib, multicenter, open-label, two-stage study consisting of a dose-escalation phase and a dose-expansion phase to evaluate the safety, tolerability, pharmacokinetics, and efficacy of venetoclax in combination with atezolizumab, carboplatin, and etoposide.

3.1.1 Overview of Study Design

In the dose-escalation stage, venetoclax will be tested first in the maintenance setting (Arm A) followed by testing in both the induction and maintenance settings (Arm B).

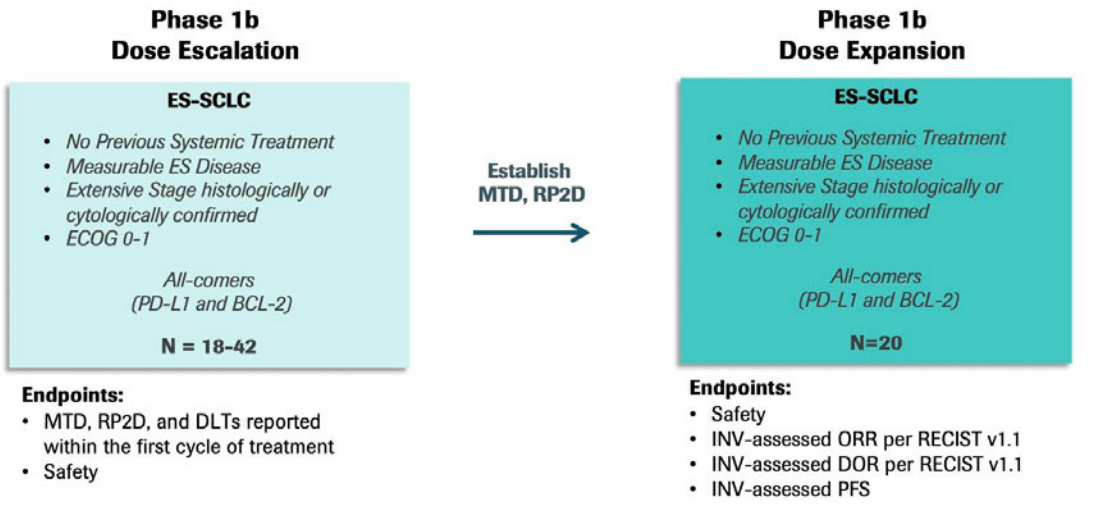
- **Arm A**: Venetoclax and atezolizumab as maintenance therapy for patients with ES-SCLC who have completed 4–6 cycles of carboplatin and etoposide first-line induction chemotherapy, with or without *atezolizumab*
- **Arm B**: Venetoclax, atezolizumab, carboplatin, and etoposide as induction therapy (4 cycles) followed by venetoclax plus atezolizumab as maintenance therapy for patients with previously untreated ES-SCLC

The dose-escalation stage will then be followed by the dose-expansion portion of the study to evaluate the safety and efficacy of adding venetoclax to induction and/or maintenance therapy at the RP2D and schedule as determined during dose–escalation.

Figure 1 presents an overview of the overall study design. A schedule of assessments for maintenance cohorts (dose-escalation and expansion) is provided in Appendix 1; and for induction plus maintenance cohorts (dose-escalation and expansion) in Appendix 2.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 30 days after previously signing the consent form. The investigator will record reasons for screen failure within the interactive voice or web-based response system (IxRS) and electronic Case Report Form (eCRF [see Section 4.5.1]).

Figure 1 Overall Study Schema



DLT = dose-limiting toxicity; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; ES = extensive-stage; INV = investigator; MTD = maximum tolerated dose; ORR = objective response rate; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RP2D = recommended Phase II dose; SCLC = small cell lung cancer.

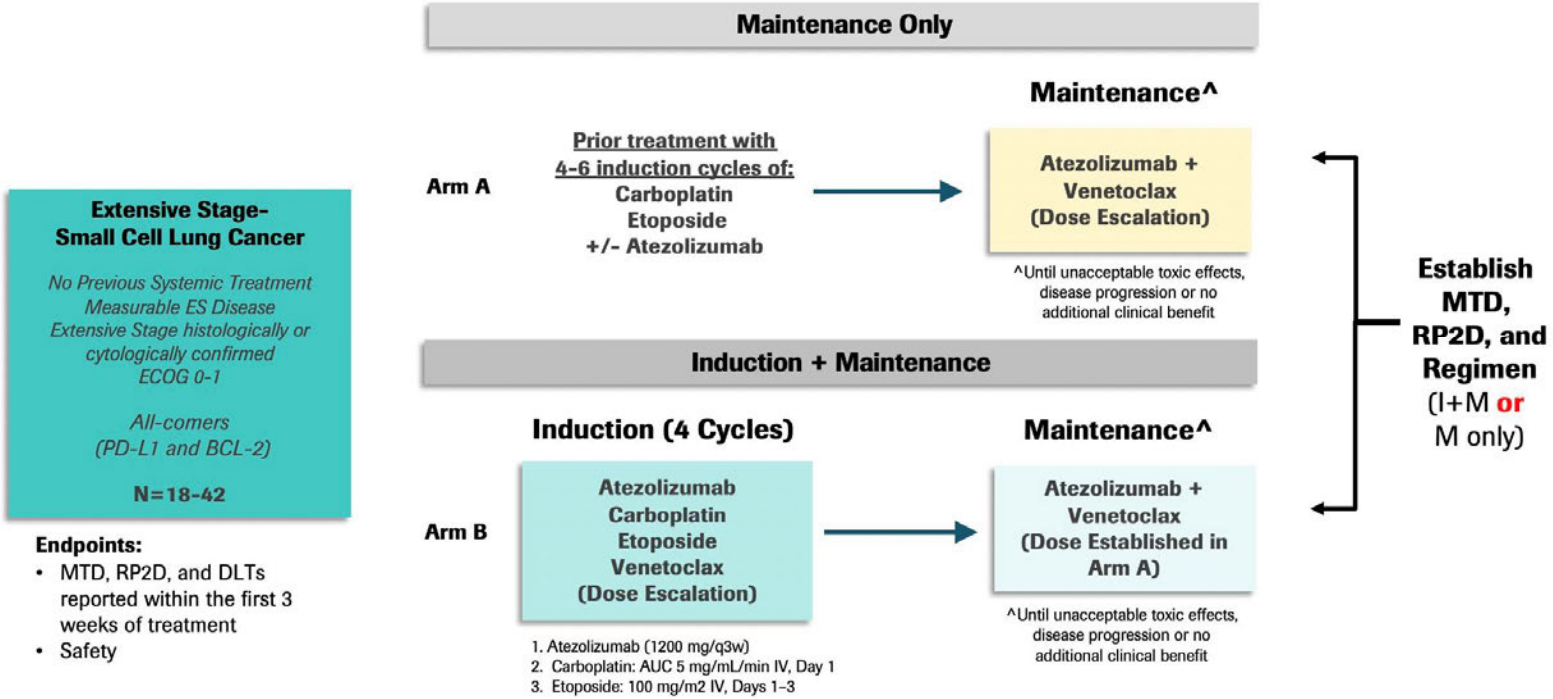
3.1.2 Dose-Escalation Phase

The purpose of the dose-escalation phase of the study is to determine the RP2D and MTD for venetoclax when given in combination with atezolizumab in the maintenance setting and in combination with atezolizumab, carboplatin, and etoposide in the induction setting (followed by venetoclax in combination with atezolizumab as maintenance therapy) in patients with ES-SCLC.

The dose-escalation cohort will use a standard 3+3 design (see Section 3.1.4) to assess the safety, tolerability, and pharmacokinetics of study treatment. Venetoclax will be tested sequentially in the maintenance setting first (Arm A). Once the MTD and the RP2D are identified for maintenance treatment, the RP2D identified in Arm A will be applied to the maintenance portion of the induction plus maintenance setting (Arm B) (Figure 2). The MTD and RP2D of venetoclax will be determined separately for maintenance and induction settings.

Within each arm, dose-escalation cohorts will be run sequentially (e.g., 200 mg followed by 400 mg, etc.; see Figure 3 and Figure 4).

Figure 2 Dose-Escalation Study Schema



ECOG = Eastern Cooperative Oncology Group; ES = extensive-stage; I = induction; IV = intravenous; M = maintenance; MTD = maximum tolerated dose; Q3W = every3 weeks; RP2D = recommended Phase II dose.

3.1.2.1 Maintenance Only (Arm A)

In the maintenance-only arm, venetoclax will be explored on a continuous dosing schedule at doses ranging from 400 mg QD to 800 mg/QD in the following dose-escalation treatment cohorts using a standard 3+3 design:

- **Maintenance Cohort A1 (Dose Level 1):**

  Venetoclax: 400 mg QD continuous on Days 1–21

  Atezolizumab: 1200 mg every 3 weeks (Q3W) on Day 1

- **Maintenance Cohort A2 (Dose Level 2):**

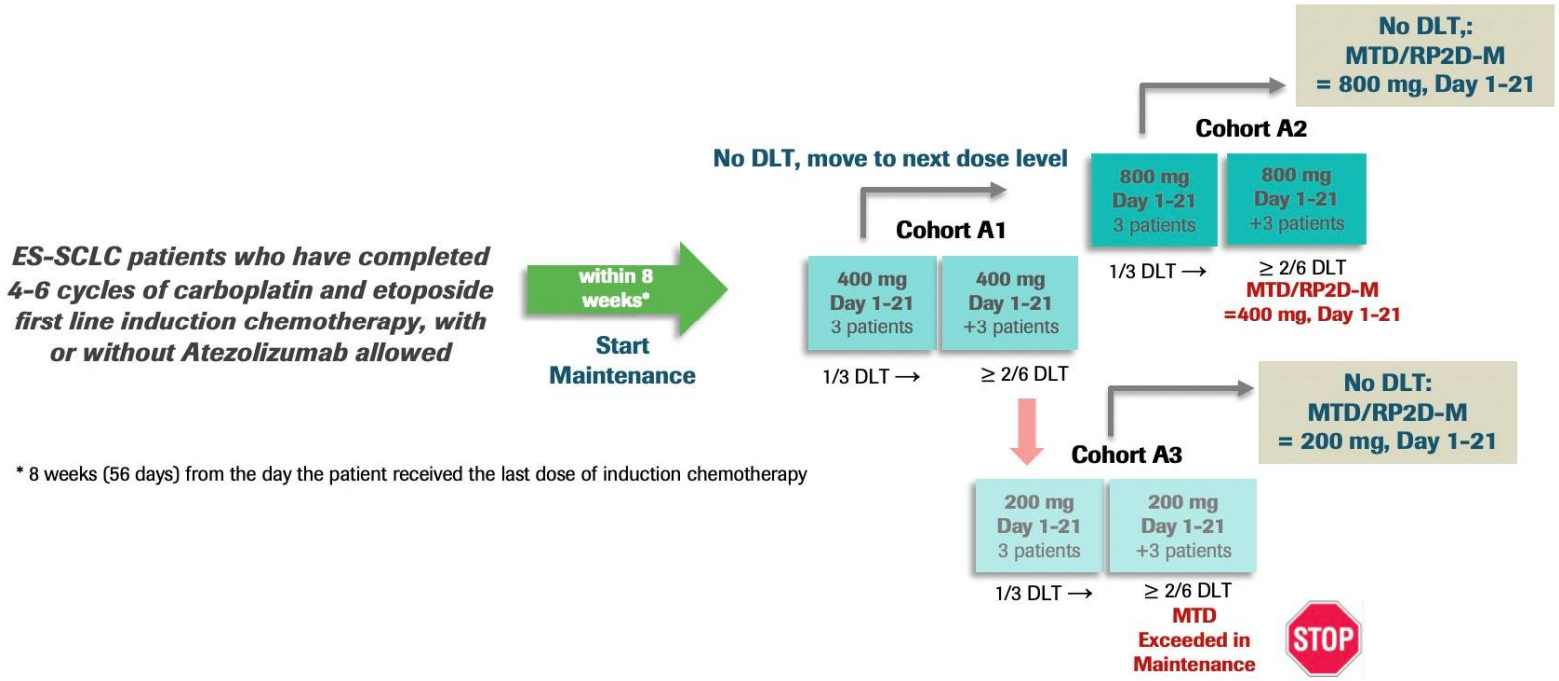
  Venetoclax: 800 mg QD continuous on Days 1–21

  Atezolizumab: 1200 mg Q3W on Day 1

Dose de-escalation to 200 mg QD continuous on Days 1–21 may be explored if DLTs are experienced and adverse events are thought to be potentially mitigated with a lower dose of venetoclax (refer to Figure 3).

Once tolerability and dose are established in the maintenance-only arm (Arm A), the induction followed by maintenance arm (Arm B) will be opened, based on thorough review led by the Medical Monitor in consultation with the Principal Investigators and a committee composed of, at a minimum, the following Sponsor representatives: statistician, safety scientist, PK scientist, and clinical scientist. Patients on maintenance therapy who do not experience unacceptable toxicity and have evidence of clinical benefit (as defined in the protocol) may continue to receive maintenance study treatment every 21 days until documented disease progression determined by investigator or unacceptable toxicity, whichever occurs first.

Figure 3 Study Schema: Dose-Escalation, Maintenance Only (Arm A)



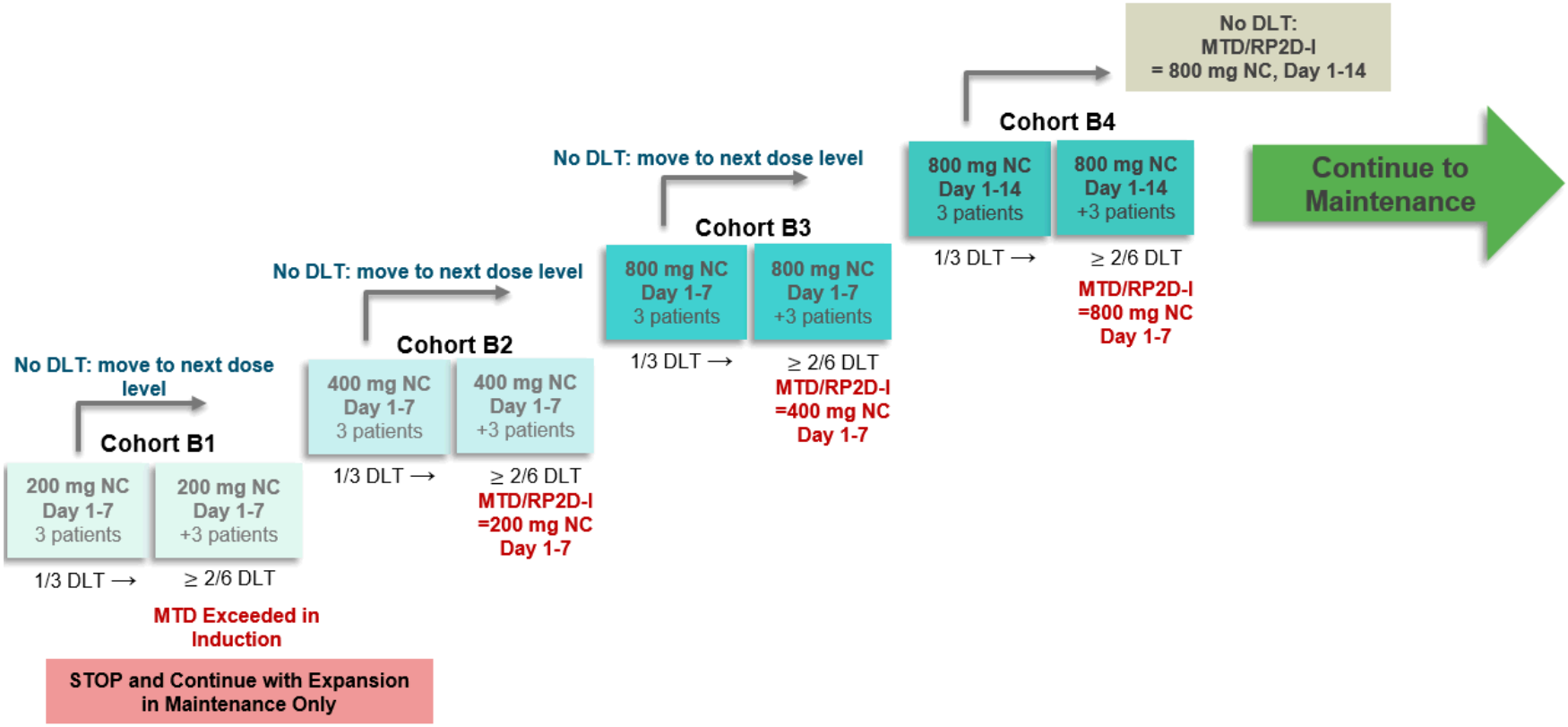
DLT = dose-limiting toxicity; ECOG = Eastern Cooperative Oncology Group; ES = extensive-stage; I = induction; M = maintenance; MTD = maximum tolerated dose; RP2D-M = recommended Phase II dose for maintenance; SCLC = small cell lung cancer.

3.1.2.2 Induction Plus Maintenance (Arm B):

In the induction plus maintenance arm (Arm B; see Figure 4), venetoclax will be explored on a non-continuous (NC) dosing schedule in the following dose-escalation treatment cohorts using a standard 3+3 design:

- **Induction Cohort B1 (Dose Level 1):**
  Venetoclax: 200 mg/QD NC on Days 1–7
  Atezolizumab: 1200 mg Q3W on Day 1
  Carboplatin: AUC 5 mg/mL min (Calvert formula) on Day 1
  Etoposide: 100 mg/m^2 on Days 1–3
- **Induction Cohort B2 (Dose Level 2):**
  Venetoclax: 400 mg/QD NC on Days 1–7
  Atezolizumab: 1200 mg Q3W on Day 1
  Carboplatin: AUC 5 mg/mL min (Calvert formula) on Day 1
  Etoposide: 100 mg/m^2 on Days 1–3
- **Induction Cohort B3 (Dose Level 3):**
  Venetoclax: 800 mg/QD NC on Days 1–7
  Atezolizumab: 1200 mg Q3W on Day 1
  Carboplatin: AUC 5 mg/mL min (Calvert formula) on Day 1
  Etoposide: 100 mg/m^2 on Days 1–3
- **Induction Cohort B4 (Dose Level 4):**
  Venetoclax: 800 mg/QD NC on Days 1–14
  Atezolizumab: 1200 mg Q3W on Day 1
  Carboplatin: AUC 5 mg/mL min (Calvert formula) on Day 1
  Etoposide: 100 mg/m^2 on Days 1–3

Figure 4 Study Schema: Dose-Escalation, Induction (Arm B)



Note: Cohorts may incorporate primary prophylactic growth factor support as described below and in Section 3.1.4.
DLT = dose-limiting toxicity; MTD = maximum tolerated dose; NC = non-continuous; RP2D-I = recommended Phase II dose for induction.

Patients may be treated in up to five NC dosing cohorts (i.e., venetoclax 200 mg Days 1–7 NC, 400 mg Days 1–7 NC, 800 mg Days 1–7 NC, 800 mg Days 1–14 NC, and any of the dose levels integrating primary prophylactic growth factor support). Specifically, at the initiation of the induction phase of dose-escalation Arm B, cohorts will be treated without primary prophylactic growth-colony stimulating factor (G-CSF). If *2 or more patients out* of the *first 6 DLT-evaluable patients* in a *particular* cohort *without primary prophylactic growth factor support experienced neutropenia-related adverse events (Grade 4 neutropenia resulting in treatment delay beyond 14 days or Grade 3–4* febrile neutropenia*),* then that *particular* cohort level will be tested again at the same dose *level* with *mandatory* primary prophylactic growth factor support (see Section 3.1.4 for additional details). Of note, primary G-CSF prophylaxis is only mandated during induction and not during maintenance therapy. Such cohorts will be designated with "-P" to denote the primary G-CSF prophylactic requirement (e.g., Cohort B1-P). Subsequent dose-escalation cohorts will then be required to incorporate primary G-CSF prophylaxis.

Patients will be treated for a total of 4 cycles of study treatment for induction. Each cycle will consist of 21 days. Dose-escalation will continue until DLTs are observed. If there is excessive toxicity and DLTs at the lowest tested venetoclax dose in induction, then venetoclax will be subsequently expanded in the maintenance setting only.

Patients initially treated in the induction arm who tolerate study treatment without excessive toxicity, and have not undergone disease progression, will then proceed to maintenance treatment with venetoclax plus atezolizumab. The venetoclax dose for the maintenance setting in Arm B will be the dose that has been cleared in the maintenance-only arm (Arm A) of the study (maintenance RP2D, RP2D-M). The venetoclax RP2D for the induction setting (induction RP2D, RP2D-I) will be based on the MTD of venetoclax in combination with atezolizumab, carboplatin and etoposide.

During the maintenance phase in either Arm A or Arm B, prophylactic cranial irradiation (PCI) is permitted (though not mandated) prior to the commencement of maintenance therapy per local standard of care. Due to the lack of data with concurrent use of PCI with either atezolizumab or venetoclax, concurrent administration of PCI during maintenance therapy is not permitted. PCI will be reported on the Prophylactic Cranial Irradiation electronic Case Report Form (eCRF). Consolidative thoracic radiation with curative intent or the intent to eliminate residual disease is not permitted. Palliative radiation for symptomatic management is allowed (refer to Section 4.4.1 for further details).

3.1.3 Definition of Dose-Limiting Toxicity

Patients will be closely monitored for adverse events during a DLT assessment period, which starts on Day 1 of Cycle 1 and continues through Day 1 of Cycle 2. *The DLT assessment period is the same for maintenance phase (Arm A) and induction phase (Arm B).* Adverse events meeting criteria for DLT within the assessment period must be

reported to the Sponsor within 24 hours. The expected start of Cycle 2 would be on Day 22 if there are no treatment delays. The same DLT criteria will be used in the maintenance and induction settings.

Determination of whether a patient is evaluable for DLT assessment will be made in accordance with the following rules:

- Patients who receive study treatment and remain on study through the DLT assessment period will be considered DLT-evaluable.
- Patients who discontinue from treatment with venetoclax prior to completing the DLT assessment period for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD determination, and will be replaced by an additional patient at that same dose level.
- Patients who receive less than 50% of planned venetoclax doses during the DLT assessment period will be considered non-evaluable for dose-escalation decisions and will be replaced by another patient in that cohort.

A DLT is defined in this trial as any one of the following events occurring during the DLT assessment period and is assessed by the investigator as possibly being related to study treatment.

The following events will be considered DLTs only if they are associated with treatment delay beyond 14 days in initiating Cycle 2, Day 1:

- Grade 4 thrombocytopenia (platelet count <25,000/mm^3)
- Grade 3 thrombocytopenia with severe bleeding
- Grade 4 anemia
- Grade 4 neutropenia (absolute neutrophil count [ANC] $<$ 500/μL)

The following events will be considered DLTs regardless of whether they result in a treatment delay:

- Any treatment-related death
- Grade 3 febrile neutropenia lasting for more than 7 days with growth factor support and supportive care
- Grade 4 febrile neutropenia of any duration
- Grade $\geq$ 3 diarrhea, nausea, or vomiting lasting for $\geq$ 72 hours despite adequate treatment and supportive care (e.g., anti-emetics, anti-diarrheals, etc.)
- Laboratory TLS lasting for $\geq$ 7 days with best supportive care or clinical TLS according to the Howard criteria (Howard et al. 2011)
- Treatment related Grade $\geq$ 3 non-hematologic, non-hepatic toxicities lasting for $\geq$72 hours

- *Laboratory abnormalities consistent with Hy's Law will be considered a DLT. Hy's Law is defined as AST and/or ALT elevation > 3 ×ULN, in conjunction with an elevation in total bilirubin to > 2 ×ULN, without findings of cholestasis (ALP within normal limits), in patients for whom no other cause of hepatotoxicity is evident.*
- *All study treatment-related adverse events requiring permanent discontinuation of any of the study drugs*

3.1.4 Dose-Escalation Rules, Determination of Dose-Limiting Toxicities, and Recommended Phase II Dose

Dose–escalation for venetoclax in the maintenance only (Arm A) as well as in the induction and maintenance (Arm B) settings will occur in accordance with the rules listed below.

Arm A (Refer to Figure 3):

- A minimum of 3 DLT-evaluable patients will initially be enrolled into each cohort.
- If none of the first 3 DLT-evaluable patients experiences a DLT, enrollment of the next cohort at the next dose level may proceed.
- If 1 of the first 3 DLT-evaluable patients experiences a DLT, the cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, enrollment of the next cohort at the next dose level may proceed.
- If 2 or more of the first 6 DLT-evaluable patients in the cohort experience a DLT, an additional 3 patients will be evaluated for DLTs at a lower dose level. If none of the first 3 DLT-evaluable patients experiences a DLT, the MTD in maintenance will have been reached.
- If 1 of the first 3 DLT-evaluable patients *at a lower* dose level experiences a DLT, *this* cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, the MTD in maintenance will have been reached.
- If 2 or more of the first 6 DLT-evaluable patients in the *lower* dose *level* cohort experience a DLT, the MTD will have been exceeded and dose-escalation in maintenance will stop.
- If the MTD is exceeded at any dose level, the highest dose at which fewer than 2 of 6 DLT-evaluable patients (i.e., ≥ 33%) experience a DLT will be declared the MTD.

  If the MTD is not exceeded at any dose level, the highest dose of venetoclax (800 mg) administered in maintenance will be declared the MTD for the maintenance setting.

Arm B (Refer to Figure 4):

- A minimum of 3 DLT-evaluable patients will initially be enrolled into each cohort.
- If none of the first 3 DLT-evaluable patients experiences a DLT, enrollment of the next cohort at the next dose level may proceed.

- If 1 of the first 3 DLT-evaluable patients experiences a DLT, the cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, enrollment of the next cohort at the next dose level may proceed.
- If 2 or more of the first 6 DLT-evaluable patients in the next cohort at the next dose level experience a DLT, the MTD in induction will have been exceeded and dose-escalation will stop.
- If the MTD is exceeded at any dose level, the highest dose at which fewer than 2 of 6 DLT-evaluable patients (i.e., ≥ 33%) experience a DLT will be declared the MTD.

  If the MTD is not exceeded at any dose level, the highest dose of venetoclax (800 mg NC Day 1–*14*) administered in induction will be declared the MTD for the induction setting.

If a particular cohort in induction dose-escalation (Arm B) exceeds MTD due to DLTs associated with neutropenia or febrile neutropenia without primary prophylactic growth factor support, then that cohort level will be tested again with primary prophylactic growth factor support. For example, if venetoclax 400 mg Day 1–7 exceeds the MTD due to DLTs associated with neutropenia or febrile neutropenia without primary prophylactic growth factor support, then primary prophylactic growth factor support will be implemented in the study and that dose level cohort will be tested again with another 3+3 cohort. Of note, primary G-CSF prophylaxis is only mandated during induction and not during maintenance therapy. Once prophylactic growth factor support is instituted, then this will be required for further escalation cohorts during all induction cycles. For guidance on use of prophylactic growth factor support, please see Appendix 10.

Patients exhibiting acceptable safety and evidence of clinical benefit (as determined by the investigator) may continue to receive study treatment until confirmed objective disease progression or unacceptable toxicity, whichever occurs first.

The Sponsor will review cumulative safety data and make recommendations regarding dose-escalation and overall study conduct on the basis of trial safety data to ensure patient safety while receiving study treatment. These include recommendations to open or suspend patient enrollment in a given dose-escalation cohort based on the overall benefit–risk profile of venetoclax in combination with atezolizumab, carboplatin, and etoposide.

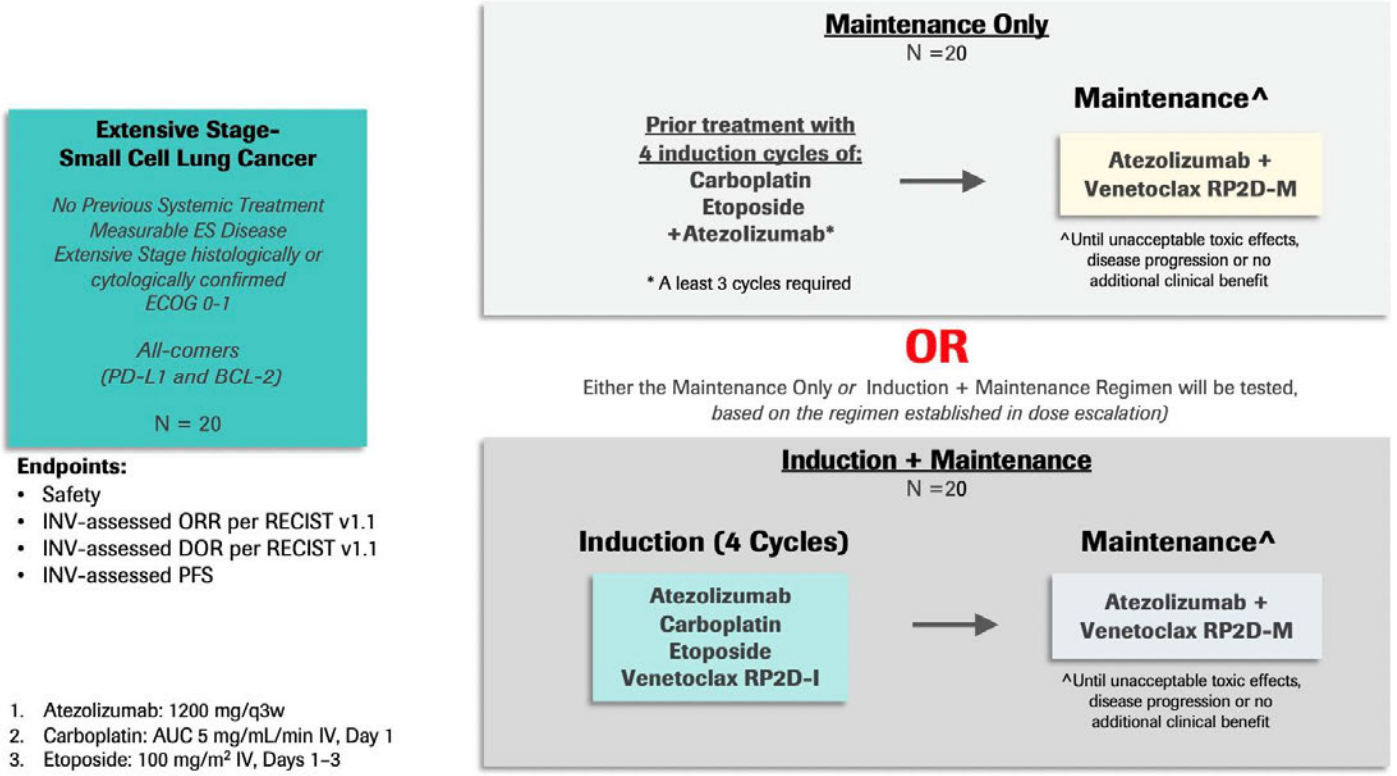
Relevant demographic, adverse event, laboratory, dose administration, and PK data (if available) will be reviewed prior to the selection of a RP2D in the maintenance (RP2D-M) and RP2D in the induction setting (RP2D-I). The RP2D-I will be based on the MTD of venetoclax when combined with standard doses of atezolizumab, carboplatin, plus etoposide and the RP2D-M will be based on the MTD of venetoclax when combined with standard dose of atezolizumab. Both RP2D-I and RP2D-M will integrate aggregate safety data during treatment. Decision making will be led by the Medical Monitor in consultation with the Principal Investigators and a committee composed of at a minimum

the following Sponsor representatives: statistician, safety scientist, PK scientist, and clinical scientist.

3.1.5 Dose-Expansion Cohort

Once the *RP2D* in the induction and in the maintenance *phase* has been established from the dose-escalation cohorts, additional patients will be enrolled in the dose-expansion cohort to further assess the safety and efficacy of venetoclax in combination with carboplatin, etoposide and/or atezolizumab. If *the RP2D* for venetoclax during induction was established, then the dose-expansion cohort will continue to test venetoclax in both induction and maintenance. If significant toxicity and DLTs in induction preclude identification of an *RP2D* for venetoclax in induction treatment, then the safety and efficacy of venetoclax will only be investigated in dose-expansion in the maintenance setting. If the maintenance-only cohort is expanded, then prior treatment with 4 induction cycles of carboplatin and etoposide as well as at least *3* cycles of *atezolizumab* will be required. If there are concerns about the tolerability of venetoclax during the dose-expansion stage, then a lower dose or alternative dosing schedule may be explored based on the severity and timing of DLTs as well as the specific adverse events encountered. For example, consideration may be given to enrolling an expansion cohort at the next lower dose level (as defined in dose-escalation stage; see Section 3.1.2). Decision making will integrate cumulative safety and efficacy data during treatment and will be led by the Medical Monitor in consultation with the Principal Investigators and a committee composed of at a minimum the following Sponsor representatives: statistician, safety scientist, PK scientist, and clinical scientist.

Figure 5 Study Schema: Dose-Expansion Cohort



DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; ES = extensive-stage; INV = investigator; MTD = maximum tolerated dose; ORR = objective response rate; PFS = progression-free survival; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RP2D-I = recommended Phase II dose for induction; RP2D-M = recommended Phase II dose for maintenance; SCLC = small cell lung cancer.

3.1.6 Treatment after Disease Progression

During the study, patients who meet criteria for disease progression per RECIST v1.1 and show evidence of clinical benefit may continue treatment at the investigator's discretion, provided that the patients meet all of the following criteria:

- Evidence of clinical benefit, as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., CNS, leptomeningeal disease, etc.) that cannot be managed by protocol-allowed medical interventions

Investigator assessment of overall tumor response at all timepoints will be based only on RECIST v1.1.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as 6 months after the last patient's radiographic last assessment. The end of the study is expected to occur 24 months after the last patient is enrolled. In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be 31 to 49 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

The current standard of care regimen for the first-line treatment for ES-SCLC in both the United States and European Union is atezolizumab plus CE. Durvalumab plus platinum chemotherapy and etoposide is also regarded as a preferred therapy (NCCN 2019). Despite the survival benefit observed with these regimen, median survival remains at approximately 1 year, leaving considerable room for improvement in outcomes. This study will enroll patients with ES-SCLC who are chemotherapy-naive for their extensive-stage disease, and for whom the experimental therapy can represent a valuable treatment option with a reasonable benefit-risk balance.

This study will enroll patients irrespective of Bcl-2 or PD-L1 expression status. Drug development in SCLC poses its own challenges with rapid clinical deterioration often precluding trial entry. Patients with SCLC frequently present with symptoms of widespread metastatic disease and may experience fast clinical deterioration; therefore, there is a need for rapid treatment initiation for these patients. In addition, tissue sample collection for investigational biomarker testing may be difficult in this patient population because the amount of tissue available in many cases is limited, therefore prospective Bcl-2 biomarker testing will not be performed. Moreover, as the benefit of atezolizumab

plus chemotherapy was observed in all-comer patients in IMpower133, this study will enroll patients with ES-SCLC whose disease is unselected for PD-L1 expression. Pre-treatment tumor tissue samples will be collected to allow for the analysis of biomarkers including but not limited to Bcl-2 and PD-L1 expression with patient outcomes.

3.3.2 Rationale for Venetoclax and/or Atezolizumab Treatment *Beyond* Initial Radiographic Progression

In studies of immunotherapeutic agents, CRs, PRs, and SD 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.

Patients with ES-SCLC experience rapid tumor growth and fast clinical deterioration and have an overall poor prognosis. First-line therapy with atezolizumab plus CE has demonstrated high response rates and significant clinical benefit. However, after disease progression, treatment options are limited and such options have shown limited efficacy and significant toxicity (see Section 1.2). Given that the greatest opportunity to achieve a clinically significant benefit from therapy is in the front-line setting and given the poor efficacy and high toxicity profile of second-line therapies, patients may be considered for treatment beyond radiographic disease progression per RECIST v1.1 at the discretion of the investigator and after appropriate discussion with the patient, only if they meet all of the criteria described in Section 3.1.6.

In addition, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Because of the potential for pseudo-progression/tumor-immune infiltration, this study will allow patients to remain on treatment after apparent radiographic disease progression per RECIST v1.1, provided all criteria in Section 3.1.6 are met. Treatment should be discontinued if clinical deterioration due to disease progression occurs at any time or if persistent disease growth is confirmed in a follow-up scan. In addition, patients should be discontinued for unacceptable toxicity or for any other signs or symptoms of deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status (see Section 4.6.1).

3.3.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered 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, as outlined in the prescribing information. Anti-tumor activity has been observed across doses ranging

from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the MTD of atezolizumab was not reached and no DLTs were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

3.3.2 Rationale for Venetoclax Dosing Schedule

Venetoclax has been investigated in multiple trials of hematologic malignancies as well as solid tumors at doses ranging from 200 mg to 1200 mg, as a monotherapy and in combination with other agents including dexamethasone, rituximab, obinutuzumab, bortezomib, and chemotherapy. Venetoclax is approved in the United States and European Union as monotherapy for the treatment of adult patients with CLL who have received at least one prior therapy. The recommended dose of venetoclax monotherapy in this setting is 400 mg QD in a ramp-up schedule (Venclexta U.S. Package Insert) and the 400 mg QD dosing is maintained during administration with rituximab. Venetoclax is also approved in combination with azacitidine or decitabine or LDAC for the treatment of newly-diagnosed AML and dosing is at 400 mg QD when in combination with azacitidine or decitabine and 600 mg QD when dosing in combination with LDAC.

3.3.2.1 Rationale for Venetoclax Dose Selection for Maintenance in Phase I Dose-Escalation Portion of the Study

For patients in the maintenance phase venetoclax will be administered in combination with atezolizumab at a starting dose of 400 mg continuous QD with potential escalation to a second dose level of 800 mg continuous QD (refer to Section 3.1.1). A 400-mg venetoclax starting dose is considered acceptable based on limited overlapping toxicities and low drug-drug interaction (DDI) potential between the two agents; toxicities from these two agents are expected to be monitorable and manageable.

The safety of continuous daily dosing of single agent venetoclax has been evaluated in hematologic malignancies. In Study M12-175, venetoclax was administered as monotherapy in patients with relapsed refractory CLL and NHL at doses of 150 mg to 1200 mg. The safety profile of venetoclax as monotherapy in NHL was tolerable and manageable, with the most common adverse events including nausea, diarrhea, and fatigue.

The safety of continuous escalating daily dosing of venetoclax up to a maximum of 800 mg in combination with atezolizumab and cobimetinib was evaluated in patients with relapsed or refractory MM in Study BO39813. In this study, venetoclax was well tolerated in combination with atezolizumab and cobimetinib or cobimetinib alone. The nature and frequencies of adverse events were consistent with known safety profiles of the individual agents, and there were minimal overlapping toxicities. Additionally, in a study of relapsed and refractory B-lymphomas (R/R NHLs), venetoclax administered in combination with atezolizumab and obinutuzumab was well tolerated and preliminary

efficacy was shown to be encouraging for a chemo-free regimen in R/R NHLs. Neutropenia was observed with the combination and primary prophylactic growth factor support was instituted (Herbaux et al. 2019). Treatment and follow-up of these patients are currently ongoing.

Furthermore, the safety of an 800 mg dose of venetoclax in SCLC is supported by findings in metastatic breast cancer studies where venetoclax was administered in combination with either tamoxifen or fulvestrant (Lok et al. 2019; Study WO40181). In these studies, 800 mg QD continuous venetoclax was well tolerated, and the nature and frequencies of adverse events were consistent with the known safety profiles of the individual agents. No Grade 5 adverse events or DLTs occurred during the DLT observation period. A ramp-up phase was not incorporated into these studies due to lower expected TLS risk in solid tumors compared to hematological malignancies. It is a well-known fact that TLS is especially common in patients with hematological malignancies with rapid cellular turnover rates such as acute lymphocytic leukemia and Burkitt lymphoma, but is very rare in patients with solid tumors (Mirrakhimov et al. 2014).

The escalation to 800 mg QD continuous venetoclax in maintenance is planned, as patients with solid tumors may require a higher dose of venetoclax when compared with the 400 mg QD label dose in hematologic malignancies such as CLL. Cancer cells in the tumor compartment may be less sensitive to venetoclax than those circulating in the peripheral blood. This is reflected in the lower EC_{50} values of venetoclax for circulating lymphocyte counts (0.00863 µg/mL) compared with tumor size (0.146 µg/mL; Freise et al. 2016). Possible explanations for this observation include (1) reduced blood flow and subsequent less efficient delivery of systemic venetoclax within a tumor; and (2) altered signaling interactions between lymphoma cells and the cells of the tumor microenvironment.

3.3.2.2 Rationale for Venetoclax Dose Selection for Induction in the Phase I Dose-Escalation Portion of the Study

Based on expected overlapping toxicities such as neutropenia, febrile neutropenia, anemia, thrombocytopenia, and gastrointestinal adverse events between venetoclax and chemotherapy, four NC dose-escalation levels, as well as an option to incorporate primary prophylactic treatment with G-CSF, have been selected for dose finding in the induction phase. A conservative and gradual approach to dose escalation is proposed, with a starting dose of 200 mg Day 1–7 NC QD, moving to 400 mg Day 1–7 NC QD, to 800 mg Day 1–7 NC QD, and to 800 mg Day 1–14 NC QD (refer to Section 3.1.1).

The dose finding strategy for the induction phase is supported by data from the VICER Study (venetoclax + rituximab, ifosfamide, carboplatin, and etoposide [R-ICE] in R/R diffuse large B-cell lymphoma [DLBCL]). In this study, venetoclax was given orally on Days 1–10 of each 21-day cycle; R-ICE was given at standard doses and schedule on Days 1–3. NC venetoclax dosing on Days 1–10 of a 21-day cycle (10/21) allowed

manageable and tolerable administration, with escalation of venetoclax doses to 800 mg in combination with R-ICE (Caimi et al. 2018).

Similar to the maintenance phase, the risk for TLS is expected to be low in solid tumors such that venetoclax ramp-up dosing is not required. Nonetheless, TLS labs will be monitored frequently especially in the first cycle and in patients who develop electrolyte changes suggestive of TLS will undergo aggressive management and further monitoring (refer to Appendix 11 for detailed guidance on TLS prophylaxis).

3.3.2.3 Rationale for Preferential Venetoclax Dose Modifications in the Setting of Overlapping Toxicities

Dose delays and dose modifications as a result of adverse events should proceed on the basis of the principle of maintaining the dose intensity of atezolizumab, carboplatin, and etoposide. The determination of dose modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment in consultation with and with the approval of the Medical Monitor.

In the event of high-grade hematologic toxicities such as neutropenia, febrile neutropenia, thrombocytopenia (overlapping toxicities for venetoclax and carboplatin etoposide), and high-grade gastrointestinal toxicities such as diarrhea (overlapping toxicity for venetoclax, atezolizumab, carboplatin, and etoposide), the dose of venetoclax should be reduced as per Table 6. The dose of carboplatin and etoposide should be reduced per standard guidance provided in Table 7. No dose reduction of atezolizumab is permitted in the study.

In each specific portion of study treatment (induction vs. maintenance), no re-escalation of venetoclax dose is allowed after dose reduction. The dose level of venetoclax in the maintenance portion (RP2D-M) identified in Arm A will not be affected by venetoclax dose reductions during the induction phase. The dose of carboplatin and etoposide can be re-escalated (even to full dose) with the approval of the Medical Monitor. For more details, see Sections 5.1.5 and 5.1.6.

3.3.3 Rationale for Dose Finding Rules

The rules for dose escalation are designed to ensure patient safety while providing an opportunity to identify the optimal venetoclax dose and schedule in combination with atezolizumab, carboplatin, and etoposide to maximize the benefit-risk profile of the combination. Key elements of dose escalation based on a standard 3+3 design are described in Section 3.1.

Rules based on the nature and timing of observed safety events have been implemented.

3.3.4 Rationale for Biomarker Assessments

SCLC is a heterogeneous disease, with PD-L1 and Bcl-2 expression having been shown to vary among patients (Ben-Ezra et al. 1994; Kaiser et al. 1996). All patients may not be equally likely to benefit from treatment with venetoclax and atezolizumab, carboplatin, and etoposide. Predictive biomarker samples (tissue and blood) collected prior to dosing will be assessed in an effort to identify those patients who are most likely to respond to venetoclax and atezolizumab, carboplatin, and etoposide. Pharmacodynamic biomarkers (tissue and blood) will be assessed to demonstrate evidence of biologic activity of venetoclax and atezolizumab, carboplatin, and etoposide in patients, to support selection of a recommended dose and dosing regimen, and to inform potential revisions to the PK sample collection schedule. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

Bcl-2 expression may have a prognostic role in SCLC, with improved survival in SCLC patients being observed in the context of lower Bcl-2 expression, consistent with in vitro data. A study evaluating Bcl-2 staining in 140 patients samples using tissue microarray indicated that patients with low intensity staining had better OS than those with high intensity staining in a Cox regression analysis (HR: 0.55; 95% CI: 0.33 to 0.94; $p = 0.03$; $n = 117$). The meta-analysis included 510 deaths in 673 cases and showed no significant effect of Bcl-2 on survival (HR: 0.91; 95%: CI 0.74 to 1.09). This may be due to differences in staining and scoring methods between the studies (Lawson et al. 2010).

Predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients with Bcl-2-driven pathogenesis who are most likely to respond to venetoclax. The study aims to explore if Bcl-2 expression might have predictive or prognostic value or may be associated with disease progression in the studied population.

Fresh tissue acquisition in some patients with SCLC may not be feasible; consequently, assessment of more easily accessible biomarkers in circulation is of high interest. In addition to identification of disease-specific, potentially prognostic, or predictive biomarkers in predose, baseline blood specimens, on-treatment collection of blood to evaluate circulating tumor DNA (ctDNA) and other circulating markers may enable identification of biomarkers informing the relationship with established clinical response assessments, the monitoring of disease progression, and the identification of markers of resistance.

Tumor tissue samples will be analyzed through use of IHC to assess protein expression, and/or RNA sequencing to assess gene expression levels. Both tissue and blood samples will be analyzed by next-generation sequencing (NGS) to identify somatic alterations that are predictive of response to study drug, are associated with progression, are associated with acquired resistance to study drug, or can increase the knowledge and understanding of disease biology.

Tissue samples will be collected for DNA extraction to enable whole genome sequencing (WGS) or whole exome sequencing (WES) to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 18–42 patients will be enrolled in the dose-escalation cohorts. An additional estimated 20 patients will be enrolled in the dose-expansion cohort of this study.

4.1.1 Inclusion Criteria

Dose Escalation, Maintenance Arm A

- Patients with ES-SCLC who have completed 4-6 cycles of carboplatin and etoposide induction chemotherapy, with or without *atezolizumab*, as their first-line therapy for extensive-stage disease and have responded (CR or PR) or have SD are eligible for the maintenance arm of the study.
- All side effects attributed to prior anti-cancer therapy must have resolved to Grade 1 or baseline.
- A maximum of 8 weeks (56 days) is allowed between last chemotherapy dose (Cycle 4, Day 3) given in induction and the start of maintenance therapy.

Dose Escalation, Induction Arm B

- Patients with no prior systemic treatment for ES-SCLC are eligible for this study.
- ANC ≥ 1,500 cells/μL without granulocyte colony-stimulating factor support

Dose Expansion, Maintenance-Only

- Patients with ES-SCLC who have completed 4 cycles of carboplatin and etoposide induction chemotherapy and at least *3* cycles of *atezolizumab* as their first-line therapy for extensive-stage disease and have *responded (CR or PR) or have* SD are eligible for the maintenance arm of the study.

Dose Escalation (Arms A and B) and Dose Expansion

- Signed Informed Consent Form
- Age ≥18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- ECOG performance status of 0 or 1
- Patients must be able to swallow pills
- Histologically or cytologically confirmed diagnosis of ES-SCLC per the Veterans Administration Lung Study Group (VALG) staging system
- Patients who received prior chemoradiotherapy for limited-stage SCLC must have been treated with curative intent and experienced a treatment-free interval of at least 6 months since last chemotherapy, radiotherapy, or chemoradiotherapy cycle prior to diagnosis of ES-SCLC
- Patients with a history of treated CNS metastases that are currently asymptomatic are eligible, provided they meet all of the following criteria:
  - Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)
  - No ongoing requirement for corticosteroids as therapy for CNS disease
  - No evidence of interim progression between the completion of CNS-directed therapy and enrollment
  - Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to enrollment, if all other criteria are met.
- Measurable disease, as defined by RECIST v1.1. Baseline measurements and evaluation of all sites of disease must be obtained ≤ 4 weeks prior to enrollment.
  - Previously irradiated lesions can only be considered as measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of disease.
- Eligible to receive a carboplatin-based chemotherapy regimen

- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to enrollment:
  - ANC ≥ 1500 cells/μL (without granulocyte-colony stimulating factor support within 7 days prior to Cycle 1, Day 1)
  - Lymphocyte count ≥ 500 cells/μL
  - Platelet count ≥ 100,000 cells/μL without transfusion
  - Hemoglobin ≥ 9.0 g/dL

    Patients may be transfused to meet this criterion.
  - INR or aPTT ≤ 1.5 × ULN

    This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose and with INR ≤ 3.5 × ULN.
  - AST (SGOT), ALT (SGPT), and alkaline phosphatase ≤ 2.5 × ULN with the following exceptions:

    Patients with documented liver metastases: AST and/or ALT ≤ 5 × ULN

    Patients with documented bone or liver metastases: alkaline phosphatase ≤ 5 × ULN
  - Serum total bilirubin ≤ 1.5 × ULN

    Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.
  - *Albumin ≥25 g/L (2.5 g/dL)*
  - Creatinine clearance (CRCL) ≥ 50 mL/min calculated with the use of the 24-hour CRCL or modified Cockcroft-Gault equation (i.e., estimation of creatinine clearance rate [eCCr]) with the use of ideal body mass (IBM) instead of mass:

    $$\text{eCCr} = \frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$

    Or, if serum creatinine is in μ mol/L:

    $$\text{eCCr} = \frac{(140 - \text{age}) \times \text{IBM (kg)} \times (1.04 \text{ if female})}{\text{serum creatinine } (\mu \text{ mol/L})}$$

- Patients must submit a pre-treatment tumor tissue sample. Any available tumor tissue sample can be submitted (fresh, paraffin-embedded tissue block, or serial cut slides [15 preferred]). The tissue sample should be submitted before or within 4 weeks after enrollment; however, patients may be enrolled into the study before the pre-treatment tumor tissue sample is submitted. If tissue is not available, approval from the Medical Monitor is required before enrolling.
- Patients must submit a blood sample for exploratory biomarker research before treatment, on-study, and following progression of disease.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use non-hormonal contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 30 days after the final dose of venetoclax, 5 months after the final dose of atezolizumab, or 6 months after the final dose of carboplatin or etoposide, whichever is longer. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq$ 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.

- Women who are not postmenopausal ($\geq$12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.

  If a serum pregnancy test has not been performed 14 days prior to dosing, a urine pregnancy test must be performed 7 days prior to dosing. If the test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.

- 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 partners, 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 treatment with chemotherapy (i.e., carboplatin and etoposide) and for at least 6 months after the final dose of carboplatin or etoposide 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, sympotothermal, or postovulation methods) 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.

4.1.2 Exclusion Criteria

- Use of non–protocol-specified anti-cancer therapies or other combination partners with carboplatin/etoposide during induction
- Symptomatic or actively progressing CNS metastases

  Note: Asymptomatic patients with treated (i.e., local CNS-directed therapy) or untreated CNS lesions 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 from CNS disease.
  - Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
  - The patient has no symptoms caused by CNS disease (i.e., no headache, nausea, vomiting, convulsion, paralysis, etc.).
  - The patient has no ongoing requirement for anticonvulsants for CNS disease.
  - The patient has no ongoing requirement for dexamethasone/corticosteroids for CNS disease (previously untreated patients must also not have any history of requiring or receiving dexamethasone/corticosteroids for CNS disease).
  - For patients with previously treated CNS metastases, there is no evidence of interim CNS progression between the completion of CNS-directed therapy and enrollment.
  - For previously untreated patients, there is no evidence of brain edema related to CNS disease (e.g., vasogenic edema).
  - For previously untreated patients, a brain magnetic resonance imaging (MRI) scan with contrast is required at screening and is the preferred modality for all subsequent scheduled follow-up tumor assessments.

    Note: Computed tomography (CT) scan with contrast may be acceptable for all subsequent scheduled follow-up tumor assessments if the following criteria are met.

    - Both brain MRI and CT scan with contrast must be performed at screening to assess untreated CNS disease.

  - The CT scan with contrast can be used to reliably evaluate lesions identified on the screening MRI with contrast.

    If CT scan with contrast cannot be used to reliably evaluate lesions identified on the screening MRI with contrast, then MRI scan with contrast must be used at all subsequent scheduled follow-up tumor assessments.

    The same modality must be used at every tumor assessment.

- Pregnant or breastfeeding, or intending to become pregnant during the study

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

- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for $\geq$1 week prior to enrollment
- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once a month or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed regardless of drainage frequency.

- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$1.5 mmol/L, total serum calcium $>$12 mg/dL, or corrected calcium $>$ULN)
- History of malignancy other than SCLC within 5 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS >90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell cancer of the skin, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.

  Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen are eligible for this study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., no psoriatic arthritis) are permitted provided that they meet the following conditions:

  - Rash must cover less than 10% of body surface area.

  - Disease is well-controlled at baseline and only requiring low potency topical steroids.
  - No acute exacerbations of underlying condition within the last 12 months requiring treatment with either psoralen plus ultraviolet A radiation (PUVA), methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral topical steroids

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- Positive test result for HIV

  All patients must be tested for HIV; patients who test positive for HIV will be excluded.

- Active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test result at screening) or hepatitis C virus (HCV)

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. HBV DNA should be obtained in these patients prior to enrollment and should be undetectable. These patients must be willing to undergo monthly DNA testing.

  Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

- Active tuberculosis
- Known infection with human T-cell leukemia virus 1
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within the previous 3 months, unstable arrhythmias, or unstable angina

  Patients with known coronary disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

- Major surgical procedure within 28 days prior to enrollment or anticipation of need for major surgical procedure during the course of the study
- Prior allogenic bone marrow transplantation or solid organ transplant

- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk for treatment complications
- Illnesses or conditions that interfere with their capacity to understand, follow, and/or comply with study procedures
- Treatment with investigational therapy with therapeutic intent within 28 days prior to enrollment
- Administration of a live, attenuated vaccine within 4 weeks before enrollment or anticipation that such a live attenuated vaccine will be required during the study

    Patients must not receive live, attenuated influenza vaccines (e.g. FluMist®) within 4 weeks prior to enrollment, during treatment, and for 5 months following the last dose of atezolizumab or chemotherapy.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1, and anti-PD-L1 therapeutic antibodies
- Treatment with systemic immunosuppressive medications (including, but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 1 week prior to enrollment

    Patients who have received acute systemic immunosuppressant medications (e.g., use of corticosteroids for nausea, vomiting, or management of or premedication for allergic reactions) may be enrolled in the study after discussion with and approval by the Medical Monitor. In those patients, the need and length of the washout period prior to enrollment will also be established in conjunction with the Medical Monitor.

    The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of allergic reactions to carboplatin or etoposide or to any of its excipients (etoposide)
- Known hypersensitivity to venetoclax or to any of its excipients

- Administration of the following agents within 7 days prior to the first dose of study drug:
  - Steroid therapy for anti-neoplastic intent (stable steroid mediation not more than 10 mg prednisolone per day or an equivalent dose of other corticosteroids for controlling CNS metastases is acceptable)
  - Strong or moderate CYP3A inhibitors (see Appendix 6 for examples)
  - Strong or moderate CYP3A inducers (see Appendix 6 for examples)

  Additional restrictions for on-study use of CYP3A inhibitors/inducers are outlined in Section 4.4.2.
- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade-containing Seville oranges), or starfruit (carambola) within 3 days before within 3 days prior to the first dose of study drug
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Inability or unwillingness to swallow a large number of tablets
- History of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a non-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 treatment assignment from an interactive voice or web-based response system (IxRS).

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMP) for this study are atezolizumab and venetoclax. Carboplatin and etoposide are background treatments and are thus considered non-investigational medicinal products (NIMPs) in this study.

Rescue medications pre-medications, and supportive medications such as acetaminophen, ibuprofen, diphenhydramine, famotidine, cimetidine and other antihistamines, antipyretics, analgesics, corticosteroids, G-CSF, H_2-receptor antagonists, β_2-adrenergic agonists are also considered NIMPs in this study.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 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 formulation and handling of atezolizumab, refer to the Atezolizumab Pharmacy Manual and Investigator's Brochure.

4.3.1.2 Venetoclax

Patients will self-administer venetoclax tablets by mouth daily. Venetoclax is formulated as 100-mg tablets; patients may take up to eight 100-mg tablets daily to receive an 800-mg continual dose. Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after the patient's first meal of the day (e.g., breakfast). For continuous venetoclax dose (Days 1–21), patients should continue taking venetoclax without a break between cycles.

For information on the formulation and handling of venetoclax, refer to the Venetoclax Pharmacy Manual and Investigator's Brochure.

4.3.1.3 Carboplatin and Etoposide

Carboplatin and etoposide will be used in the commercially available formulation.

For information on the formulation, packaging, and handling of carboplatin and etoposide, refer to the prescribing information for each drug.

4.3.2 Study Treatment Dosage, Administration, Sequence, and Compliance

Atezolizumab will be given at fixed dose of 1200 mg by IV infusion every 21 [±2] days in both induction and maintenance. For more information on the formulation, packaging, and handling of atezolizumab, please refer to the prescribing information.

Carboplatin and etoposide induction therapy will be administered as follows:

During induction, patients will be treated with carboplatin and etoposide chemotherapy. For information on the formulation, packaging, and handling of these therapies, please see the prescribing information for each drug.

Standard doses of each agent will be administered for a total of four 21-day cycles during induction.

- Carboplatin AUC 5 mg/mL min (Calvert formula dosing) IV infusion over 30–60 minutes on Day 1 of each cycle after completion of atezolizumab IV infusion with standard anti-emetics per local practice guidelines.

- Etoposide 100 mg/m^2 IV on Days 1–3 of each cycle. On Day 1 of each cycle, etoposide should be administered intravenously over 60 minutes following carboplatin administration. On Days 2 and 3 of each cycle, etoposide (100 mg/m^2) should be administered intravenously over 60 minutes. Premedication should be administered according to local standard of care.

On Day 1 of each cycle, all eligible patients will receive treatment in the following order:

Induction: atezolizumab → carboplatin → etoposide→ venetoclax

Maintenance: atezolizumab → venetoclax

On Days 2 and 3, patients will receive etoposide infusions.

Because the effects of corticosteroids on T-cell proliferation have the potential to attenuate atezolizumab-mediated anti-tumor immune activity, premedication with corticosteroids should be minimized to the extent that is clinically feasible. Secondly, at the initiation of the induction phase of dose-escalation Arm B, cohorts will be treated without primary prophylactic G-CSF. The administration of secondary prophylactic G-CSF for high-frequency febrile neutropenia, severe neutropenia, or prolonged neutropenia must be discussed and agreed upon between the investigator and the Medical Monitor. Please refer to Appendix 10 or administration details, which are in accordance with institutional standards and ASCO, NCCN, or ESMO guidelines. Of note, if and once primary prophylactic G-CSF is deemed to be necessary as determined in the dose-escalation phase (see Section 3.1.2.2), then this requirement will be implemented during induction therapy for all subsequent patients.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

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 8. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Cycles in which no chemotherapy is given do not count toward the total number of induction chemotherapy cycles.

After the induction phase, patients will begin maintenance therapy with atezolizumab plus venetoclax.

The suggested infusion times for carboplatin and etoposide may be adapted in accordance with local standard of care.

Any dose modification should be noted on the Study Drug Administration 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.

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 8.

Guidelines for dose modification and treatment interruption or discontinuation for carboplatin and etoposide are provided in Sections 5.1.5 and 5.1.5.3.

4.3.2.1 Atezolizumab

All patients will receive 1200 mg atezolizumab administered by IV infusion on Day 1 of each 21-day cycle. The atezolizumab dose is fixed and is not dependent on body weight. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in Appendix 10 and Appendix 13. Guidance on study drug administration in the context of management of specific adverse events is provided in Section 5.

For further details on dose preparation, storage, and administration instructions for atezolizumab, please refer to the pharmacy manual and/or the Atezolizumab Investigator's Brochure.

4.3.2.2 Venetoclax

At the start of each cycle, patients will be supplied with sufficient venetoclax tablets for that cycle. A drug diary will be provided to the patient to record oral administration of doses, including the date and time of dosing. Patients will be instructed to return empty bottles or unused tablets.

The investigator is responsible for monitoring patient compliance by monitoring the patient diary and counting unused tablets. Patient compliance with the assigned daily dose of study medication will be assessed by standard pill counts. Previously distributed bottles will be returned to the clinic and tablets counted. Any discrepancy will be resolved with the patient at each clinic visit and documented in the patient record.

Each dose of venetoclax will be taken orally once daily with approximately 240 mL of water within approximately 30 minutes after the completion of breakfast or patient's first meal of the day. Patients should self-administer venetoclax at approximately the same time each morning. On days that PK sampling is required, the patient's first meal of the day and all study treatment doses should occur in the clinic to ensure accurate timing of the PK sampling. On those days, the time of each dose of venetoclax will be recorded to the nearest minute.

A meal containing approximately 30% of the total caloric content from fat is recommended to ensure adequate absorption of venetoclax. The following is an example of a breakfast that contains approximately 520 Kcal and has 30% of the total caloric content of the meal from fat that is, approximately 17 grams of fat: one box

cereal (30–40 g), skim milk (240 mL), one boiled egg, one slice of toast (15 g) with 1 tablespoon of margarine (14 g). The toast and margarine may be replaced with one medium croissant or two large pancakes. If there is a substantial period of time between the patient's regular time of breakfast and their venetoclax dosing in the clinic on PK sampling days, the patients may have a low-fat snack in the morning. The patients must be instructed not to take their study treatment with the snack and to take their study treatments in the clinic after a meal.

Venetoclax tablets should be swallowed whole and never be chewed, cut, or crushed. If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another venetoclax dose should be taken, and the second dose should be noted in the drug diary. If tablets are not intact or if vomiting occurs more than 15 minutes after taking venetoclax, no replacement dose is to be taken. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose with food as soon as possible, ensuring that the dose is taken within 8 hours of the missed dose. Otherwise, the dose should not be taken.

Following the administration of atezolizumab and an observation period (see Table 2), patients will receive venetoclax.

Guidance on study drug administration in the context of management of specific adverse events is provided in Section 5.

Table 2 Administration of First and Subsequent Atezolizumab Infusions

	First Infusion	Subsequent Infusions
Atezolizumab infusion	• No premedication is allowed for the first infusion of atezolizumab. • Record the patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) within 60 minutes prior to starting the infusion of atezolizumab. • Infuse atezolizumab 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.	• If the patient experienced an IRR during any previous infusion of atezolizumab, premedication with an antihistamine and/or antipyretic may be administered for Cycle ≥ 2 and beyond at the discretion of the treating physician. • Record the patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) within 30 minutes before starting the infusion of atezolizumab. • If the patient tolerated the first infusion of atezolizumab well without infusion-associated adverse events, the next infusion of atezolizumab may be infused over 30 (± 10) minutes. • If no reaction occurs, continue subsequent infusions of atezolizumab over 30 (±10) minutes. • Continue to record vital signs within 30 minutes before starting the infusion of atezolizumab. • Record vital signs during the infusion of atezolizumab if clinically indicated.
Observation period after infusion of atezolizumab	• After the infusion of atezolizumab, the patient begins a 60minute observation period. • Record the patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) at 30 (±10) minutes after the infusion of atezolizumab.	• If the patient tolerated the first or a subsequent infusion of atezolizumab (without premedication) well without infusion-associated adverse events, the observation period after the next and following infusions may be reduced to 30 minutes. • If the patient experienced infusion-associated adverse events in the previous infusion, the observation period should be 60 minutes. • If clinically indicated, record the patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) at 15 (±10) minutes after the infusion of atezolizumab.

IRR = infusion-related reaction.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 13.

4.3.2.3 Atezolizumab/Venetoclax

The following rules apply as long as neither atezolizumab nor venetoclax has been permanently discontinued:

- Treatment cycles will normally begin with dosing of atezolizumab on Day 1 of each 21-day cycle. If atezolizumab is delayed for related toxicity, it is recommended that the venetoclax is also delayed. However, if venetoclax is delayed for related toxicity, atezolizumab may be continued, if considered appropriate at the discretion of the investigator.
- In case of delays in dosing of one study drug (atezolizumab or venetoclax) for drug-related toxicity while the other study drug (atezolizumab or venetoclax) is given as planned, it is recommended that the study drug being delayed be administered at the next scheduled infusion (i.e., at the next scheduled 21-day cycle).

Carboplatin and/or etoposide may be administered as planned in the event that atezolizumab and/or venetoclax dose(s) are delayed. If carboplatin and/or etoposide doses must be delayed, atezolizumab and/or venetoclax may be administered as planned.

Guidelines for treatment interruption or discontinuation are provided in Sections 4.6.1 and 5.1.5.

4.3.2.4 Carboplatin and Etoposide

Carboplatin

During the induction phase, carboplatin will be administered after completion of atezolizumab by IV infusion over 30–60 minutes to achieve an initial target AUC of 5 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines. Because the effects of corticosteroids on T-cell proliferation have the potential to attenuate atezolizumab-mediated anti-tumor immune activity, premedication with corticosteroids should be minimized to the extent that is clinically feasible (see Section 4.4.2). Carboplatin infusion times may be adapted in accordance with local standard of care.

The carboplatin dose of AUC 5 will be calculated using the Calvert formula (Calvert et al. 1989):

Calvert Formula

$$\text{Total dose (mg)} = (\text{target AUC}) \times (\text{glomerular filtration rate [GFR]} + 25)$$

NOTE: The GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min.

For the purposes of this protocol, the GFR is considered to be equivalent to the CRCL. The CRCL is calculated by institutional guidelines or by the method of Cockcroft and Gault (1976) using the following formula:

$$\text{CRCL} = \frac{(140 - \text{age}) \times (\text{wt})}{72 \times \text{Scr}} \quad (\times 0.85 \text{ if female})$$

Where: CRCL = creatinine clearance in mL/min
age = patient's age in years
wt = patient's weight in kg
Scr = serum creatinine in mg/dL

NOTE: For patients with an abnormally low serum creatinine level, estimate the GFR through use of a minimum creatinine level of 0.8 mg/dL or cap the estimated GFR at 125 mL/min.

If a patient's GFR is estimated based on serum creatinine measurements by the isotope dilution mass spectroscopy method, the U.S. Food and Drug Administration (FDA) recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. On the basis of the Calvert formula described in the carboplatin label, the maximum doses can be calculated as follows:

$$\text{Maximum carboplatin dose (mg)} = \text{target AUC (mg} \times \text{min/mL)} \times (\text{GFR} + 25 \text{ mL/min})$$

The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC = 5, the maximum dose is 5 x (125 + 25) = $5 \times 150 = 750$ mg.
For a target AUC = 4, the maximum dose is 4 x (125 + 25) = $4 \times 150 = 600$ mg.

Refer to the FDA's communication regarding carboplatin dosing with use of the following Web site for more details:

http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm228974.htm

Guidelines for treatment interruption or discontinuation are provided in Sections 4.6.1 and 5.1.5.

Etoposide

During the induction phase, on Day 1 of each cycle, etoposide (100 mg/m^2) will be administered by IV infusion over 60 minutes following carboplatin administration. On Days 2 and 3 of each cycle, etoposide (100 mg/m^2) will be administered by IV infusion over 60 minutes. Premedication should be administered according to local standard of care. Because the effects of corticosteroids on T-cell proliferation have the potential to attenuate atezolizumab-mediated anti-tumor immune activity, premedication with

corticosteroids should be minimized to the extent that is clinically feasible (see Section 4.4.2). Etoposide infusion times may be adapted in accordance with local standard of care.

Guidelines for treatment interruption or discontinuation are provided in Sections 4.6.1 and 5.1.5.

Refer to the local prescribing information for material on potential drug interactions between etoposide or carboplatin and concomitant medications.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. 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 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 the Drug Inventory Log.

4.3.4 Continued Access to Atezolizumab and Venetoclax

The Sponsor will offer continued access to Roche IMPs venetoclax and atezolizumab free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMPs venetoclax and atezolizumab after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMPs venetoclax and atezolizumab after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)

- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for breast cancer
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for breast cancer
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

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

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

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 treatment from 7 days prior to initiation of study drug to the study completion/treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 4.1.1)
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated influenza vaccinations
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease (COPD) or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
    - Patients who received acute, low-dose systemic immunosuppressant medication 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 after Medical Monitor confirmation has been obtained.

- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

    In patients without documentation of progression of disease, it is strongly encouraged to maximize supportive care for symptomatic management and avoid radiotherapy that will interfere with the assessment of target lesions.

    Treatment with venetoclax and atezolizumab may be continued during palliative radiotherapy.

  Definitive radiotherapy with curative intent (not palliative) is not permitted.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-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 8).

4.4.2 Prohibited and Cautionary Therapy

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 local therapy under certain circumstances (see Section 4.4.1 for details).
- Investigational therapy is prohibited within 21 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 atezolizumab and/or venetoclax treatment, and for 5 months after the final dose of atezolizumab and at least 28 days after the final dose of venetoclax.

- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 drug-elimination half-lives (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.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.
- Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator. Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 13 for details).
    - Patients who received acute, low-dose systemic immunosuppressant medication 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 after Medical Monitor confirmation has been obtained.
    - Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for COPD or asthma, or low-dose mineralocorticoids for orthostatic hypotension or low-dose mineralocorticoids and corticosteroids for adrenal insufficiency are eligible for the study.

Some additional therapies are prohibited only for specific study phases, or are allowed with caution, restrictions, and/or dose adjustments. These are described in Table 3 and are to be implemented after relevant exclusion criteria for these medications are met (see Section 4.1.2).

Of particular note, venetoclax is a substrate of CYP3A and therefore venetoclax exposure can be impacted by concomitant strong and moderate of CYP3A inducers and inhibitors.

Relevant restrictions and dosing recommendations for concurrent CYP3A inhibitors/inducers are described in *Table 3 and* Table 4.

After discontinuation of a moderate or strong CYP3A inhibitor that led to a venetoclax dose reduction as per the following guidelines, the investigator should wait for 3 days before increasing the venetoclax dose back to the original maintenance/target dose.

Table 3 Therapies Prohibited for Specific Study Phases, or Allowed with Caution, Restrictions, and/or Dose Adjustments

Therapy	Phase Ib Dose Escalation		Phase Ib *Dose* Expansion
	DLT Window [a]	Post DLT Window [a] at Cohort-Designated Dose	Cohort-Designated Dose
Strong CYP3A inhibitors [b]	Prohibited	Avoid and consider alternative medications. Consult with the Medical Monitor if considering use. If usage is approved by the Medical Monitor, reduce venetoclax dose by at least 4-fold (see Table 4) and follow applicable local prescribing information.	
Moderate CYP3A inhibitors [b]	Prohibited	Avoid and consider alternative medications. Consult with the Medical Monitor if considering use. If usage is approved by the Medical Monitor, reduce venetoclax dose by 2-fold (see Table 4).	
Strong CYP3A inducer [b]	Prohibited		
Moderate CYP3A inducer [b]	Prohibited		Exclude through completion of the first cycle of venetoclax. After the first cycle, avoid and consider alternative medications with less induction. If used, contact the Medical Monitor for guidance.
P-gp inhibitors [b]	If P-gp inhibitor must be used, monitor closely for toxicities and follow the applicable local prescribing information		
P-gp substrates [b]	Concomitant use of narrow therapeutic index P-gp substrates should be avoided. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax.		
Warfarin and coumarin derivatives (*e.g.*, phenprocoumon)	Use with caution with close monitoring of the international normalized ratio (INR).		

Table 3 Therapies Prohibited for Specific Study Phases, or Allowed with Caution, Restrictions, and/or Dose Adjustments (cont.)

Therapy	Phase Ib Dose Escalation		Phase Ib *Dose* Expansion
	DLT Window [a]	Post DLT Window [a] at Cohort-Designated Dose	Cohort-Designated Dose
Corticosteroids and TNF-α inhibitors	These medications may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Consider alternatives, including antihistamines in situations where these medications would be routinely administered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator. Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (see Appendix 13).		

DLT = dose-limiting toxicity; P-gp = P-glycoprotein.

[a] DLT window applicable to dose-escalation stage only.

[b] See Appendix 6 for examples of CYP3A inhibitors/inducers and P-gp substrates/inhibitors.

Table 4 Venetoclax Dose Reductions for Strong and Moderate CYP3A Inhibitors

Venetoclax Assigned Dose (mg)	Venetoclax Reduced Dose (mg)	
	Strong CYP3A Inhibitors	Moderate CYP3A Inhibitors
200	Consult with Medical Monitor	100
400	100 (70 for posaconazole in U.S. and countries with USPI-based approval)	200
600		300
800	200	400

U.S. = United States; USPI = United States Prescribing Information.

Appendix 6 contains examples of CYP3A4 inhibitors/inducers and P-gp substrates/inhibitors. Additional examples of these classes of medications are provided at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

The above lists of medications are not necessarily comprehensive; the investigator should also consult the prescribing information for any concomitant medication when determining the DDI potential.

In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed. A decision may be made to allow the use of prohibited medications on a case by case basis, following discussion with the Medical Monitor and assessment of the benefit–risk ratio.

Patients who require the use of any therapies when they are prohibited (unless an allowance is made after consultation with the Medical Monitor) will be discontinued from study treatment and followed for safety outcomes for 4 weeks after the last dose of study treatment or until initiation of another subsequent anti-cancer therapy, whichever comes first.

Refer to the local prescribing information for information on potential drug interactions between etoposide or carboplatin and concomitant medications.

4.4.2.1 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 4.4.2 may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Food

Use of the following foods is prohibited for at least 3 days prior to initiation of treatment, throughout venetoclax administration and for 28 days after last dose of study treatment.

- Constituents of these foods have been shown to inhibit CYP3A4, the major enzyme responsible for the metabolism of venetoclax. Consumption of these foods could lead to increased venetoclax exposure:
  - Grapefruit
  - Grapefruit products
  - Seville oranges (including marmalade-containing Seville oranges)
  - Star fruit (carambola)

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 and Appendix 2. All activities should 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 dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

Screening tests and evaluations will be performed within 28 days prior to Day 1 of Cycle 1. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 of Cycle 1 may be used; such tests do not need to be repeated for screening.

All treatment visits must occur ± 3 days from the scheduled date unless otherwise noted (see Appendix 1 and Appendix 2). All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion unless otherwise noted.

If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule. If treatment was postponed for fewer than 3 days, the patient can resume the original schedule.

The following assessments may be performed ≤ 96 hours before Day 1 of each cycle:

- ECOG performance status
- Limited physical examination
- Local laboratory tests

Screening assessments performed ≤ 96 hours before Day 1 of Cycle 1 are not required to be repeated on Day 1 of Cycle 1.

4.5.1 Informed Consent Forms and Screening Log

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.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, 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. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. 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, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions 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, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Vital signs should be measured within 60 minutes prior to each atezolizumab infusion and, if clinically indicated, during or after the infusion. In addition, vital signs should be

measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1 and Appendix 2).

For the first infusion of atezolizumab, measure vital signs every 15 (±5) minutes during the infusion and within 30 (±10) minutes after the infusion. For subsequent administration of atezolizumab, measure vital signs during each infusion only as clinically indicated and within 15 (±10) minutes after the end of each infusion. Additional vital signs should be measured during the infusion if clinically indicated or if symptoms occurred in the prior infusion.

Table 5 Timing for Vital Sign Measurements for First and Subsequent Infusions

Drug	Timing for Vital Sign Measurements	
	First Infusion	Subsequent Infusions
Atezolizumab	• Within 60 minutes prior to the atezolizumab infusion • Record patient's vital signs during or after the infusion if clinically indicated.	• Within 60 minutes prior to the atezolizumab infusion • Record patient's vital signs during or after the infusion if clinically indicated

4.5.5 Tumor and Response Evaluations

Screening and subsequent tumor assessments must include CT scans (with oral and/or IV contrast unless contraindicated). A CT scan of the pelvis is required at screening and as clinically indicated or as per local standard-of-care at subsequent response evaluations. MRI scans with contrast of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance).

A CT (with contrast) or MRI scan with contrast (if CT contrast is contraindicated) of the head must be done at screening to evaluate CNS metastasis in all patients. If CT with contrast is performed and the presence of brain metastases is considered equivocal, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline.

Patients with active or untreated symptomatic CNS metastases are not eligible for the study (see Section 4.1.2). Patients with untreated asymptomatic CNS metastasis at screening may be eligible. For untreated patients, brain MRI scan with contrast at screening is required, and need to meet all eligibility criteria as specified in Section 4.1.2.

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.

Further investigations such as 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.

Tumor assessments performed as standard-of-care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. All known sites of disease, including measurable and/or non-measurable disease, must be documented at screening and re-assessed at each subsequent tumor evaluation.

At subsequent (post-screening) tumor assessments, patients with a history of treated brain metastases at screening are not required to undergo brain scans unless clinically indicated (e.g., in patients with neurological symptoms). The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans).

For patients with previously untreated CNS metastases, a brain MRI scan with contrast is required at screening and is the preferred modality for all subsequent scheduled follow-up tumor assessments. Note: CT scan with contrast may be acceptable for all subsequent scheduled follow-up tumor assessments if the following criteria are met: (1) Both brain MRI and CT scan with contrast must be performed at screening to assess untreated CNS disease, and (2) The CT scan with contrast can be used to reliably evaluate lesions identified on the screening MRI with contrast. If CT scan with contrast cannot be used to reliably evaluate lesions identified on the screening MRI with contrast, then MRI scan with contrast must be used at all subsequent scheduled follow-up tumor assessments. The same modality must be used at every tumor assessment.

Untreated CNS disease must be recorded in the Tumor Assessment eCRF per RECIST 1.1 at screening as well as at subsequent scheduled follow-up tumor assessments.

Patients will undergo tumor assessments at baseline and at every 6 weeks (±7 days) for 48 weeks following Day 1 of Cycle 1 regardless of treatment delays. After the completion of the Week 48 tumor assessment, tumor assessment will be required every 9 weeks (±7 days) regardless of treatment delays, until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first (see Section 3.1.6). At the investigator's discretion, scans may be performed at any time if progressive disease or loss of clinical benefit is suspected. *Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will undergo tumor assessments at the frequency described above, which is every 6 weeks (± 7 days) for 48 weeks following Cycle 1, Day 1 and then every 9 weeks (± 7 days) thereafter, until study treatment is discontinued.*

Response will be assessed by the investigator on the imaging modalities detailed above, using RECIST v1.1 (see Appendix 5). The investigator's assessment of overall tumor response at all timepoints should only be based on RECIST v1.1. Assessments should be performed by the same evaluator if possible to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

Study treatment may be continued as long as patients are experiencing clinical benefit as assessed by the investigator in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status. Patients who meet criteria for disease progression per RECIST v1.1 will be permitted to continue study treatment if they meet all of the criteria specified in Section 3.1.6.

Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by Sponsor, whichever occurs first. Patients who start a new anti-cancer therapy in the absence of radiographic disease progression per RECIST v1.1 will continue tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Investigator assessment of overall tumor response at all timepoints will be only based on RECIST v1.1.

4.5.6 Other Disease-Specific Assessments

Tumor samples from the primary tumor (or metastatic site, in the absence of primary site) are to be assessed for expression of Bcl-2 and other markers of lung cancer biology (i.e., EGFR, ROS, ALK, other Bcl-2 family members, etc.), mutations in cancer-related genes assessed by NGS of DNA, and expression of cancer-related genes assessed by quantification of RNA.

- Bcl-2 expression status will be determined by central laboratory testing using the Ventana Bcl-2 IHC assay. Bcl-2 high is defined as $\geq$ 50% of tumor cells stained with an intensity of IHC 2+ or 3+, and Bcl-2 low is defined as $\geq$ 50% stained with an intensity of IHC 0 or 1+, and < 50% stained an intensity of IHC 2+ or 3+.

4.5.7 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 (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)

- Chemistry panel (serum): glucose, BUN or urea, sodium, magnesium, potassium, chloride, bicarbonate, total CO_2 (if assessed), total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin

  TLS laboratory assessments include serum creatinine, uric acid, potassium, calcium, phosphorus, and LDH.

- 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)
- Epstein-Barr virus (EBV) serology (EBV IgM, EBV IgG, and/or EBNA) and/or EBV PCR

  If the patient has positive serology for EBV IgG and/or Epstein-Barr nuclear antigen, then EBV IgM testing and/or EBV PCR is required prior to enrollment for consideration of eligibility.

- HIV serology
- HBV serology: HBsAg, 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.

- 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.

- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine 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 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).

- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

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

- Plasma samples for venetoclax PK analysis
- Serum samples for atezolizumab analysis

- Serum samples for atezolizumab immunogenicity analysis
- Plasma samples for carboplatin analysis
- Plasma samples for etoposide analysis

Note: Alternative PK and ADA assessments may be explored if there is substantial difficulty in obtaining the timepoints listed in Appendix 3. Depending on the results from interim PK and ADA analyses, the frequency of PK and ADA sampling may be reduced or halted later in the study.

- Blood samples for exploratory research on biomarkers and biomarker assay development
- Archival or newly collected tumor tissue sample obtained at baseline for determination of Bcl-2 expression and for exploratory research on biomarkers and biomarker assay development:

  For baseline Bcl-2 and Bcl-2 family protein expression, formalin-fixed paraffin-embedded (FFPE) samples prepared from resections, core needle, excisional, incisional, punch, or forceps biopsies. If these sample types are not available, any type of specimen (including fine-needle aspiration, cell pellet specimens (e.g., from pleural effusion and lavage samples) is acceptable.

  For baseline expression of transcripts for Bcl-2 family members and other apoptotic genes, FFPE samples prepared from resections, core needle, excisional, incisional, punch, or forceps biopsies. If these sample types are not available, any type of specimen (including fine-needle aspiration, cell pellet specimens [e.g., from pleural effusion and lavage samples], and/or ctDNA samples are acceptable.

  A representative FFPE tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. If less than 15 slides are available, the patient may still be eligible for the study, after Medical Monitor approval has been obtained.
- Tumor tissue sample obtained at the time of progression, if deemed clinically feasible, for exploratory research on biomarkers and biomarker assay development

  Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core needle biopsy, or excisional, incisional, punch, or forceps biopsy are preferred.

Exploratory biomarker research may include, but will not be limited to, Bcl-2 family members, ctDNA analysis, analysis of genes or gene signatures associated with apoptosis, tumor immunobiology, T-cell receptor repertoire, or circulating biomarkers. 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. DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by

distinguishing germline variants from somatic variants. NGS methods may include WGS or WES of tissue and blood samples, but WGS or WES of blood samples will be performed only at participating sites (see Section 4.5.9).

Screening blood and tumor tissue samples, including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

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 4.5.11), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional pharmacokinetics (e.g., PK biomarkers or relevant analytes/catabolites/metabolites) and immunogenicity characterization and for PK or 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.
- Blood, plasma, serum, and tumor tissue samples collected for biomarker research and biomarker assay development will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the exception of tissue samples that undergo WGS or WES, which will be stored until they are no longer needed or until they are exhausted However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

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, including data on genomic variants, 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.

4.5.8 Electrocardiograms

An ECG is required at screening and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

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.

4.5.9 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants 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, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research 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 WGS or WES, this section of the protocol (Section 4.5.9) will not be applicable at that site.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

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

Refer to Section 4.5.7 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.10 Optional Tumor Biopsies

Consenting patients may undergo an optional tumor biopsy (if deemed clinically feasible by the investigator) anytime during treatment and/or during the survival follow-up phase. Preferred sample types include FFPE samples prepared from resections, core needle, excisional, incisional, punch, or forceps biopsies. If these sample types are not available, any type of specimen (including fine-needle aspiration, cell pellet specimens [e.g., from pleural effusion and lavage samples]) is acceptable.

The Informed Consent Form will contain a separate section that addresses optional biopsies. 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 4.5.7. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.7 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 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 biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation

- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples 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 4.5.11) will not be applicable at that site.

4.5.11.3 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 Bcl-2, diseases, or drug safety:

- Blood samples collected at predose
- Additional archival tumor tissue samples (e.g., from an earlier biopsy) collected at screening
- Tumor tissue samples from biopsies performed at the investigator's discretion during the study
- Leftover blood, serum, plasma, PBMC, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

RBR samples 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).

4.5.11.4 Confidentiality

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

Patient medical information associated with RBR samples 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 samples, 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 samples 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.

4.5.11.5 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 consent 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 samples. 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 samples and data will continue to be used as part of the RBR research.

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent 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 samples 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 RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and 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 consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.11.7 Monitoring and Oversight

RBR samples 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 samples 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 discontinue study treatment if they experience any of the following:

- Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results if available, and the patient's clinical status
- 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 on study treatment
- Use of another non–protocol-specified anti-cancer therapy (see Section 4.4.2)

- Pregnancy
- Radiographic disease progression per RECIST v1.1 (unless treating beyond radiographic progression; see below)

However, to better accommodate standard clinical practice which is guided by the fact that patients with ES-SCLC whose disease progresses after first-line treatment have limited treatment options and such options also have limited efficacy and significant toxicity, patients may be considered for treatment beyond radiographic progression per RECIST v1.1 at the discretion of the investigator and after appropriate discussion with the patient, only if all of the following criteria are met:

- Evidence of clinical benefit as assessed by the investigator
- No 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

Treatment should be discontinued if clinical deterioration due to disease progression occurs at any time or if persistent disease growth is confirmed in a follow-up scan. In addition, patients should be discontinued for unacceptable toxicity or for any other signs or symptoms of deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit $\leq$30 days after the final dose of study treatment (see Appendix 1). The visit at which response assessment shows progressive disease 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 and PRO assessments as outlined in the schedule of activities (see Appendix 1 and Appendix 2).

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) (see Appendix 1 and Appendix 2). Information on subsequent anti-cancer therapies will include systemic therapies (e.g., chemotherapy, targeted therapy, hormonal therapy, or CIT), surgery (e.g., resection of metastatic disease), and radiation procedures (e.g., radiotherapy to a tumor lesion).

4.6.2 Patient Discontinuation from the 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 patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Loss to follow-up
- 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 a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

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

The safety plan for patients in this study is based on clinical experience with venetoclax as well as atezolizumab plus carboplatin and etoposide in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections 5.1.1–5.1.4).

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 venetoclax and atezolizumab plus carboplatin etoposide 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. Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Appendix 10, Appendix 11, Appendix 12, and Appendix 13. Refer to Sections 5.2–5.7 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

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, meningoencephalitis, myocarditis, nephritis, and myositis. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Refer to Appendix 13 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Etoposide

Etoposide is known to cause bone marrow suppression including myelosuppression, anemia, thrombocytopenia, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea), hepatotoxicity, and alopecia. Etoposide-based chemotherapy is considered to be moderately emetogenic. Etoposide carries a risk of secondary hematologic malignancy. Patients will be monitored for etoposide-related adverse events.

For more details regarding the safety profile of etoposide, refer to the etoposide prescribing information.

5.1.3 Risks Associated with Carboplatin

Carboplatin is known to cause bone marrow suppression including myelosuppression, anemia, and thrombocytopenia. Carboplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for carboplatin-related adverse events.

For more details regarding the safety profile of carboplatin, refer to the carboplatin prescribing information.

5.1.4 Risks Associated with Venetoclax

Clinical experience gained thus far with venetoclax has demonstrated that it is generally well tolerated, and toxicities appear to be mostly manageable and/or reversible; see the Venetoclax Investigator's Brochure for more information.

On the basis of clinical data to date, the following known and potential risks with venetoclax are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.5.1.

5.1.4.1 Tumor Lysis Syndrome

Available data suggest that in patients with non-CLL, with the exception of those with mantle cell lymphoma, the risk of TLS is low with venetoclax. Due to different biology between ES-SCLC and hematological malignancies, the risk of TLS is considered to be low in patients with ES-SCLC.

Nevertheless, patients should be advised to remain well hydrated for the first week of study drug administration. Although not mandatory, at the discretion of the investigator, a prophylactic oral agent (e.g., allopurinol 300 mg QD) may be initiated in patients who are deemed to be at the risk of TLS in order to reduce the uric acid level. Laboratory values obtained before the dose of venetoclax are to be used to determine whether a patient developed a change related to TLS. Laboratory results of the 24-hour postdose must be reviewed before receiving the dose of venetoclax for that day. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix 11.

Patients with TLS should be treated as per institutional practice and local guidelines, including correction of electrolyte abnormalities and monitoring of renal function and fluid balance. Recommendations for initial management of electrolyte imbalances and prevention of TLS are provided in Appendix 11. In some cases, dialysis may be indicated. Guidelines for defining TLS are provided in Appendix 9.

5.1.4.2 Neutropenia

Neutropenia is an important identified risk for venetoclax. Clinical data from the oncology studies suggest that the neutropenia adverse events are observed among subjects who receive venetoclax as a single agent or in combination with other therapeutic agents, with higher frequency observed in some combination studies. Serious adverse events of neutropenia or neutropenia events that lead to discontinuations are few across the entire venetoclax oncology program. Neutropenia management guidelines are provided in Table 10 and Appendix 12. Granulocyte colony stimulating factors are permitted according to local practice, and patients will be monitored and treated promptly in case of infection.

5.1.4.3 Serious Infections

Serious infection is an important identified risk for venetoclax. Infections have been reported in the oncology clinical studies; however, these events are confounded by the underlying disease, comorbidities, and other immunosuppressive medications. To date, no clear relationship has been noted between serious infectious events and neutropenia. The types of infectious events observed generally have been consistent with those anticipated in the elderly population of heavily pretreated subjects with hematologic malignancies and are similar across all indications. Infections are closely monitored in venetoclax program across all indications. Patients should be advised to report fever and should be assessed for further management as per standard medical practice. In the oncology studies, recommendations are included in the protocol regarding the need for anti-infective prophylaxis per standard of care (e.g., NCCN for oncology subjects).

5.1.4.4 Other Hematological Effects

Anemia has been reported across oncology studies investigating venetoclax, with a higher frequency in some studies in which venetoclax is combined with other reference therapies; however, most of the events were non-serious and confounded by disease factors and prior therapies.

Thrombocytopenia adverse events have been reported in oncology studies investigating venetoclax, with a higher frequency in those studies in which venetoclax was combined with other chemotherapeutic agents. However, most of the events were non-serious and assessment of these events is confounded by the patients' underlying hematologic malignancy disease state, prior therapies, and preexisting thrombocytopenia, including autoimmune thrombocytopenia in several patients.

Lymphopenia has been observed in nonclinical studies and in the phase I clinical study conducted in heavily pretreated patients with CLL and NHL. While opportunistic infections have been reported in the clinical program, data are confounded by the patients' underlying disease and prior therapies. Patients in this study who develop lymphopenia are potentially at risk for atypical infections. As such, prophylaxis against varicella zoster virus and *Pneumocystis jiroveci* pneumonia should be considered and implemented (if applicable) as per local institutional practice

5.1.4.5 Reproductive System Effects and Pregnancy

This study enrolls both male and female patients. The effect of Bcl-2 inhibition on pregnancy has not been fully characterized. In animal studies, venetoclax resulted in increased post implantation loss, and decreased fetal body weights were observed in the mouse embryo-fetal development study at the highest dosage administered. Venetoclax was not teratogenic. Two human pregnancies have been reported in the clinical program with venetoclax so far, including one pregnancy of a partner; in both cases, a live infant with no neonatal complication, congenital anomalies, or birth defects was delivered.

In nonclinical studies, venetoclax has shown a potential to cause reproductive and embryo-fetal developmental toxicities as single agent. No reproductive or teratogenicity studies in animals have been conducted with atezolizumab. The PD-L1/PD-1 signaling pathway is well established as essential in maternal/fetal tolerance and embryo-fetal survival during gestation. Administration of atezolizumab is expected to have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo lethality. Consequently, both venetoclax and atezolizumab should not be administered to pregnant women, and they must be discontinued if a patient becomes pregnant. Additionally, patients are advised to remain abstinent (i.e., refrain from heterosexual intercourse) or use non-hormonal contraceptive methods with a failure rate of <1% per year during the treatment period and for 30 days after the last dose of study drug. Please refer to Section 4.1.1 for further details on study eligibility and contraceptive requirements for patients.

5.1.4.6 Treatment-Emergent Malignancies (Second Primary Malignancies)

Events of second primary malignancies have been reported across the venetoclax hematologic oncology program. However, no causal association with the venetoclax administration has been confirmed, and no pattern has been observed. The overall observed incidence rate of malignancy in the venetoclax clinical trial programs were comparable to that reported in the general population. The second primary malignancies will be closely monitored in this study.

5.1.5 Dose Modification

Reasons for dose modifications including dose delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF. The severity of adverse events will be graded according to NCI CTCAE v5.0.0.

- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment and the dose or administration of that component is delayed or modified, the dose or administration of the other study treatment components do not require modification and may be administered if there is no contraindication.
- When treatment is temporarily interrupted because of toxicity caused by atezolizumab, carboplatin, or etoposide, the treatment cycles should be restarted such that the atezolizumab infusions remain synchronized and aligned with the chemotherapy schedule.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one chemotherapy drug, the dose of the other chemotherapy drug does not require modification.

The investigator may use discretion in modifying or accelerating the dose modification guidelines described below depending on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing patient compliance and access to supportive care.

5.1.5.1 Venetoclax Dose Modifications

Although patients with adverse events are to be managed according to the particular clinical circumstances based on the investigator's medical judgment, dose reduction of venetoclax by one and, if needed, two dose levels will be allowed depending on the type and severity of the toxicity encountered (see Table 6). Each dose reduction of venetoclax will occur by 200 mg (e.g., the starting dose of 800 mg will be reduced to 600 mg, then to 400 mg). *Dose reduction by two dose levels (e.g., reducing from 800 mg to 400 mg directly) is not permitted.* Such patients may continue to receive atezolizumab plus carboplatin and etoposide at the discretion of the investigator in the induction phase and atezolizumab as a single agent in the maintenance phase. Patients requiring clarification regarding management of adverse events and dosing and all patients requiring more than two dose reductions should be discussed with the Medical Monitor. All dose modifications/adjustments must be clearly documented in the patient's source notes and eCRF.

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at the reduced dose level, unless further dose reduction is allowed. Dose re-escalation is not allowed.

Table 6 Venetoclax Dose Reduction

Venetoclax Current Dose Level	Venetoclax Dose Reduction
800 mg	600 mg
600 mg	400 mg
400 mg	200 mg
200 mg	100 mg
100 mg	Discontinue venetoclax

5.1.5.2 Atezolizumab Dose Modification, Treatment Delays, or Treatment Discontinuation and Management of Specific Adverse Events

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment with atezolizumab for up to 105 days beyond the last dose if they experience an adverse event that requires a dose to be withheld. If atezolizumab is withheld because of adverse events for more than 105 days beyond the last dose, then the patient will be discontinued from atezolizumab/ treatment. Exceptions require Medical Monitor approval.

If a patient must be tapered off steroids used to treat adverse events, atezolizumab may be withheld for additional time beyond 105 days from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤10 mg/day. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Dose interruptions for reason(s) other than adverse events, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

5.1.5.3 Chemotherapy Dose Modifications, Treatment Delays, or Treatment Discontinuation and Management of Specific Adverse Events

Dose modifications for carboplatin and etoposide are permitted for toxicity according to the prescribing information and local standard of care.

Dose modification guidelines are provided below.

Treatment with carboplatin or etoposide should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or Grade 4 toxicity after two dose reductions or treatment is delayed for more than 63 days due to toxicities.

Hematologic Toxicity

At the start of each cycle, the ANC should be ≥1500/μL and the platelet count should be ≥100,000/μL. Treatment should be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) and NCCN guidelines (Smith et al. 2006; NCCN 2019) or as per institutional guidelines. Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest platelet and neutrophil values from the previous cycle (see Table 7). Increased frequency of lab assessments (e.g., neutrophil and platelet counts) on Cycle 1, Day 8 and Cycle 1, Day 15 are used to better characterize the impact of and response to treatment. Since such assessments are not routinely performed, they will not be used for dose modifications for subsequent cycles. Therefore, Cycle 2 dose adjustments will be based on assessments performed after Cycle1, Day 21.

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Table 7 Chemotherapy Dose Modification for Hematologic Toxicities

Toxicity [a]	Dose
ANC $<$500/μL and platelets $\geq$50,000/μL	75% of previous dose
Platelets $<$25,000/μL, regardless of ANC	75% of previous dose
Platelets $<$50,000/μL with Grade $\geq$2 bleeding, regardless of ANC	50% of previous dose
ANC $<$1000/μL plus fever of $\geq$38.5°C	75% of previous dose

[a] Nadir of prior cycle with the exception of Cycle 1, where neutrophil and platelet assessments performed after Cycle 1, Day 21 will be used for dose adjustment.

The dose of chemotherapy can be re-escalated (even to full dose) in subsequent cycles if cytopenias have improved due to venetoclax reduction with the approval of Medical Monitor. This is to try to maintain dose intensity of standard of care chemotherapy, especially if cytopenias resolve with venetoclax dose reductions.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

If chemotherapy is withheld because of hematologic toxicity, full blood counts (including differential WBC) should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment can then be resumed.

No dose reductions are recommended for anemia. Patients should be supported per the investigator's institution's guidelines.

Non-Hematologic Toxicity

For a non-hematologic toxicity (see Table 8), treatment should be delayed for up to 63 days until resolution to less than or equal to the patient's baseline value (or Grade $\leq$ 1 if the patient did not have that toxicity at baseline). Dose reductions at the start of the subsequent cycle should be made on the basis of non-hematologic toxicities from the dose administered in the preceding cycle. Table 8 provides recommended dose modifications for non-hematologic toxicities.

Table 8 Dose Modifications or Treatment Discontinuation for Non-Hematologic Toxicities

Toxicity		Adjusted Dose as % of Previous Dose [a]
Diarrhea	Grade 3 or 4 [b]	75%
Nausea/vomiting	Grade 3 or 4 [c]	75%
Neurotoxicity	Grade 2	75%
	Grade 3 or 4	50% or permanent discontinuation
Transaminase elevation	Grade 3	75%
	Grade 4	Discontinue
Other	Grade 3 or 4	75%

AUC = area under the concentration–time curve.

[a] If deemed appropriate by the investigator, adjust carboplatin dose to the specified percentage of the previous AUC.

[b] Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication or any grade of diarrhea requiring hospitalization.

[c] Despite the use of anti-emetics.

Diarrhea should be controlled with adequate anti-diarrheal medication. Nausea and/or vomiting may be controlled with adequate anti-emetics. For Grade 3 or 4 neurotoxicity, chemotherapy should be resumed at 50% of the previous dose upon improvement or discontinued immediately (based on investigator's clinical judgment).

Suggested recommendations for dose modification of etoposide for renal impairment are provided in Table 9.

Table 9 Etoposide Dose Modification for Renal Impairment

Creatinine Clearance (mL/min)	Etoposide Dose
>50	100%
15–50	75% of dose

5.1.6 Management Guidelines

5.1.6.1 Management of Venetoclax-Specific Adverse Events

Refer to Appendix 12 for details on management of venetoclax-specific adverse events.

5.1.6.2 Management of Atezolizumab-Specific Adverse Events

Refer to Appendix 13 for details on the management of atezolizumab-specific adverse events, including systemic immune activation. See Appendix 8 for anaphylaxis precautions.

5.1.6.3 Management of Potential Overlapping Toxicities

The main overlapping toxicities based on the individual safety profile of venetoclax and atezolizumab, carboplatin, and etoposide are expected to be hematologic toxicities such as neutropenia, febrile neutropenia, and thrombocytopenia (in the case of venetoclax, etoposide and carboplatin); and gastrointestinal toxicities such as diarrhea, nausea, and vomiting (in the case of venetoclax, atezolizumab, etoposide and carboplatin).

Table 10 below provides management guidelines for specific overlapping toxicities with venetoclax, atezolizumab and carboplatin etoposide. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hepatotoxicity, skin and gastrointestinal toxicity) may be unclear when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with carboplatin and etoposide (e.g., dermatitis, infusion-associated symptoms) could be exacerbated by the immunostimulatory activity of atezolizumab.

Toxicities should initially be managed according to the recommendations in Sections 5.1.5.1–5.1.5.3, Table 10, Appendix 12, and Appendix 13 with dose holds and modifications (if applicable) applied to the component of the study drug judged to be the primary cause. For severe (Grade 3) or persistent Grade 1–2 diarrhea, an endoscopic evaluation should be considered. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology for adverse events listed above. If, in the opinion of the investigator, atezolizumab is a potential inciting factor, the dose of atezolizumab may be held for a maximum of 105 days beyond the last infusion (see Section 5.1.5.2). Exceptions require Medical Monitor approval. Prompt symptomatic management is appropriate for mild immune-mediated adverse events. In severe cases, immune-mediated toxicities may be acutely managed with systemic corticosteroids or TNF-α inhibitors. These cases should be discussed with the Medical Monitor.

Table 10 Management Guidelines for Specific Adverse Events with Venetoclax, Atezolizumab, and Carboplatin Etoposide

Event	Management

Neutropenia, Grade 3 (ANC < 1000–500/mm^3) [a]	• Withhold venetoclax.
	• If counts recover to ANC 1500/mm^3:
	  ○ Resume treatment with venetoclax at previous dose.
	  ○ Administer atezolizumab plus carboplatin and etoposide at previous dose during induction treatment.
	  .

Neutropenia, Grade 4 (ANC count < 500/mm^3) [a]	• Withhold venetoclax.
	• Withhold atezolizumab plus carboplatin and etoposide.
	• Administer treatment including G-CSF or growth factors for neutropenia as indicated or as per institutional guidelines.
	• If counts recover to ANC 1500/mm^3:
	  ○ Resume venetoclax at one dose level reduction (see Table 6).
	  ○ Administer carboplatin and etoposide at 75% of previous dose (see Table 7).
	  Dose of carboplatin and etoposide can be re-escalated (even to full dose) in subsequent cycles with the approval of Medical Monitor (see Section 5.1.5.2).
	• Administer atezolizumab at previous dose level.
	• If patient develops recurrent Grade 4 neutropenia despite growth factor support and following venetoclax dose reduction to 100 mg and two dose reductions for carboplatin etoposide, discontinue venetoclax and carboplatin etoposide during the induction phase.

Febrile neutropenia, Grade 3-4 (ANC < 1000/μL) plus fever of > 38.5°C	• Withhold venetoclax.
	• Withhold atezolizumab plus carboplatin and etoposide.
	• Administer treatment with growth factors per institutional guidelines.
	• Upon resolution of Grade ≥ 3 febrile neutropenia (ANC > 1500/mm^3):
	  ○ Resume venetoclax at one dose level reduction (see Table 6).
	  ○ Administer carboplatin and etoposide at 75% of previous dose (see Table 7).
	  Dose of carboplatin and etoposide can be re-escalated (even to full dose) in subsequent cycles with the approval of Medical Monitor (see Section 5.1.5.2).
	  ○ Administer atezolizumab at previous dose level.
	• If patient develops recurrent Grade 3–4 febrile neutropenia despite growth factor support and following venetoclax dose reduction to 100 mg and two dose reductions for carboplatin etoposide, discontinue venetoclax and carboplatin etoposide during the induction phase.

Table 10 Management Guidelines for Specific Adverse Events with Venetoclax, Atezolizumab, and Carboplatin Etoposide (cont.)

Event	Management

Thrombocytopenia, Grade 3 (platelet count < 50,000–25,000/μL) with Grade ≥ 2 bleeding	• Withhold venetoclax.
	• Withhold atezolizumab plus carboplatin etoposide.
	• If platelet count recovers to ≥ 100,000/mm^3):
	  ○ Resume venetoclax at one dose level reduction (see Table 6).
	  ○ Administer carboplatin and etoposide at 50% of previous dose (see Table 7).
	  Dose of carboplatin and etoposide can be re-escalated (even to full dose) in subsequent cycles with the approval of Medical Monitor (see Section 5.1.5.2).
	  ○ Administer atezolizumab at previous dose level.
	• If patient develops recurrent Grade 3 thrombocytopenia with Grade ≥ 2 bleeding following venetoclax dose reduction to 100 mg and two dose reductions for carboplatin etoposide, discontinue venetoclax and carboplatin etoposide during the induction phase.

Thrombocytopenia, Grade 4 (platelets <25,000/μL) [a]	• Withhold venetoclax.
	• Withhold atezolizumab plus carboplatin and etoposide.
	• Administer platelet transfusion if platelet count is <10,000/μL or as per institutional guidelines.
	• If platelet count rises to ≥ 100,000/mm^3:
	  ○ Resume venetoclax at one dose level reduction (see Table 6).
	  ○ Administer carboplatin and etoposide at 75% of previous dose (see Table 7).
	  Dose of carboplatin and etoposide can be re-escalated (even to full dose) in subsequent cycles with the approval of Medical Monitor (see Section 5.1.5.2).
	  ○ Administer atezolizumab at previous dose level.
	• If patient develops recurrent Grade 4 thrombocytopenia following venetoclax dose reduction to 100 mg and two dose reductions for carboplatin etoposide, discontinue venetoclax and carboplatin etoposide during the induction phase.

Diarrhea, Grade 3	• Withhold venetoclax.
	• Withhold atezolizumab plus carboplatin and etoposide.
	• Administer anti-diarrheals per institutional guidelines (e.g. loperamide 4 mg initial dose up to a maximum of 16 mg per day)
	• Upon resolution of Grade 3 diarrhea to Grade ≤ 1:
	  ○ Resume treatment with venetoclax at the previous dose.
	  ○ Administer carboplatin and etoposide at previous dose (see Table 8).
	  ○ Administer atezolizumab at previous dose level.

Table 10 Management Guidelines for Specific Adverse Events with Venetoclax, Atezolizumab, and Carboplatin Etoposide (cont.)

Event	Management
Diarrhea, Grade 3 (cont.)	• For uncontrolled Grade 3 diarrhea that occurs on adequate anti-diarrhea medication or any grade of diarrhea requiring hospitalization: ○ Reduce venetoclax by one dose level (see Table 7). ○ Administer carboplatin and etoposide at 75% of previous dose (see Table 8). Dose of carboplatin and etoposide can be re-escalated (even to full dose) with the approval of Medical Monitor (see Section 5.1.5.2). ○ Administer atezolizumab at previous dose.
Diarrhea, Grade 4	• Withhold venetoclax. • Withhold atezolizumab plus carboplatin etoposide. • Administer anti-diarrheals per institutional guidelines (e.g., loperamide 4 mg initial dose up to a maximum of 16 mg per day) • Upon resolution of Grade 4 diarrhea to Grade ≤ 1: ○ Resume treatment with venetoclax at one dose level reduction (see Table 7) ○ Administer carboplatin and etoposide at 75% of previous dose (see Table 8). Dose of carboplatin and etoposide can be re-escalated (even to full dose) with the approval of Medical Monitor (see Section 5.1.5.2). ○ Administer atezolizumab at previous dose. • For uncontrolled Grade 4 diarrhea that occurs despite adequate anti-diarrhea medication or any grade of diarrhea requiring hospitalization: ○ Further reduce venetoclax by one dose level (see Table 7). ○ Administer carboplatin and etoposide at 75% of previous dose (see Table 8). ○ Administer atezolizumab at previous dose.
Hepatic event, Grade 2	• Monitor LFTs more frequently until return to baseline Events of > 5 days duration: • Withhold atezolizumab for up to 12 weeks after event onset. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • 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.

Table 10 Management Guidelines for Specific Adverse Events with Venetoclax, Atezolizumab, and Carboplatin Etoposide (cont.)

Event	Management

Hepatic event, Grade 3	• Discontinue atezolizumab.
	• Withhold venetoclax.
	• Withhold carboplatin and etoposide.
	• If hepatic event resolves to ≤ Grade 1:
	  ○ Resume venetoclax at one dose level reduction (see Table 6).
	  ○ Administer carboplatin and etoposide at 75% of previous dose (see Table 8).

Hepatic event, Grade 4	• Discontinue atezolizumab. • Discontinue venetoclax. • Discontinue carboplatin and etoposide.

ANC = absolute neutrophil count; G-CSF = growth-colony stimulating factor.

[a] Dose modifications (as specified in the table above) should be made based on ANC and platelet count assessment on Day 1 of each cycle. No dose modifications are required based on ANC and platelet count assessment done on Cycle 1, Day 8 and Cycle 1, Day 15.

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 5.4.

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 this study 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 $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, and systemic inflammatory response 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)
- Tumor Lysis Syndrome
- Grade 4 thrombocytopenia

- Grade 4 Febrile neutropenia

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 5.4–5.6.

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 last dose of study drug 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 90 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 (v5.0) will be used for assessing adverse event severity. Table 11 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 11 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 the most recent version of NCI CTCAE (v5.0), 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.

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 12):

- 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 12 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	An adverse event will be considered related, unless it fulfills the criteria specified below. 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 Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

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 gastrointestinal 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., alkaline phosphatase and bilirubin 5 × 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 blood pressure), 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 ($>3\times$ULN) 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 $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN 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 SCLC 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 SCLC

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 SCLC

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 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, 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 or venetoclax 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 or venetoclax, 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.

5.3.5.13 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

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)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information 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

Medical Monitor Contact Information

Medical Monitor/Roche Medical Responsible: [redacted] M.D.

Mobile Telephone No.: [redacted]

Alternate Medical Monitor Contact Information

Medical Monitor/Roche Medical Responsible: [redacted] M.D., Ph.D.

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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 Serious Adverse Event/Adverse Event of Special Interest Reporting 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, serious adverse events and adverse events of special interest will be reported until 90 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 Serious Adverse Event/Adverse Event of Special Interest Reporting 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 after the reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 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 30 days after the final dose of venetoclax, 5 months after the final dose of atezolizumab, or 6 months after the final dose of carboplatin or etoposide, whichever *occurs last*. 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.

5.4.3.2 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 30 days after the final dose of venetoclax, 5 months after the final dose of atezolizumab, or 6 months after the final dose of carboplatin or etoposide, whichever *occurs last*. 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.

5.4.3.3 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.

5.4.3.4 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).

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, email, 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 reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the final dose of study treatment or until initiation of new 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 Serious Adverse Event/Adverse Event of Special Interest Reporting 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.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Atezolizumab	Atezolizumab Investigator's Brochure
Venetoclax	Venetoclax Investigator's Brochure

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.

The Sponsor will monitor safety data during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

The estimated sample size of the dose-escalation phase follows from the dose-escalation rules of a standard 3+3 algorithm. It is anticipated that enrollment of two cohorts of 3–6 patients each in the maintenance phase, as well as up to five cohorts of 3–6 patients each in the induction phase, for a total of 18–42 patients, will be required to establish the RP2D for maintenance (RP2D-M) and the RP2D for the induction setting (RP2D-I) during the dose-escalation phase.

A sample of 20 patients will be sufficient to provide adequate precision for the point *estimates. Assuming an observed ORR of 80% for the induction plus maintenance setting (Arm B), with 20 patients,* the lower bound of the two-sided 80% CI *will* rule out a probability of response of 63*%. Assuming an observed ORR of 5% for the maintenance-only setting (Arm A), with 20 patients, the lower bound of the two-sided 80% CI will rule out a probability of response of 0*%.

An 80% CI for true underlying ORR values of *0.05, 0.1,* 0.7, 0.75, and 0.8 are provided in Table 13.

Table 13 Operating Characteristics for Proposed Study Design for Several Possible True Underlying Overall Response Rate

	True Underlying ORR				
	5%	*10%*	**70%**	**75%**	**80%**
80% confidence interval for true ORR	(1%, 18%)	(3%, 24%)	(53%, 83%)	(59%, 87%)	(64%, 91%)

[a] Confidence intervals are based on the assumption that the point estimate is equal to the true underlying value of the objective response rate (ORR) in each column.

For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such event in a cohort of 20 patients is 87.8%, 64.2%, and 18.2%, respectively. Table 14 describes exact 90% CIs for a range of observed proportions of adverse events based on a sample size of 20 patients.

Table 14 90% Confidence Interval Estimates for Potential Adverse Event Rates

Observed Event Rate	Exact 90% Confidence Interval for the Potential Adverse Event Rates
1%	(0%, 16%)
5%	(0%, 22%)
10%	(2%, 28%)
20%	(7%, 40%)
30%	(14%, 51%)

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study drug administration, and discontinuation from the study will be summarized separately for the maintenance arm (Arm A) and the induction arm (Arm B) of the dose-escalation phase (by dose and overall) and for the dose-expansion phase. The reasons for study drug discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, ECOG performance status, and lung cancer history) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented separately for the maintenance arm (Arm A) and the induction and maintenance arm (Arm B) of the dose-escalation phase (by dose and overall) and for the dose-expansion phase.

6.4 SAFETY ANALYSES

The safety analysis population will consist of all enrolled patients who received at least one dose of study treatment, with patients grouped according to treatment received.

Summaries of safety will be presented separately for the maintenance arm (Arm A) and the induction and maintenance arm (Arm B) of the dose-escalation phase (by dose and overall) and for the dose-expansion phase.

6.4.1 Analyses of Exposure, Adverse Event, Laboratory, Vital Sign, and ECG Data

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, 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.

6.5 EFFICACY ANALYSES

The analysis population for the efficacy analyses will consist of all enrolled patients in the dose-expansion cohort, with patients grouped according to their assigned dose levels and treatment schedules.

6.5.1 Primary Efficacy Endpoint

The primary efficacy objective for the Phase Ib dose-expansion cohort is to evaluate the preliminary efficacy of venetoclax in combination with atezolizumab as maintenance therapy or venetoclax in combination with atezolizumab, carboplatin, and etoposide as induction therapy followed by venetoclax plus atezolizumab as maintenance therapy on the basis of the following endpoint:

- ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions $\geq$4 weeks apart, as determined by the investigator according to RECIST v1.1 criteria.

Patients with no disease assessments for any reason will be classified as non-responders. An estimate of ORR with 90% exact CI will be presented using the method of Pearson Clopper.

6.5.2 Secondary Efficacy Endpoints

The secondary efficacy objective for the Phase Ib dose-expansion cohort is to evaluate the preliminary efficacy of venetoclax in combination with atezolizumab as maintenance therapy or venetoclax in combination with atezolizumab, carboplatin, and etoposide as induction therapy or venetoclax and atezolizumab as maintenance therapy on the basis of the following endpoints:

- DOR
- PFS
- OS
- PFS rate at 6 months
- OS rate at 1 year

6.5.2.1 Duration of Response

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, as determined by the investigator according to RECIST v1.1 criteria. Data for patients without the occurrence of disease progression or death as of the clinical data cutoff will be censored at the time of the last tumor assessment.

The Kaplan-Meier approach will be used to estimate median DOR. The Kaplan-Meier curve of time to DOR will be provided. Only patients achieving a CR or PR will be included in the assessment of DOR.

6.5.2.2 Progression-Free Survival

PFS after enrollment is defined as the time from enrollment to the first occurrence of disease progression or relapse or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 criteria. Data for patients without the occurrence of disease progression or death as of the clinical data cutoff date will be censored at the time of last tumor assessment (or the time of enrollment plus 1 day if no tumor assessment was performed after the baseline visit).

The Kaplan-Meier approach will be used to estimate median PFS. The Kaplan-Meier curve of time to PFS will be provided.

6.5.2.3 Overall Survival

OS after enrollment is defined as the time from enrollment to death from any cause. Data for patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Data from patients without postbaseline information will be censored at the date of enrollment plus 1 day.

OS will be analyzed using the same methodology as PFS (see Section 6.5.2.2).

6.5.2.4 Progression-Free Survival Rate at 6 Months

PFS rate at 6 months, defined as the proportion of patients who have not experienced disease progression, relapse, or death from any cause at 6 months, as determined by the investigator according to RECIST 1.1 criteria.

The PFS rate at 6 months will be estimated using the Kaplan-Meier methodology. A two-sided 90% CI of the PFS rate at 6 months will be presented based on Greenwood's method of estimating the variance of the KM estimate.

6.5.2.5 Overall Survival Rate at 1 Year

OS rate at 1 year, defined as the proportion of patients who have not experienced death from any cause at 1 year timepoint.

The OS rate at 1 year will be analyzed using the same methodology as the PFS rate at 6 months (see Section 6.5.2.4).

6.6 PHARMACOKINETIC ANALYSES

Individual PK concentration data will be tabulated and summarized (e.g., mean, standard deviation, coefficient of variation, median, minimum, and maximum) after appropriate grouping. PK parameters may also be calculated as data allow (e.g., C_{max}, AUC, clearance, volume of distribution, half-life, etc.) and tabulated and/or summarized after appropriate grouping. Population PK analyses of concentration data (with or without the PK data from other studies) may be conducted as appropriate. Potential PK DDIs may be assessed by comparison of PK for agents administered in this study with relevant historical data. Potential correlations between exposure and response (e.g., PD, efficacy, ECG, and safety endpoints) may also be explored, if warranted.

The results of Population PK analyses and exploratory exposure-response analyses may be reported separately from the Clinical Study Report. At the discretion of the Sponsor, all analyses may be extended to include relevant biotransformation products of the study treatments administered in this study.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment.

The numbers and proportions of ADA positive patients (for atezolizumab) and ADA negative patients (for atezolizumab) at baseline (baseline prevalence) and after drug administration (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 have 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 ADA negative if they are ADA negative or have 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).

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

6.8 BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies in effort to understand the association of these markers with study treatment response. Results will be presented in a separate report.

6.9 INTERIM ANALYSIS

None planned.

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 that must be kept with the study records. Acknowledgement of receipt of the data 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 IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 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.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

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 applicable 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 Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of 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.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. 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

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 Sponsor 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.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

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 (see definition of end of study in Section 3.2).

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 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 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.

9.5 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.

Approximately 10−12 sites globally will participate to enroll approximately 62 patients. 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 4.5.7. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.6 DISSEMINATION 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, at scientific congresses, in clinical trial registries, 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 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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.

9.7 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
Schedule of Activities: Dose-Escalation Maintenance Only *(Arm A) and Dose-Expansion Maintenance Only*

Assessment or Procedure	Screening Period	Treatment Period [a]					Treatment Discontinuation	Survival Follow-Up
		Maintenance Cycle 1 [b]				Maintenance Subsequent Cycles Every 21 Days (±3)	≤30 Days after Last Dose of Study Treatment	Every 3 Months After Disease Progression
Day (Window)	–28 to –1	1	2 [c]	8 (±1) [c]	15 (±2) [c]	1		
Informed consent	x							
Pre-treatment tumor tissue specimen for further biomarker testing	x [d]							
Medical history and baseline conditions	x							
SCLC cancer history	x							
Vital signs [e]	x	x	x	x	x	x	x	
Weight	x	x				x	x	
Height	x							
Complete physical examination	x							
Limited physical examination [f]		x	x	x	x	x	x	
ECOG performance status	x	x	x	x	x	x	x	
12-lead ECG	x	x [g]					x [g]	
Hematology [h]	x [i]	x	x	x	x	x	x	
Serum chemistry [j]	x [i]	x	x	x	x	x		
TLS labs	within 3 days of C1D1 or prior to C1D1 dose	x [k]	x [k]					
Coagulation test (aPTT or INR)	x [i]						x	
Pregnancy test (women of childbearing potential only)	x [l]	x [m]				x [m]	x [m]	
TSH, free T3, free T4 [n]	x	x [o]				x [o]	x	

Appendix 1: Schedule of Activities: Dose-Escalation Maintenance Only (Arm A) and Dose-Expansion Maintenance Only (cont.)

Assessment or Procedure	Screening Period	Treatment Period [a]					Treatment Discontinuation	Survival Follow-Up
		Maintenance Cycle 1 [b]				Maintenance Subsequent Cycles Every 21 Days (±3)	≤30 Days after Last Dose of Study Treatment	Every 3 Months After Disease Progression
Day (Window)	–28 to –1	1	2 [c]	8 (±1) [c]	15 (±2) [c]	1		
HIV, HBV, HCV, EBV serology [p]	x							
Urinalysis [q]	x	As clinically indicated						
Maintenance treatment administration: Venetoclax + atezolizumab		x [r]				x [r]		
Prophylactic cranial irradiation		x [s]				x [s]		
Tumor response assessment	x [t]	x [u]				x [u]		x [v]
PK/ADA		x *See Appendix 3: Table 1*				*x* *See Appendix 3: Table 1*	x *See Appendix 3: Table 1*	
Blood sample for biomarker analysis		x C1D1				C2D1, C3D1, C4D1, and every odd cycle	x See Appendix 4	
Tissue sample for biomarkers	x							
Optional tumor biopsy after induction treatment (if patient signs consent)		Any time during maintenance treatment						
Optional tumor biopsy at the time of radiographic progression (if patient signs consent) [w]		At the time of radiographic progression						
Optional tumor biopsy at other timepoints (RBR only)		Any time during treatment or survival follow-up						
Optional biopsy for DNA extraction (RBR only)		x						
Adverse events	x	x	x	x	x	x	x [x]	x [x]
Concomitant medications	x [y]	x [y]	x [y]	x [y]	x [y]	x [y]	x [y]	
Survival and anti-cancer therapy follow-up								x [z]

ADA = anti-drug antibody; C = Cycle; CT = computed tomography; D = Day; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EBV = Epstein-Barr virus; FFPE = formalin-fixed paraffin-embedded; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PCI = prophylactic cranial irradiation; PCR = polymerase chain reaction; PD = pharmacodynamic; PD-L1 = programmed death–ligand 1; PK = pharmacokinetic; PCI = prophylactic cranial irradiation; RBR = Roche Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; SCLC = small cell lung cancer; TLS = tumor lysis syndrome; TSH = thyroid-stimulating hormone.

[a] Assessments should be performed before study drug infusion unless otherwise noted.
[b] Cycle 1 must be performed within 5 days after the patient is enrolled. Screening assessments performed ≤ 96 hours before Cycle 1, Day 1 are not required to be repeated for Cycle 1, Day 1. In addition, ECOG performance status, limited physical examination, and local laboratory tests may be performed ≤ 96 hours before Day 1 of each cycle.
[c] Day 2, Day 8, and Day 15 assessments are not necessary during the dose-expansion phase, with the exception of PK sampling (refer to Appendix 4).
[d] A pre-treatment tumor tissue (archival or freshly obtained) sample should be submitted before or within 4 weeks after enrollment. This specimen must be accompanied by the associated pathology report. Although any available tumor tissue sample can be submitted, it is strongly encouraged that representative tumor specimens in paraffin blocks (preferred) or 15 (or more) serial, freshly cut, unstained slides be submitted.
[e] Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure, and temperature. Vital signs should be recorded as described in Section 4.5.4.
[f] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.
[g] ECG recordings will be obtained when clinically indicated.
[h] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count.
[i] At screening, the patient must have adequate hematologic and end-organ function defined by laboratory test results obtained within 14 days prior to enrollment.
[j] Serum chemistry includes BUN or urea, sodium, potassium, magnesium, chloride, bicarbonate or total CO_2 if considered standard of care in the region, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.
[k] TLS assessment frequency during the dose-expansion phase will be determined based on a comprehensive review of data in the dose-escalation phase. TLS labs include serum creatinine, calcium, phosphorous, uric acid, potassium, and LDH. If the screening assessments were done within 3 days prior to Cycle 1 Day 1, there is no need to repeat the TLS panel at Cycle 1 Day 1. Refer to Appendix 9 and Appendix 11 for further instructions.
[l] Serum pregnancy test within 14 days before Cycle 1, Day 1.
[m] Urine pregnancy tests; if a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.
[n] Total T3 will be tested only at sites where free T3 is not performed.

[o] Thyroid function testing (TSH, free T3, free T4) collected on Day 1 of Cycles 1, 4, 8, and 12, and every fourth cycle thereafter.

[p] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the study. Patients with active hepatitis B (chronic or acute; defined as having a positive HBsAg test result at screening) will be excluded from the study. Patients with past or resolved HBV infection (defined as the presence of HBcAb and absence of HBsAg) are eligible; HBV DNA should be obtained in these patients prior to enrollment. Patients with HCV will be excluded from the study; patients who test positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

[q] Urinalysis by dipstick (specific gravity, pH, glucose, protein, ketones, and blood). Urinalysis is required at screening and will be obtained when clinically indicated.

[r] For atezolizumab, the initial dose will be administered over 60 (±15) minutes. If the first infusion is well tolerated, subsequent infusions may be administered over 30 (±10) minutes (see Section 4.3.2.1). Venetoclax is administered QD for *21* days as described in Section 3.1.2; also see Section 4.3.2.2.

[s] During the maintenance phase, PCI is permitted as per local standard of care and will be reported on the Prophylactic Cranial Irradiation eCRF.

[t] CT scans (with oral/IV contrast unless contraindicated) or MRI scans of the chest and abdomen. A CT or MRI scan of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. A CT (with contrast) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients.

[u] Perform every 6 weeks (± 7 days) for 48 weeks following Cycle 1, Day 1 and then every 9 weeks (± 7 days) thereafter, after completion of the Week 48 tumor assessment, regardless of treatment delays, until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will undergo tumor assessments *at the frequency described above* until study treatment is discontinued.

[v] If the patient discontinued study treatment for any reason other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration), tumor assessments will continue at the same frequency as would have been followed if the patient had remained on study treatment (i.e., every 6 weeks [± 7 days] for 48 weeks following Cycle 1, Day 1 and then every 9 weeks [± 7 days] thereafter) until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first, even if the patient starts another anti-cancer therapy after study treatment discontinuation, unless consent is withdrawn.

[w] Optional tumor biopsy at radiographic disease progression, if clinically feasible, preferably within 40 days of radiographic progression or prior to start of the next anti-cancer therapy, whichever occurs first.

[x] All serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study drug, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study drug, whichever occurs first. After this period, all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment. These events should be reported through use of the Adverse Event eCRF.

[y] From 7 days before screening until the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

[z] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits every 3 months or more frequently until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the 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, study staff may use a public information source (e.g., county records), when permissible, to obtain information about survival status only.

Appendix 2
Schedule of Activities: Dose-Escalation *Induction + Maintenance* (Arm B) and Dose-Expansion Induction + Maintenance

Assessment or Procedure	Screening Period	Treatment Period [a]														Treatment Discon.	Survival Follow-Up
		Induction Cycle 1					Induction Cycle 2 (±3 Days) [b]				Induction Cycles 3–4 (±3 Days) [b]			Maint. Cycle 1	Maint. Subseq. Cycles Every 21 Days (±3)	≤30 Days after Last Dose of Study Treatment	Every 3 Months After Disease Prog.
Day (Window)	–28 to –1	1	2[c]	3	8 [c] (±1)	15 [c] (±2)	1	2–3	8 [c] (±1)	15 [c] (±2)	1	2–3	*15 [c] (±2)*	1	1		
Informed consent	x																
Pre-treatment tumor tissue specimen for further biomarker testing	x [d]																
Medical history and baseline conditions	x																
SCLC cancer history	x																
Vital signs [e]	x	x	x	x	x	x	x	x			x	x		x	x	x	
Weight	x	x					x				x			x	x	*x*	
Height	x																
Complete physical examination [f]	x																
Limited physical examination		x			x	x	x				x			x	x	*x*	
ECOG performance status	x	x			x	x	x				x			x	x	*x*	

Appendix 2: Schedule of Activities: Dose-Escalation Induction + Maintenance (Arm B) and Dose-Expansion Induction + Maintenance (cont.)

Assessment or Procedure	Screening Period	Treatment Period [a]														Treatment Discon.	Survival Follow-Up
		Induction Cycle 1					Induction Cycle 2 (±3 Days) [b]				Induction Cycles 3–4 (±3 Days) [b]			Maint. Cycle 1	Maint. Subseq. Cycles Every 21 Days (±3)	≤30 Days after Last Dose of Study Treatment	Every 3 Months After Disease Prog.
Day (Window)	–28 to –1	1	2[c]	3	8[c] (±1)	15[c] (±2)	1	2–3	8[c] (±1)	15[c] (±2)	1	2–3	*15[c] (±2)*	1	1		
12-lead ECG	x	x[g]												x[g]		x[g]	
Hematology [h]	x[i]	x	x		x	x	x			*x*	x		x	x	x	*x*	
Serum chemistry [j]	x[i]	x	x		x	x	x				x			x	*x*		
TLS labs [k]	within 3 days of C1D1 or prior to C1D1 dose	x	x		x												
Coagulation test (aPTT or INR)	x[i]															*x*	
Pregnancy test (women of childbearing potential only)	x[l]	x[m]									x[m]			x[m]	x[m]	x[m]	
TSH, free T3, free T4 [n]	x	x[o]									x[o]			x[o]	x[o]	x	
HIV, HBV, HCV, *EBV* serology [p]	x																
Urinalysis [q]	x[q]	Perform as clinically indicated															

Appendix 2: Schedule of Activities: Dose-Escalation Induction + Maintenance (Arm B) and Dose-Expansion Induction + Maintenance (cont.)

Assessment or Procedure	Screening Period	Treatment Period [a]													Treatment Discon.	Survival Follow-Up
		Induction Cycle 1					Induction Cycle 2 (±3 Days) [b]				Induction Cycles 3–4 (±3 Days) [b]			Maint. Cycle 1	Maint. Subseq. Cycles Every 21 Days (±3)	≤30 Days after Last Dose of Study Treatment	Every 3 Months After Disease Prog.
Day (Window)	–28 to –1	1	2[c]	3	8[c] (±1)	15[c] (±2)	1	2–3	8[c] (±1)	15[c] (±2)	1	2–3	*15[c] (±2)*	1	1		
Induction treatment administration:[cc] venetoclax + atezolizumab + carboplatin + etoposide		X[i]	x	x			x	x			x[r]	x					
Maintenance treatment administration: Venetoclax + atezolizumab														x	x		
Prophylactic cranial irradiation														x[s]	x[s]		
Tumor response assessment	x[t]	X[u]									x[u]				x[u]		x[v]
PK/ADA		x[w]					x[w]				*x*[w]			x *See Appendix 3, Table 1*			

Appendix 2: Schedule of Activities: Dose-Escalation Induction + Maintenance (Arm B) and Dose-Expansion Induction + Maintenance (cont.)

Assessment or Procedure	Screening Period	Treatment Period [a]													Treatment Discon.	Survival Follow-Up
		Induction Cycle 1					Induction Cycle 2 (±3 Days) [b]				Induction Cycles 3–4 (±3 Days) [b]			Maint. Cycle 1	Maint. Subseq. Cycles Every 21 Days (±3)	≤30 Days after Last Dose of Study Treatment	Every 3 Months After Disease Prog.
Day (Window)	–28 to –1	1	2[c]	3	8[c] (±1)	15[c] (±2)	1	2–3	8[c] (±1)	15[c] (±2)	1	2–3	*15[c] (±2)*	1	1		
Blood Sample for biomarker analysis		x	x		x	x	x				x			*x*	C2D1, C3D1, C4D1 and every odd cycle	x See Appendix 4	
Tissue sample for biomarkers	x	Optional See *Appendix 4*														x *See Appendix 4*	
Optional tumor biopsy after induction treatment (if patient signs consent)														After induction treatment			
Optional tumor biopsy at the time of radiographic progression (if patient signs consent) [x]		At the time of initial radiographic progression															

Appendix 2: Schedule of Activities: Dose-Escalation Induction + Maintenance (Arm B) and Dose-Expansion Induction + Maintenance (cont.)

Assessment or Procedure	Screening Period	Treatment Period [a]													Treatment Discon.	Survival Follow-Up
		Induction Cycle 1					Induction Cycle 2 (±3 Days) [b]				Induction Cycles 3–4 (±3 Days) [b]			Maint. Cycle 1	Maint. Subseq. Cycles Every 21 Days (±3)	≤30 Days after Last Dose of Study Treatment	Every 3 Months After Disease Prog.
Day (Window)	–28 to –1	1	2[c]	3	8[c] (±1)	15[c] (±2)	1	2–3	8[c] (±1)	15[c] (±2)	1	2–3	15[c] (±2)	1	1		
Optional tumor biopsy at other timepoints (RBR only)		Any time during study treatment or survival follow-up															
Optional biopsy for DNA extraction (RBR only)		x															
Adverse events		x	x	x	x	x	x	x	x[y]	x[y]	x			x	x	x[z]	x[z]
Concomitant medications [aa]		x	x		x	x	x		x	x	x			x	x	x	
Survival and anti-cancer therapy follow-up																	x[bb]

ADA=anti-drug antibody; C=Cycle; CT=computed tomography; D=Day; discon. =discontinuation; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; FFPE=formalin-fixed paraffin-embedded; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; maint. =maintenance; MRI=magnetic resonance imaging; PCI=prophylactic cranial irradiation; PCR=polymerase chain reaction; PD=pharmacodynamic; PD-L1=programmed death–ligand 1; PK=pharmacokinetic; PCI=prophylactic cranial irradiation; prog=progression; RBR=Roche Biosample Repository; RECIST=Response Evaluation Criteria in Solid Tumors; SCLC=small cell lung cancer; subseq. =subsequent; TLS=tumor lysis syndrome; TSH=thyroid-stimulating hormone.

[a] Assessments should be performed before study drug infusion unless otherwise noted.

[b] Cycle 1 must be performed within 5 days after the patient is enrolled. Screening assessments performed ≤ 96 hours before Cycle 1, Day 1 are not required to be repeated for Cycle 1, Day 1. In addition, ECOG performance status, limited physical examination, and local laboratory tests may be performed ≤ 96 hours before Day 1 of each cycle.

[c] Day 2, Day 8, and Day 15 assessments are not necessary during the dose-expansion phase, with the exception of PK sampling (refer to Appendix 4).

[d] A pre-treatment tumor tissue (archival or freshly obtained) sample should be submitted before or within 4 weeks after enrollment. This specimen must be accompanied by the associated pathology report. Although any available tumor tissue sample can be submitted, it is strongly encouraged that representative tumor specimens in paraffin blocks (preferred) or 15 (or more) serial, freshly cut, unstained slides be submitted.

[e] Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure, and temperature. Vital signs should be recorded as described in Section 4.5.4.

[f] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[g] ECG recordings will be obtained when clinically indicated.

[h] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count.

[i] At screening, the patient must have adequate hematologic and end-organ function defined by laboratory test results obtained within 14 days prior to enrollment.

[j] Serum chemistry includes BUN or urea, sodium, potassium, magnesium, chloride, bicarbonate or total CO^2 if considered standard of care in the region, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.

[k] TLS assessment frequency during the dose-expansion phase will be determined based on a comprehensive review of data in the dose-escalation phase. TLS labs include serum creatinine, calcium, phosphorous, uric acid, potassium, and LDH. If the screening assessments were done within 3 days prior to Cycle 1 Day 1, there is no need to repeat the TLS panel at Cycle 1 Day 1. Refer to Appendix 9 and Appendix 11 for further instructions.

[l] Serum pregnancy test within 14 days before Cycle 1, Day 1.

[m] Urine pregnancy tests; if a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

[n] Total T3 will be tested only at sites where free T3 is not performed.

[o] Thyroid function testing (TSH, free T3, free T4) collected on Day 1 of Cycles 1, 4, 8, and 12, and every fourth cycle thereafter.

[p] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the study. Patients with active hepatitis B (chronic or acute; defined as having a positive HBsAg test result at screening) will be excluded from the study. Patients with past or resolved HBV infection (defined as the presence of HBcAb and absence of HBsAg) are eligible; HBV DNA should be obtained in these patients prior to enrollment. Patients with HCV will be excluded from the study; patients who test positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

[q] Urinalysis by dipstick (specific gravity, pH, glucose, protein, ketones, and blood). Urinalysis is required at screening and will be obtained when clinically indicated.

[r] For atezolizumab, the initial dose will be administered over 60 (± 15) minutes. If the first infusion is well tolerated, subsequent infusions may be administered over 30 (± 10) minutes. For carboplatin and etoposide, study drug will be administered as described.

[s] During the maintenance phase, PCI is permitted as per local standard of care and will be reported on the Prophylactic Cranial Irradiation eCRF.

[t] CT scans (with oral/IV contrast unless contraindicated) or MRI scans of the chest and abdomen. A CT or MRI scan of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. A CT (with contrast) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients.

[u] Perform every 6 weeks (± 7 days) for 48 weeks following Cycle 1, Day 1 and then every 9 weeks (± 7 days) thereafter, after completion of the Week 48 tumor assessment, regardless of treatment delays, until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will undergo tumor assessments *at the frequency described above* until study treatment is discontinued.

[v] If the patient discontinued study treatment for any reason other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration), tumor assessments will continue at the same frequency as would have been followed if the patient had remained on study treatment (i.e., every 6 weeks [± 7 days] for 48 weeks following Cycle 1, Day 1 and then every 9 weeks [± 7 days] thereafter) until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first, even if the patient starts another anti-cancer therapy after study treatment discontinuation, unless consent is withdrawn.

[w] *See Appendix 3, Table 2.*

[x] Optional tumor biopsy at radiographic disease progression, if clinically feasible, preferably within 40 days of radiographic progression or prior to start of the next anti-cancer therapy, whichever occurs is sooner.

[y] Phone call from the site to the patient to assess adverse events as described in Section 5.2.1. The rationale for this phone call is to characterize the impact of and response to treatment, such assessments allow follow-up that is more frequent than the visit, which is every 3 weeks, will be useful in management.

[z] All serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study drug, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study drug, whichever occurs first. After this period, all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment. These events should be reported through use of the Adverse Event eCRF.

[aa] From 7 days before screening until the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

[bb] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits every 3 months or more frequently until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the 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, study staff may use a public information source (e.g., county records), when permissible, to obtain information about survival status only.

[cc] On Day 1 of each cycle, patients will receive treatment in the following order: 1) atezolizumab, 2) carboplatin, 3) etoposide, and 4) venetoclax. On Days 2 and 3, patients will receive etoposide infusions. Refer to Section 4.3.2 for specific details. Venetoclax is administered QD for 7 or 14 days as described in Section 3.1.2.

Appendix 3
Schedule of Pharmacokinetic and Immunogenicity Sampling

Table *1* **Maintenance Phase** *of Dose-Escalation Arms A & B and Maintenance Phase of Dose-Expansion Cohort*

Study Visit *(Maintenance Phase)*	**Venetoclax PK (Plasma Sample)**	**Atezolizumab PK (Serum Sample)**	**Atezolizumab ADA (Serum Sample)**
Cycle 1, Day 1		**Pre-infusion of atezolizumab**	Pre-infusion of atezolizumab
Cycle 2, Day 1	**Predose** (Within 1 hour before dosing) **4 hours postdose** (± 20 minutes)	**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing)	**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing)
Cycle 3, Day 1		**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing)	**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing)
Cycle 4, Day 1	**Predose** (Within 1 hour before dosing) **4 hours postdose** (± 20 minutes)	**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing) **30 minutes after** end of atezolizumab infusion (± 10 minutes)	**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing)
Cycle 8, Day 1		**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing)	**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing)
Cycle 12, Day 1		**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing)	**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing)
Cycle 16, Day 1		**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing)	**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing)
At Treatment *Discontinuation*[a]		**Anytime during visit**	**Anytime during visit**

ADA = anti-drug antibody; PK = pharmacokinetic.

Notes:

PK and ADA samples are to be collected, prepared, and shipped according to procedures outlined in the separate laboratory manual.

Record exact date and time of venetoclax dosing on the day of and the day prior to the date of PK sampling. Patients should record doses taken at home in a dosing diary.

Record the date and time of administration of atezolizumab on the day of PK sampling.

Record exact date and time of all PK sample collections.

Sample collection times are relative to the administration of the study drug being measured.

[a] *Only one sample will be taken at Treatment Discontinuation. Patients may need to discontinue treatment in either the induction or the maintenance phase. Therefore, this sample appears in both Table 1 and Table 2 of Appendix 3.*

Table 2 Induction Phase of Dose-Escalation Arm B and Induction Phase of Dose-Expansion Cohort

Study Visit *(Induction Phase)*	**Venetoclax PK (Plasma Sample)** [a]	**Atezolizumab PK (Serum Sample)**	**Atezolizumab ADA (Serum Sample)**	**Carboplatin PK (Plasma Sample)** [b]	**Etoposide PK (Plasma Sample)** [b]
Cycle 1, Day 1	**6 hours postdose** (± 20 minutes)	**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing) **30 minutes after** end of atezolizumab infusion	**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing)	**Pre-infusion** (within 1 hour before dosing) **5–10 min prior to end of infusion** **1 hours after end of infusion** (± 10 minutes) **3 hours after end of infusion** (± 10 minutes) **5 hours after end of infusion** (± 10 minutes)	**Pre-infusion** (within 1 hour before dosing) **5–10 min prior to end of infusion** **1 hours after end of infusion** (± 10 minutes) **3 hours after end of infusion** (± 10 minutes) **5 hours after end of infusion** (± 10 minutes)
Cycle 1 Day 2	**Predose** (within 1 hour before dosing)			**24 hours after end of prior day infusion** (± 2 hours)	**24 hours after end of prior day infusion and prior to dosing on C1D2** (± 2 hours)
Cycle 1 Day 3 (Day 4 or Day 5 are also acceptable to avoid weekend/ holidays)	**Predose** (within 1 hour before dosing) **4 hours postdose** (± 20 minutes)				
Cycle 1 Day 8	**Predose** (within 1 hour before dosing)				
Cycle 2, Day 1		**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing)	**Pre-infusion** of atezolizumab (Within 24 hours prior to dosing)		

Table 2 Induction Phase of Dose-Escalation Arm B and Induction Phase of Dose-Expansion Cohort (cont.)

Study Visit (Induction Phase)	Venetoclax PK (Plasma Sample) [a]	Atezolizumab PK (Serum Sample)	Atezolizumab ADA (Serum Sample)	Carboplatin PK (Plasma Sample) [b]	Etoposide PK (Plasma Sample) [b]
Cycle 4, Day 1		Pre-infusion of atezolizumab (Within 24 hours prior to dosing) **30 minutes after end of** atezolizumab infusion (± 10 minutes)	Pre-infusion of atezolizumab (Within 24 hours prior to dosing)		
At Treatment Discontinuation[c]		Anytime during visit	Anytime during visit		

ADA = anti-drug antibody; PK = pharmacokinetic; RP2D = recommended Phase II dose.

Notes:

PK and ADA samples are to be collected, prepared and shipped according to procedures outlined in the separate laboratory manual.

Record exact date and time of venetoclax dosing on the day of and the day prior to the date of PK sampling. Patients should record doses taken at home in a dosing diary.

Record the date and time of administration of atezolizumab, carboplatin, and etoposide on the day of PK sampling.

Record exact date and time of all PK sample collections

Sample collection times are relative to the administration of the study drug being measured.

[a] If subject will receive venetoclax in the maintenance phase only, then venetoclax PK samples will not be taken in the induction phase.

[b] Carboplatin and etoposide PK sampling will only be done for patients enrolling into the expansion phase (i.e., after dose-escalation is complete and a RP2D for venetoclax has been determined).

[c] *Only one sample will be taken at Treatment Discontinuation. Patients may need to discontinue treatment in either the induction or the maintenance phase. Therefore, this sample appears in both Table 1 and Table 2 of Appendix 3.*

Appendix 4
Schedule of Biomarker Assessments

Table 1 Blood Samples for Biomarker Analysis

Treatment Period	*Visit*	*Timepoint*	*Sample Type*
Induction and Maintenance	**Cycle 1, Day 1**	Pre-infusion	*Blood for plasma and serum* Whole blood sample
			Whole blood *RBR* sample *for genetic research (for consented patients)*
Induction	**Cycle 1, Day 2**	Pre-infusion	Whole blood sample
	Cycle 1, Day 8	*At anytime during the visit*	Whole blood sample
	Cycle *1*, Day *15*	*At anytime during the visit*	Blood for plasma and serum Whole blood sample
	Cycle *2-4*, Day 1	Pre-infusion	Blood for plasma and serum Whole blood sample
Maintenance	**Cycle *1*-4, Day 1** *(and every subsequent odd cycle), Day 1*	Pre-infusion	Blood for plasma and serum
	Every Cycle~~,~~ Day 1	Pre-infusion	Whole blood sample
Induction and Maintenance	**Study Treatment/Early Discontinuation Visit**	At any time during *the* visit	Blood for plasma and serum Whole blood sample

Table 2 Tissue Sample for Biomarker Analysis

Visit	Timepoint	Requirement	Sample Type
Screening	Pre-infusion	Mandatory	FFPE block or partial block preferred or up to 15 freshly serial cut, unstained slides
Anytime During Study Treatment or During Survival follow-up phase	Pre-infusion	Optional	• Fresh Core Biopsy (3 cores) • FFPE block or partial block preferred or up to 15 freshly serial cut, unstained slides
Study Treatment/Early Discontinuation Visit	At time of study treatment/ early discontinuation visit (if the reason for discontinuation was PD) [a]	Mandatory (if deemed clinically feasible)	• Fresh Core Biopsy (3 cores) at site of progression if accessible or from any other lesion • FFPE block or partial block preferred or up to 15 freshly serial cut, unstained slides

[a] Must be taken before next line of therapy begins. In case new line therapy is purely anti-hormonal, biopsy could be taken after it is started.

Appendix 5
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 $\leq$ 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 $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 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 ≥ 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) since 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 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, since 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 intravenous (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 the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of

non-target disease or new lesions on a different modality, since 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 used 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 should 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 since 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 CR criteria are met, since 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 since 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 at prior timepoints (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 schedule 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.

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.

Table 2 Criteria for Overall Response at a Single Timepoint: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

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 "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 and Table 2.

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.

REFERENCES

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 6
Examples of Prohibited and Cautionary Medications

Table 1 Examples of Strong and Moderate CYP3A Inhibitors and Inducers

CYP3A Inhibitors		CYP3A Inducers	
Strong	**Moderate**	**Strong**	**Moderate**
boceprevir	aprepitant	apalutamide	bosentan
clarithromycin	ciprofloxacin	carbamazepine	efavirenz
cobicistat	conivaptan	enzalutamide	etravirine
danoprevir	crizotinib	mitotane	phenobarbital
dasabuvir	cyclosporine	phenytoin	primidone
elvitegravir	diltiazem	rifampin	
idelalisib	dronedarone	St. John's Wort	
indinavir	erythromycin		
itraconazole	fluconazole		
ketoconazole	fluvoxamine		
lopinavir	imatinib		
nefazodone	tofisopam		
nelfinavir	verapamil		
ombitasvir			
paritaprevir			
posaconazole			
ritonavir			
saquinavir			
telaprevir			
telithromycin			
tipranavir			
troleandomycin			
voriconazole			

[a] These are anti-cancer agents; consult the Medical Monitor before use.

Refer to Section 4.4.2 for guidance related to prohibited and cautionary medications.

Table 2. Examples of P-gp Substrates and Inhibitors

P-gp	
Substrates	**Inhibitors** [a]
dabigatran	amiodarone
digoxin	carvedilol
etexilate	clarithromycin
fexofenadine	dronedarone
	itraconazole
	lapatinib
	lopinavir
	propafenone
	quinidine
	ranolazine
	ritonavir
	saquinavir
	telaprevir
	tipranavir
	verapamil

P-gp = P-glycoprotein.

Note: Refer to Section 4.4.2 for guidance related to prohibited and cautionary medications.

Appendix 7
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). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Grave's 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 • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cirrhosis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix 8
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- 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. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 9
Guidelines for Defining Tumor Lysis Syndrome

All tumor lysis syndrome events should be graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 criteria.

Howard et al. (2011) defined laboratory tumor lysis syndrome as the presence of two or more electrolyte changes above or below the thresholds described above occurring during the same 24-hour period within 3 days before the start of therapy or 7 days after the start of therapy. For the purposes of this study, this window applies to the initiation of any study therapy and each dose–escalation of venetoclax. Furthermore, this assessment assumes that a patient has or will receive adequate hydration (±alkalinization) and a hypouricemic agent(s).

Table 1 Howard Definition of Laboratory Tumor Lysis Syndrome

Laboratory Assessment	Range
Uric acid	>476 μmol/L (>8.0 mg/dL)
Potassium	>6.0 mmol/L (>6.0 mEq/L)
Phosphorous	>1.5 mmol/L (>4.5 mg/dL)
Corrected calcium	<1.75 mmol/L (<7.0 mg/dL) or ionized calcium <1.12 (0.3 mmol/L) [a]

Note: Howard et al. (2011) defined laboratory tumor lysis syndrome as the presence of two or more electrolyte changes above or below the thresholds described above occurring during the same 24-hour period within 3 days before the start of therapy or 7 days afterward. For the purposes of this study, this window applies to the initiation of any study therapy and each dose escalation of venetoclax. Furthermore, this assessment assumes that a patient has or will receive adequate hydration (± alkalization) and a hypouricemic agent(s).

[a] The corrected calcium level in mg/dL is the measured calcium in mg/dL + (0.8 × [4-albumin in g/dL

Table 2 Howard Definition of Clinical Tumor Lysis Syndrome

The presence of laboratory TLS and one or more of the following criteria:
Creatinine[a]: An increase in serum creatinine level of 0.3 mg/dL (26.5 µmol/L); a single value >1.5 times the ULN of the age appropriate normal range if no baseline creatinine measurement is available; or the presence of oliguria, defined as average urine output of <0.5 mL/kg/hour for 6 hours
Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia[b]

TLS=tumor lysis syndrome; ULN=upper limit of normal.

[a] Acute kidney injury is defined as an increase in the creatinine level of ≥0.3 mg/dL (26.5 umol/L) or a period of oliguria lasting ≥6 hours. By definition, if acute kidney injury is present, the patient has clinical TLS.

[b] Not directly attributable to a therapeutic agent.

REFERENCE

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. New Engl J Med 2011;364:1844–54.

Appendix 10
Recommendations for Secondary Prophylaxis with Growth Factors

Event	Management
Febrile neutropenia	Administer Growth factors no sooner than 24 hrs after the last dose of etoposide in the subsequent cycle
Grade 4 persistent neutropenia (lasting > 1 week)	Administer Growth factors no sooner than 24 hrs after last dose of etoposide in the subsequent cycle

Appendix 11
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

FIRST DOSE OF VENETOCLAX

- Within the first 24 hours after the first dose, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- Intravenous (IV) fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150–200 mL/hr; not $<$ 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of tumor lysis syndrome (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of tumor lysis syndrome is established, ongoing intensive monitoring and multidisciplinary management will be as per institutional protocols.

In addition to the recommendations for patients receiving first dose of venetoclax:

- For potassium increase $\geq$ 0.5 mmol/L from baseline, or any value $>$ 5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT and follow first guideline.
- For phosphorus increase of $>$ 0.5 mg/dL AND $>$ 4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.

Appendix 12
Guidelines for Management of Patients Who Experience Adverse Events Associated with Venetoclax

Event	Management
Non-hematologic Toxicity (Not specifically described in Table 9)	
Grade 3 or 4 non-hematologic events	• Delay venetoclax for a maximum of 28 days. First episode: If improvement to Grade ≤ 1 or baseline, resume previous doses of venetoclax. For subsequent episodes: If improvement to Grade ≤ 1 or baseline, restart venetoclax at one dose level reduction. • Certain treatment-emergent non-hematologic adverse events (e.g., venous thromboembolic events) may be managed and become clinically stable following medical intervention but may not improve to Grade ≤ 1 according to the NCI CTCAE definitions. In such cases, if a patient is clinically stable, resumption of study drug may be possible after consultation with the Medical Monitor.
Grade 2 related non-hematologic toxicity	• Delay treatment with venetoclax until resolution to Grade ≤ 1 (or baseline status) for a maximum of 28 days. • After resolution, resume full dose of venetoclax
Grade 1 non-hematologic toxicity	• No dose reduction or delay.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Toxicities associated or possibly associated with atezolizumab 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.

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 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.

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have 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. Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • 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.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab.–Eligible patients 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 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.

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • 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. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • 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.

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 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 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone 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.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 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, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and MRI of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. 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., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. 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.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

Table 6 Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated myocarditis, Grade 3-4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone 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.

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

INFUSION-RELATED REACTIONS

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

Guidelines for medical management of IRRs during Cycle 1 are provided in Table 7. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 7 Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• 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.
IRR, Grade 2	• Interrupt atezolizumab infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs.
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • Permanently discontinue atezolizumab and contact Medical Monitor. [a]

IRR = infusion-related reaction.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. 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 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone 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.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limited, with or without pruritus. 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 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, 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. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. 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. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. 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 11.

Table 11 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone 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.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

RENAL EVENTS

Immune-mediated nephritis has been associated with the administration of atezolizumab. 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.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • 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.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. 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 increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 13 Management Guidelines for Immune-Mediated Myositis (cont.)

Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); 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, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); 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.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq 181 \times 10^9$/L (181,000/μL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids and/or an immunosuppressive agent. • 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.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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