PROTOCOL

TITLE:	**A PHASE II, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED STUDY OF MTIG7192A, AN ANTI-TIGIT ANTIBODY, IN COMBINATION WITH ATEZOLIZUMAB IN CHEMOTHERAPY-NAIVE PATIENTS WITH LOCALLY ADVANCED OR METASTATIC NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO40290
VERSION NUMBER:	3
EUDRACT NUMBER:	2018-000280-81
IND NUMBER:	129258
NCT NUMBER:	NCT03563716
TEST PRODUCTS:	MTIG7192A (RO7092284) Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
APPROVAL DATE:	See electronic data stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
06-Feb-2020 21:45:32	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
2	10 December 2018
1	14 March 2018

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Protocol GO40290 has been amended to modify the safety information based on evolving clinical data observed to date. [redacted] Changes to the protocol, along with a rationale for each change, are summarized below:

- The potential and identified risks for MTIG7192A and atezolizumab have been updated to align with current Investigator's Brochures for MTIG7192A (also known as tiragolumab) and atezolizumab. [redacted]
- To align with the Atezolizumab Investigator's Brochure, Version 15, "immune-related" has been changed to "immune-mediated" when describing events associated with atezolizumab [redacted]
- References to the Immune-Modified Response Evaluation Criteria in Solid Tumors have been removed from the protocol to align with current changing practice-standards. [redacted]
- Language has been revised to clarify the timing of adverse event reporting [redacted]
- To address a request by the [redacted] systemic immune activation has been replaced by hemophagocytic lymphohistiocytosis and macrophage activation syndrome in the list of potential risks for atezolizumab single agent and in combination with other modulating drugs [redacted] and the management guidelines for systemic immune activation have been replaced with management guidelines for hemophagocytic lymphohistiocytosis and macrophage activation syndrome [redacted]
- The Medical Monitor has been changed to [redacted], M.D., and contact information updated (Section 5.4.1).

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 II, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED STUDY OF MTIG7192A, AN ANTI-TIGIT ANTIBODY, IN COMBINATION WITH ATEZOLIZUMAB IN CHEMOTHERAPY-NAIVE PATIENTS WITH LOCALLY ADVANCED OR METASTATIC NON–SMALL CELL LUNG CANCER**
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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 the contract research organization ([redacted]).

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED STUDY OF MTIG7192A, AN ANTI-TIGIT ANTIBODY, IN COMBINATION WITH ATEZOLIZUMAB IN CHEMOTHERAPY-NAIVE PATIENTS WITH LOCALLY ADVANCED OR METASTATIC NON–SMALL CELL LUNG CANCER**
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NCT NUMBER:	NCT03563716
TEST PRODUCTS:	MTIG7192A (RO7092284) Atezolizumab (RO5541267)
PHASE:	Phase II
INDICATION:	Non–small cell lung cancer
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the safety and efficacy of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab in chemotherapy-naive patients with locally advanced unresectable or metastatic PD-L1–selected non–small cell lung cancer (NSCLC), excluding patients with a sensitizing *EGFR* mutation or *ALK* translocation. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab, as measured by objective response rate (ORR) and progression-free survival (PFS)	• ORR, defined as a complete response or partial response on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1 • PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab, as measured by duration of objective response (DOR) and overall survival (OS)	• DOR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first • OS, defined as the time from randomization to death from any cause

Safety Objective	Corresponding Endpoints
• To evaluate the safety and tolerability of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab	• Incidence, nature, and severity of adverse events, graded according to the NCI CTCAE v4.0 • Clinically significant changes from baseline in vital signs, physical findings, and clinical laboratory results during and following administration of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK profile of MTIG7192A and atezolizumab	• Serum concentrations of MTIG7192A or atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to MTIG7192A and atezolizumab	• Incidence of treatment-emergent ADAs and their potential impact on safety, efficacy, and pharmacokinetics
Exploratory Patient-Reported Outcome Objective	**Corresponding Endpoints**
• To evaluate the benefit of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab, in terms of patient-relevant concepts including symptoms, daily functioning, and health-related quality of life (HRQoL)	• Clinically significant changes in symptoms, function, and HRQoL scales from the patient-completed EORTC QLQ-C30
Exploratory Biomarker Objectives	**Corresponding Endpoints**
• [redacted] • [redacted]	• [redacted] • [redacted]

ADA = anti-drug antibody; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HRQoL = health-related quality of life; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; TIGIT = T-cell immunoreceptor with Ig and ITIM domains.

Study Design

Description of Study

This is a Phase II, global, multicenter, randomized, blinded, placebo-controlled study, designed to evaluate the safety and efficacy of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated, locally advanced unresectable or metastatic PD-L1–selected NSCLC.

Male and female patients aged ≥ 18 years with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 who have previously untreated, locally advanced unresectable or metastatic PD-L1–selected NSCLC are eligible.

For the purposes of PD-L1 selection, formalin-fixed tumor samples assessed locally by the commercially available PD-L1 IHC 22C3 pharmDx assays (Dako) will be accepted. Other assays for PD-L1 expression levels will not be accepted for purposes of PD-L1 selection. PD-L1–selected tumors will be defined as tumors with a tumor proportion score (TPS) ≥ 1% by the PD-L1 IHC 22C3 pharmDx assay. Patients that do not have prior testing by the PD-L1 IHC 22C3 pharmDx assay will be prospectively tested for PD-L1 expression by central testing using the commercially available PD-L1 IHC 22C3 pharmDx assays (Dako).

Patients whose tumors have a known *EGFR* mutation or *ALK* rearrangement will be excluded from this study. Patients with tumors of non-squamous histology with unknown *EGFR* or *ALK* mutational status will be required to be tested prior to enrollment. Patients with tumors of squamous histology who have an unknown *EGFR* or *ALK* mutational status will not be required to be tested at pre-screening/screening.

Eligible patients will be randomized 1:1 to receive either MTIG7192A plus atezolizumab or placebo plus atezolizumab.

Eligible patients will be stratified by the PD-L1 IHC 22C3 pharmDx assay result (TPS 1% to 49% vs. TPS ≥ 50%), tumor histology (non-squamous vs. squamous), and patient's history of tobacco use (yes vs. no).

In the experimental arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion every 3 weeks (Q3W) on Day 1 of each 21-day cycle and MTIG7192A at its recommended Phase II dose of 600 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle.

In the control arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle and placebo administered by IV infusion Q3W on Day 1 of each 21-day cycle.

Patients will undergo tumor assessments by standard RECIST v1.1 at baseline and at every 6 weeks thereafter (approximately every 2 cycles) for the first 36 weeks (approximately up to Cycle 12) following randomization. After 36 weeks (or after Cycle 12) from randomization, patients who have not experienced disease progression will undergo tumor assessment every 9 (± 1) weeks (approximately every 3 cycles).

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 treatment (MTIG7192A plus atezolizumab or placebo plus atezolizumab) if they meet all of the criteria.

Patients will undergo tumor assessments until disease progression per RECIST v.1.1 or until treatment discontinuation, whichever occurs later. In the absence of disease progression, tumor assessments should continue, if feasible, until patients start new anti-cancer therapy, consent is withdrawn, death, or study termination by the Sponsor, whichever occurs first.

Patients in whom radiographic disease progression is confirmed at a subsequent tumor assessment may be permitted to continue study treatment (MTIG7192A plus atezolizumab or placebo plus atezolizumab) at the discretion of the investigator if they show evidence of clinical benefit and continue to meet the criteria listed above.

[redacted]

[redacted]

In order not to confound the OS endpoint, crossover will not be allowed from the control arm (placebo plus atezolizumab) to the experimental arm (MTIG7192A plus atezolizumab).

During the study, patients will also be asked to complete a PRO survey at the beginning of the study, at the same visits as tumor assessments are scheduled, and at treatment discontinuation.

During the study, serum samples will be collected to monitor MTIG7192A or atezolizumab PK and to detect the presence of antibodies to MTIG7192A or atezolizumab. [redacted]

Safety assessments will include the incidence, nature, and severity of adverse events, protocol-mandated vital signs, laboratory abnormalities, and other protocol-specified tests that are deemed critical to the safety evaluation of the study. Events and tests will be graded per NCI CTCAE v4.0.

After initiation of study treatment, all adverse events will be reported until *30 days* after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators should report any serious adverse events or other adverse events of *special interest until 90 days after the last dose of study* treatment *or until initiation of new systemic anti-cancer therapy, whichever occurs first.* 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 drug(s) or trial-related procedures until a final outcome can be reported.

After study treatment discontinuation, patients will be followed for survival status and subsequent anti-cancer therapies, approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

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 after discussion with the Medical Monitor and 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 ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing
- Written consent to acknowledge discussion with the treating investigator of the benefit–risk balance of continuing study treatment beyond radiographic progression, including deferring other treatment options

If radiographic disease progression is confirmed at a subsequent tumor assessment, patients may be considered for continued study treatment at the investigator's discretion after discussion with the Medical Monitor, if they continue to meet the above criteria and have continued clinical benefit, as evidenced by at least one of the following:

- Tumor shrinkage (at least 30% decrease in diameter from baseline) of one or more evaluable lesions, or
- Improvement in one or more symptoms or signs attributable to the underlying cancer (e.g., decreased requirement for narcotics for pain, decreased dyspnea associated with pleural effusion, or weight gain) as assessed by the investigator

For patients who consented to treatment beyond progression, new lesions should be entered in the electronic Case Report Form (eCRF). The Sponsor will derive overall tumor assessment as per RECIST v1.1 and investigator assessment of overall tumor response at all timepoints should be *also* based on RECIST v1.1.

Number of Patients

Approximately 50–65 sites globally will participate in the study and will enroll approximately 120 patients with previously untreated, locally advanced unresectable or metastatic NSCLC that is PD-L1–selected.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Ability to comply with the study protocol, in the judgment of the investigator
- ECOG Performance Status of 0 or 1
- Histologically or cytologically documented locally advanced unresectable NSCLC (i.e., Stage IIIB not eligible for definitive chemoradiotherapy), recurrent, or metastatic NSCLC (i.e., Stage IV) (per the Union Internationale Contre le Cancer/American Joint Committee on Cancer [UICC/AJCC] staging system) of either squamous or non-squamous histology

  [redacted]
- No prior systemic treatment for locally advanced unresectable or metastatic NSCLC

  [redacted]
- Tumor PD-L1 expression with a TPS ≥ 1%, as determined by the PD-L1 IHC 22C3 pharmDx assay performed by a local laboratory or by a central laboratory on previously obtained archival tumor tissue or tissue obtained from a biopsy at screening
- Confirmed availability of representative tumor specimens in formalin-fixed, paraffin-embedded (FFPE) blocks (preferred) or at least [redacted] unstained serial slides, along with an associated pathology report. If central testing for *EGFR* mutations and/or *ALK* translocations are required, an additional [redacted] unstained slides need to be provided.

  [redacted]

- Measurable disease, as defined by RECIST v1.1
- Life expectancy ≥ 12 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory results, obtained within 14 days prior to the first study treatment (Cycle 1, Day 1 [C1D1]):
- For women of childbearing potential (including women who have had a tubal ligation): Serum pregnancy test must be performed and documented as negative within 14 days prior to C1D1
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of study drugs. 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 has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

Hormonal contraceptive methods must be supplemented by a barrier method plus spermicide.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as specified below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 90 days after the last dose of study treatment 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 study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

Cancer-Specific Exclusions

- Patients with NSCLC known to have a sensitizing mutation in the *EGFR* gene or an *ALK* fusion oncogene are excluded from the study as follows:

[redacted]

- Patients with the pulmonary lymphoepithelioma-like carcinoma subtype of NSCLC
- Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases

[redacted]

- Spinal cord compression not definitively treated with surgery and/or radiation, and/or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 2 weeks prior to screening

- History of leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (i.e., once monthly or more frequently)

- Uncontrolled tumor-related pain

- Uncontrolled hypercalcemia (ionized calcium > 1.5 mmol/L or calcium > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab

- Malignancies other than NSCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death and/or treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer)

General Medical Exclusions

- Inability to comply with study and/or follow-up procedures
- Pregnant, lactating, or breastfeeding women
- Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results (e.g., uncontrolled major seizure disorder or superior vena cava syndrome)
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease, or current alcohol abuse
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction or cerebrovascular accident within 3 months prior to randomization, unstable arrhythmias, or unstable angina
- Severe infections within 4 weeks prior to initiation of study treatment, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received oral or IV antibiotics (including antifungals) within 2 weeks prior to randomization

- Major surgical procedure within 4 weeks prior to randomization, or anticipation of need for a major surgical procedure during the course of the study
- Inability to understand the local language(s) for which the EORTC QLQ-C30 is available
- Any other disease, 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, that may affect the interpretation of the results, or that may render the patient at high risk from treatment complications

Treatment-Specific Exclusions

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to CHO cell products or any component of the atezolizumab formulation
- Active or history of autoimmune disease [redacted]
- Prior allogeneic bone marrow transplantation or prior solid organ transplantation
- History of idiopathic pulmonary fibrosis (including pneumonitis), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), drug induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan [redacted]
- Positive test for HIV at screening [redacted]
- Patients with active HBV infection, defined as having a positive hepatitis B surface antigen (HBsAg) test at screening [redacted]
- Patients with active HCV infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening [redacted]
- Patients with active Epstein-Barr virus (EBV) infection and patients with known or suspected chronic active EBV infection at screening [redacted]
- Active tuberculosis

- Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation that such a live attenuated vaccine will be required during the study

[redacted]

- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone > 10 mg/day, cyclophosphamide, azathioprine, methotrexate, thalidomide, and tumor necrosis factor [TNF-α] antagonists) within 2 weeks prior to randomization

[redacted]

End of Study

The end of this study is defined as the date when the last data required for all study analysis are collected.

Length of Study

[redacted]

In addition, the Sponsor may decide to terminate the study at any time. If the Sponsor decides to terminate the study, patients who are still receiving study treatment or undergoing survival follow-up may be enrolled in an extension study or a non-interventional study, if available.

Investigational Medicinal Products

Test Product (Investigational Drug)

Atezolizumab at a fixed dose of 1200 mg will be administered first by IV infusion Q3W on Day 1 of each 21-day cycle. MTIG7192A at a fixed dose of 600 mg will be then be administered by IV infusion Q3W on Day 1 of each 21-day cycle.

Comparator

Atezolizumab at a fixed dose of 1200 mg will be administered first by IV infusion Q3W on Day 1 of each 21-day cycle. Placebo will be then be administered by IV infusion Q3W on Day 1 of each 21-day cycle.

Statistical Methods

Primary Analysis

Progression-free survival (PFS) is defined as the time from randomization to the date of first documented disease progression or death, whichever occurs first. Disease progression for PFS analysis will be determined on the basis of investigator assessment using RECIST v1.1. [redacted]

Data for a patient without disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment (or at the date of randomization plus 1 day if no tumor assessment was performed after the baseline visit). Data from a patient who is lost to follow-up will be included in the analysis and censored on the last date of tumor assessment that the patient was known to be progression free.

[redacted]

Objective response rate (ORR) is defined as the percentage of patients who have experienced a complete response (CR) or partial response (PR) on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1. Objective response will be evaluated by treatment arm. Patients without postbaseline overall response assessments will be counted as non-responders.

[redacted]

Determination of Sample Size

Approximately 30 months after the first patient has enrolled in the study, it is estimated that 120 patients (approximately 60 patients in each arm) [redacted]

Interim Analyses

Periodic analyses of cumulative safety data and one interim analysis of efficacy data are planned for this study. [redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
1L	first-line
2L	second-line
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ALK	anaplastic lymphoma kinase
anti–CTLA-4	anti-cytotoxic T lymphocyte–associated protein 4
anti-HBc	antibody to hepatitis B core antigen
BSC	best supportive care
CHO	Chinese hamster ovary
CIT	cancer immunotherapy
CMV	cytomegalovirus
CR	complete response
CRO	contract research organization
CT	computed tomography
DLT	dose-limiting toxicity
DOR	duration of response
EAE	experimental autoimmune encephalitis
EBV	Epstein-Barr virus
EBNA	Epstein-Barr nuclear antigen
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30
FDA	(U.S.) Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
HRQoL	health-related quality of life

Abbreviation	Definition
IC	(tumor-infiltrating) immune cell
ICH	International Council for Harmonisation
IFNγ	interferon-gamma
IHC	Immunohistochemistry
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRF	independent review facility
IRR	infusion-related reaction
ITT	intent-to-treat (population)
IxRS	interactive voice or web-based response system
KRAS	Kirsten rat sarcoma viral oncogene homolog
Mab	monoclonal antibody
MAS	*macrophage activation syndrome*
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NK	natural killer cells
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	pharamcodynamic(s)
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PS	performance status
PVR	poliovirus receptor
Q3W	every 3 weeks
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
TC	tumor cell
TIGIT	T-cell immunoreceptor with Ig and ITIM domains

Abbreviation	Definition
TNF-α	tumor necrosis factor-α
TPS	tumor proportion score
TTD	time to deterioration
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON LUNG CANCER

Lung cancer remains the leading cause of cancer deaths worldwide, accounting for approximately 13% of all new cancers in 2012 (Torre et al. 2015). In 2017 in the United States, it was estimated that there were 222,500 new cases of lung cancer (116,990 in men and 105,510 in women) and 155,870 lung cancer deaths (American Cancer Society 2017). Similar data from Europe estimate that in 2017, there were 275,700 lung cancer deaths (183,400 in men and 92,300 in women) (Malvezzi et al. 2017).

Non–small cell lung cancer (NSCLC) is the predominant subtype, accounting for approximately 85% of all cases (Molina et al. 2008; Howlader et al. 2014). NSCLC can be divided into two major histologic types: adenocarcinoma and squamous cell carcinoma (Travis et al. 2011). Adenocarcinoma histology accounts for more than half of all NSCLC, while squamous cell histology accounts for approximately 25% of NSCLC (Langer et al. 2010). The remaining cases of NSCLC are represented by large cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and poorly differentiated histology.

The overall 5-year survival rate for advanced disease treated with chemotherapy remains poor, depending on geographic location (Cetin et al. 2011). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status, and a history of unintentional weight loss. More than half of the patients with NSCLC are diagnosed with distant disease, which directly contributes to the poor survival prospects.

There are recognized differences in disease characteristics between adenocarcinoma and squamous NSCLC. First, squamous tumors commonly present in the central airways and typically remain localized in the bronchial epithelium (Hirsch et al. 2008), whereas non-squamous tumors are more commonly located in the lung parenchyma distal to the central airways. Evaluation of NSCLC tumor tissue reveals cytological differences between the squamous cell type (characterized by keratinization, intracellular bridges, and central necrosis) and adenocarcinoma (characterized by glandular architecture). In cases where the tumor sample is poorly differentiated or there is limited tissue available, immunohistochemical (IHC) biomarkers may support the histological diagnosis. Thyroid transcription factor-1 (TTF-1) is infrequently expressed in squamous cells and strongly expressed in adenocarcinoma. In contrast, p63, CK5/6, and 34-E12 are strongly expressed in squamous cell carcinoma and less frequently in adenocarcinoma (Travis et al. 2011).

Genetic changes that have prognostic and/or predictive significance in NSCLC include mutations in the epidermal growth factor receptor (*EGFR*) gene, rearrangements in the anaplastic lymphoma kinase (*ALK*) gene, and mutations in the Kirsten rat sarcoma viral

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

1.2 FIRST-LINE TREATMENT FOR NON–SMALL CELL LUNG CANCER WITHOUT AN *EGFR* MUTATION OR *ALK* REARRANGEMENT

Patients with previously untreated NSCLC that does not harbor a driver mutation that confers sensitivity to a targeted agent are typically treated with chemotherapy. The first evidence that chemotherapy produced a significant survival benefit in patients with advanced NSCLC came in 1995; a meta-analysis showed that platinum-based doublet chemotherapy conferred a 2-month improvement in median survival over best supportive care (BSC) (NSCLC Collaborative Group 1995). In addition, the European Big Lung Trial demonstrated the potential benefits of chemotherapy. In this study, 725 patients with advanced NSCLC were randomly assigned to BSC plus cisplatin-based chemotherapy or BSC alone (Spiro et al. 2004). Patients allocated to chemotherapy had a significantly longer median survival than did those patients managed with BSC alone (8 vs. 5.7 months).

The benefit conferred by platinum-based chemotherapy regimens appears to have reached a plateau in objective response rate (ORR; approximately 15% to 22%) and median survival (7–10 months). The addition of bevacizumab to carboplatin and paclitaxel in non-squamous NSCLC resulted in an increase in response rate from 15% to 35% and an increase in median overall survival (OS) from 10 to 12 months (see Table 1).

Table 1 Randomized Phase III Studies in Patients with Previously Untreated Non–Small Cell Lung Cancer

Treatment Group	ORR (%)	Median PFS (months)	Median OS (months)	OS HR (95% CI)
Chemotherapy [a]				
Cisplatin and paclitaxel (n = 288)	21	3.4	7.8	
Cisplatin and gemcitabine (n = 288)	22	4.2	8.1	
Cisplatin and docetaxel (n = 289)	17	3.7	7.4	
Carboplatin and paclitaxel (n = 290)	17	3.1	8.1	
Chemotherapy + biologic [b]				
Carboplatin and paclitaxel (n = 444)	15	4.5	10.3	0.79
Carboplatin, paclitaxel, and bevacizumab, non-squamous (n = 434)	35	6.2	12.3	0.67, 0.92
Chemotherapy [c]				
Cisplatin and pemetrexed, overall (n = 839)	31	4.8	10.3	0.94
Cisplatin and gemcitabine, overall (n = 830)	28	5.1	10.3	0.84, 1.05
Cisplatin and pemetrexed, non-squamous	NR	5.3	11.8	0.81
Cisplatin and gemcitabine, non-squamous	NR	4.7	10.4	0.70, 0.94
Cisplatin and pemetrexed, squamous	NR	4.4	9.4	1.23
Cisplatin and gemcitabine, squamous	NR	5.5	10.8	1.00, 1.51
Chemotherapy [d]				
Carboplatin and nab-paclitaxel, overall (n = 521)	33	6.3	12.1	0.922
Carboplatin and paclitaxel, overall (n = 531)	25	5.8	11.2	0.797, 1.066
Carboplatin and nab-paclitaxel, non-squamous (n = 221)	26	6.9	13.1	0.950
Carboplatin and paclitaxel, non-squamous (n = 292)	25	6.5	13.0	NR
Carboplatin and nab-paclitaxel, squamous (n = 300)	41	5.6	10.7	0.890
Carboplatin and paclitaxel, squamous (n = 229)	24	5.7	9.5	0.719, 1.101

Table 1 Randomized Phase III Studies in Patients with Previously Untreated Non–Small Cell Lung Cancer (cont.)

Treatment Group	ORR (%)	Median PFS (months)	Median OS (months)	OS HR (95% CI)
Chemotherapy + biologic [e]				
Cisplatin and vinorelbine (n = 568)	29	4.8	10.1	0.871
Cisplatin, vinorelbine, and cetuximab (n = 557)	36	4.8	11.3	0.762, 0.996
Immunotherapy [f]				
Pembrolizumab, PD-L1 positive (TPS ≥ 50%) (n = 154)	45	10.3	Not reached	0.60
Platinum-based chemotherapies, PD-L1 positive (TPS ≥ 50%) (n = 151)	28	6.0	Not reached	0.41, 0.89

HR = hazard ratio; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TPS = tumor proportion score.

[a] Schiller et al. 2002.

[b] Sandler et al. 2006.

[c] Scagliotti et al. 2008.

[d] Socinski et al. 2012.

[e] Pirker et al. 2009.

[f] Reck et al. 2016.

Despite the limited survival benefit conferred by cytotoxic chemotherapy, platinum-based regimens remain the standard first-line (1L) option for most patients with metastatic NSCLC not harboring an activating *EGFR* mutation or *ALK* gene rearrangement. In particular, for newly diagnosed advanced-stage non-squamous NSCLC, standard of care is a platinum-based doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. The combination of a platinum-based doublet with pemetrexed has been more widely used because of a better tolerability and safety profile. Currently, the standard of care for newly diagnosed advanced-stage squamous NSCLC includes gemcitabine in combination with a platinum agent.

Overall, these chemotherapy regimens are associated with substantial toxicities (such as febrile neutropenia, myelosuppression, nausea, alopecia, nephropathy, and neuropathy) and are generally poorly tolerated by elderly patients and by poor-performance-status patients. Therefore, novel therapies that deliver an improved therapeutic index are urgently needed for NSCLC.

Immune checkpoint inhibitors, including PD-L1/PD-1 blocking antibodies, have emerged as a new therapeutic option for 1L treatment of metastatic NSCLC. Study KEYNOTE-024 was a Phase III, randomized, open-label study evaluating the PD-1 blocking antibody pembrolizumab given as monotherapy compared with platinum-based chemotherapy in patients who had previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells (TCs) (Reck et al. 2016). In this study, median progression-free survival (PFS) was 10.3 months in the pembrolizumab group versus 6 months in the chemotherapy group (hazard ratio [HR] = 0.50; 95% CI: 0.37, 0.68; $p < 0.001$). The estimated rate of OS at 6 months was 80.2% (95% CI: 72.9%, 85.7%) in the pembrolizumab group versus 72.4% (95% CI: 64.5%, 78.9%) in the chemotherapy group; median OS was not reached in either group. OS was significantly longer in the pembrolizumab group than in the chemotherapy group (HR = 0.60; 95% CI: 0.41, 0.89; $p < 0.005$). On the basis of this study, pembrolizumab was approved by the U.S. Food and Drug Administration (FDA) and by the European Medicines Agency for 1L treatment of metastatic NSCLC in patients whose tumors have high PD-L1 expression (tumor proportion score [TPS] $\geq$ 50%) with no *EGFR* or *ALK* gene aberrations.

Despite improvements in the treatment of patients with advanced NSCLC that have resulted in longer survival times and reduced disease-related symptoms, nearly all patients experience disease progression. Cancer immunotherapies, in particular antibodies that block PD-L1/PD1, offer the possibility of long-term disease control. Pembrolizumab is associated with significantly longer PFS and OS in previously untreated patients with advanced NSCLC (with PD-L1 expression on at least 50% of TCs) than was platinum-based chemotherapy (Reck et al. 2016). In the second-line (2L) cancer immunotherapy (CIT)-naive metastatic NSCLC setting, the anti–PD-L1 antibody atezolizumab (see Section 1.7), as well as the anti–PD-1 antibodies nivolumab and pembrolizumab, provide similar clinically meaningful benefit in either unselected or PD-L1–selected patients with advanced NSCLC; however, the majority of patients still

remain unresponsive or progress on anti–PD-L1/PD-1 treatment, and the escape mechanisms to anti–PD-L1/PD-1 treatment are poorly understood. Consequently, new molecules and combinations, including novel immunotherapy combinations, are urgently needed to address this unmet medical need and are currently being evaluated in ongoing clinical studies to further enhance our understanding of the mechanisms underlying the potential efficacy of immunotherapy (Dempke et al. 2015).

1.3 TIGIT PATHWAY IN CANCER AS POTENTIAL ANTI-CANCER THERAPY

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

TIGIT is expressed in a wide variety of human tumors, including NSCLC, and is highly correlated with T-cell infiltration and PD-1 expression (Johnston et al. 2014). Fluorescence-activated cell sorting analysis on fresh tumor samples showed that TIGIT and PD-1 are also co-expressed on tumor infiltrating T-cells. TIGIT expression ranges from 30% to 80% and 50% to 80% on tumor-infiltrating CD4+ and CD8+ T cells, respectively (Johnston et al. 2014). It has also been reported that tumor-infiltrating lymphocytes from early-stage primary NSCLCs co-express TIGIT with PD-1, suggesting that TIGIT expression may be important throughout the development of NSCLC (Tassi et al. 2017).

Therefore, TIGIT is a potential target for therapeutic intervention aimed at restoring the immune response against the tumor, especially in NSCLC. Agents that inhibit the activity of TIGIT may relieve an important source of tumor-associated immune suppression and may enhance the activity of other immune-based therapies, such as atezolizumab. Early nonclinical results using genetically deficient mice and blocking antibodies reveal a key role for TIGIT in regulating T-cell responses. Together these data support the hypothesis that anti-TIGIT in combination with anti–PD-L1 may reactivate anti-tumor immunity in NSCLC to provide clinical benefit to patients (see Section 1.5).

1.4 PD-L1/PD-1 PATHWAY IN CANCER

PD-L1 is a cell surface protein that is broadly expressed by TCs and tumor-infiltrating immune cells (ICs) in many human cancers, including lung cancer. PD-L1 binds to PD-1 and B7.1, two known inhibitory receptors whose expression on activated T cells is sustained in states of chronic stimulation such as chronic infection or cancer (Blank et al. 2005; Keir et al. 2008). Ligation of PD-L1 with PD-1 or B7.1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to a functional inactivation or inhibition of T cells. Aberrant expression of PD-L1 on TCs has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathways represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

Indeed, inhibitors of PD-L1 or PD-1 have demonstrated clinical efficacy or promising anti-tumor activity in a wide range of tumor types including NSCLC (Herbst et al. 2014, 2016; Borghaei et al. 2015; Garon et al. 2015; Gettinger et al. 2015; Fehrenbacher et al. 2016; Rosenberg et al. 2016). The evidenced benefit has led to approvals of anti–PD-1 antibodies (nivolumab and pembrolizumab) and an anti–PD-L1 antibody (atezolizumab) in metastatic NSCLC (see Keytruda® [pembrolizumab] U.S. Package Insert, Opdivo® [nivolumab] U.S. Package Insert, and Tecentriq® [atezolizumab] U.S. Package Insert). Nevertheless, many patients with NSCLC treated with PD-L1/PD-1 blockade alone do not experience sustained clinical benefit, underscoring the need to explore CIT combinations with the potential to overcome intrinsic or acquired resistance to checkpoint inhibition. Antagonists that target additional inhibitory receptors have the potential to enhance such anti-tumor T-cell responses. Hence, such co-inhibitory antagonists have emerged as attractive combination partners for anti–PD-L1/PD-1 on the basis of their complementary mechanism of action.

Combined immune checkpoint inhibition has been shown to enhance efficacy in clinical studies. It was first reported that a Phase I combination study of an anti–PD-1 antibody (nivolumab) with an anti-cytotoxic T lymphocyte–associated protein 4 (anti–CTLA-4) antibody (ipilimumab) in patients with advanced melanoma resulted in rapid and pronounced tumor responses in patients receiving the maximum combination doses that were shown to be associated with an acceptable risk-benefit (Wolchok et al. 2013). This combination of nivolumab and ipilimumab was also studied as a 1L treatment in patients with metastatic NSCLC in another Phase I study, yielding ORRs of 38% to 47% with two different dose schedules for ipilimumab, and median duration of response (DOR) was not yet reached at the time of reporting (Hellman et al. 2017). However, this combination of nivolumab and ipilimumab results in increased toxicity, as Grade 3–4 adverse events occurred in 33% to 37% of patients, with the most commonly reported treatment-related adverse events being increased lipase and pneumonitis. A similar combination of the anti–PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab in patients with NSCLC in a Phase Ib study reported an ORR of 23%, with similar increased adverse events (Antonia et al. 2016). Combined immune

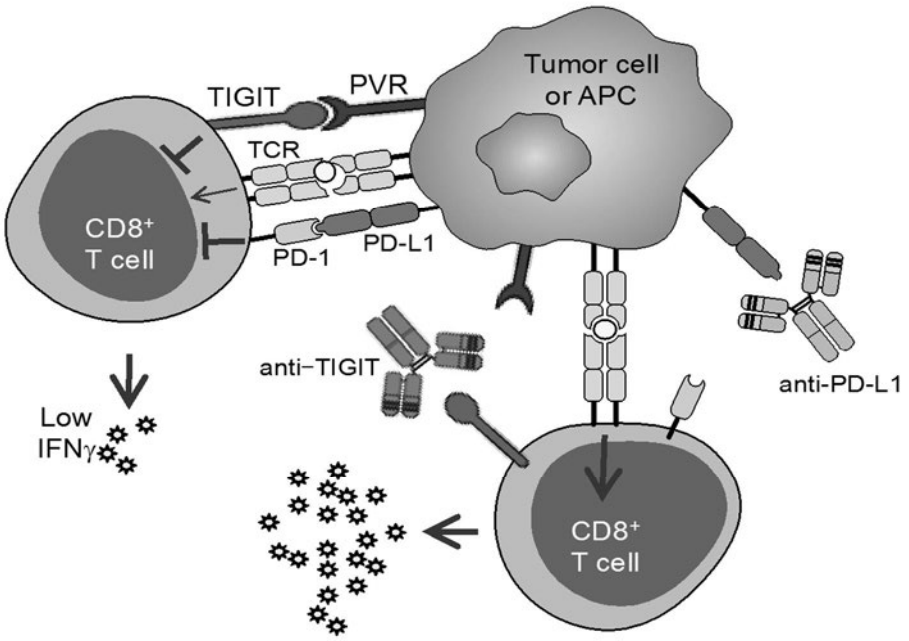
checkpoint inhibition can result in increased response rates in patients with metastatic NSCLC, although such an increase in efficacy may also increase toxicity; therefore, an immune combination with potentially decreased toxicity but similar efficacy is desired.

1.5 COMBINED INHIBITION OF THE TIGIT AND PD-L1/PD-1 PATHWAYS AS POTENTIAL ANTI-CANCER THERAPY

The inhibitory immunoreceptor TIGIT has been shown to limit the effector function of tumor-associated lymphocytes. Activation of TIGIT on T cells and NK cells limits proliferation, effector cytokine production, and killing of target TCs. Therefore, in the context of the tumor microenvironment, TIGIT acts to limit anti-tumor immune responses. Interference with the TIGIT/PVR interaction may enhance the magnitude and quality of the tumor-specific T-cell responses through increased expansion of T cells as well as improved T-cell priming and/or effector function. Because TIGIT and PD-1 are coordinately expressed by infiltrating T cells in several human tumors, inhibition of the TIGIT/PVR pathway may complement and potentiate the anti-tumor activity of a PD-L1 pathway inhibitor such as atezolizumab.

In preclinical models, concomitant blockade of both TIGIT and PD-L1/PD-1 pathways demonstrated superior efficacy over the respective single-agent treatments. [redacted] On the basis of these studies, it is hypothesized that the combination of anti-TIGIT with anti–PD-L1/PD-1 may result in activation of anti-tumor immune responses leading to enhanced killing of TCs and improved clinical responses in patients with metastatic NSCLC than with either agent alone (Figure 1).

Figure 1 Proposed Model for Re-Activating Tumor-Specific T Cells by TIGIT Inhibition and PD-L1 Inhibition



APC = antigen-presenting cell, IFNγ = interferon-gamma, PVR = poliovirus receptor; TCR = T-cell receptor; TIGIT = T-cell immunoreceptor with Ig and ITIM domains.

1.6 BACKGROUND ON MTIG7192A

MTIG7192A (also known as tiragolumab) is a fully human IgG1/kappa monoclonal antibody (MAb) [redacted]

Therapeutic blockade of TIGIT by MTIG7192A represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of the tumor-specific T-cell responses, which may result in improved meaningful anti-tumor activity when MTIG7192A is used as a single agent or in combination with other cancer immunotherapies.

MTIG7192A is being investigated as a potential therapy against tumors in humans.

Please refer to the MTIG7192A Investigator's Brochure for additional details on the nonclinical and clinical studies for MTIG7192A.

1.6.1 Summary of Nonclinical Data with MTIG7192A

The nonclinical strategy for MTIG7192A was to demonstrate in vitro and in vivo pharmacology, to evaluate the pharmacokinetic (PK) profile, to demonstrate an acceptable safety profile, [redacted] Comprehensive pharmacology, PK, and toxicology evaluations were thus undertaken with MTIG7192A.

The completed nonclinical pharmacology studies demonstrate that MTIG7192A binds TIGIT and prevents TIGIT/PVR interactions. [redacted] In the CT26 syngeneic colon tumor model, co-inhibition of the TIGIT/PVR and PD-L1/PD-1 pathways improves anti-tumor activity when compared with inhibition of only one pathway with either monotherapy in the absence of body weight loss or any other observable adverse responses. Taken together, these data provide a rationale for evaluating the combination of anti-TIGIT with anti–PD-L1 in clinical studies.

[redacted] Overall, the nonclinical PK behavior observed for MTIG7192A is consistent with that expected for a receptor-targeting human IgG1 MAb. [redacted] On the basis of the proposed mechanism of action of MTIG7192A, possible safety risks to patients following TIGIT/PVR pathway inhibition include heightened immune responses and the potential to increase the frequency and/or the severity of immune-associated inflammatory lesions. These potential effects are considered to be monitorable and are expected to be manageable (see Section 5.1 for the safety plan).

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for MTIG7192A supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway and supported entry into clinical studies.

Please refer to the MTIG7192A Investigator's Brochure for additional details on nonclinical studies.

1.6.2 Clinical Experience with MTIG7192A

Please refer to the MTIG7192A Investigator's Brochure for details on all clinical studies conducted to date.

1.6.2.1 Ongoing Clinical Studies with MTIG7192A

[redacted]

Available single-agent and combination safety and preliminary efficacy data from Study GO30103 and combination preliminary safety data from the current Study GO40290 are summarized below.

1.6.2.2 Clinical Safety of MTIG7192A

[redacted]

[redacted]

The safety profile of MTIG7192A as a single agent and in combination with atezolizumab is observed to be consistent across different tumor indications. [redacted]

1.6.2.2.1 Single-Agent Clinical Safety of MTIG7192A

[redacted]

[redacted]

[redacted]

Please refer to the MTIG7192A Investigator's Brochure for details on the adverse events observed in patients treated with MTIG7192A.

1.6.2.2.2 Clinical Safety of MTIG7192A Plus Atezolizumab

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

In the current Phase II study (GO40290), [redacted]

[redacted]

[redacted]

Please refer to the MTIG7192A Investigator's Brochure for details on the adverse events observed in patients treated with MTIG7192A plus atezolizumab.

1.6.2.3 Clinical Activity of MTIG7192A Plus Atezolizumab

[redacted]

Please refer to the MTIG7192A Investigator's Brochure for details on clinical activity in all patients treated to date with MTIG7192A as a single agent or in combination with atezolizumab, regardless of tumor type.

1.6.2.4 Clinical Pharmacokinetics and Immunogenicity of MTIG7192A

[redacted], preliminary PK data are available from patients treated with MTIG7192A as a single agent at multiple dose levels [redacted]

Please refer to the MTIG7192A Investigator's Brochure for details on the clinical pharmacokinetics of MTIG7192A.

1.7 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 MAb 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 CIT.

Atezolizumab is approved for the treatment of patients with metastatic NSCLC after prior chemotherapy and for the treatment of patients with metastatic urothelial carcinoma after prior chemotherapy.

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

1.7.1 Summary of Nonclinical Studies for Atezolizumab

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine the in vivo PK behavior, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacologic, PK, and toxicologic evaluations were thus undertaken with atezolizumab.

The safety, PK, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support IV administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, PK, and toxicokinetics of atezolizumab.

Overall, the nonclinical PK and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway and supported entry into clinical studies in patients.

Please refer to the current Atezolizumab Investigator's Brochure for further details on the nonclinical studies.

1.7.2 Clinical Experience with Atezolizumab in NSCLC

1.7.2.1 Ongoing Clinical Studies with Atezolizumab in NSCLC

Atezolizumab is currently being tested in multiple Phase I, II, and III studies in NSCLC, both as monotherapy and in combination with several anti-cancer therapies (please see the Atezolizumab Investigator's Brochure for study descriptions). The single agent and combination safety and efficacy data for atezolizumab in NSCLC include, but are not limited to, data from the following studies:

- Study PCD4989g: a Phase Ia, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of activity of atezolizumab as a single agent in patients with locally advanced or metastatic malignancies, including NSCLC
- Study GO28753 (POPLAR): a randomized, Phase II, open-label study assessing the clinical benefit of atezolizumab versus docetaxel in patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen
- Study GO28754 (BIRCH): a Phase II, open-label study assessing the clinical benefit of atezolizumab in patients with PD-L1–selected locally advanced or metastatic NSCLC in all lines of therapy (previously untreated to heavily pretreated)

- Study GO28915 (OAK): a randomized, Phase III, open-label study assessing the efficacy and safety of atezolizumab versus docetaxel in patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen
- Study GO29436 (IMpower150): a randomized, Phase III, open-label study evaluating the efficacy and safety of atezolizumab plus carboplatin plus paclitaxel with or without bevacizumab compared with carboplatin plus paclitaxel plus bevacizumab in chemotherapy-naive patients with Stage IV non-squamous NSCLC

In addition, the following studies of atezolizumab as a single agent or in combination with chemotherapy and/or immunotherapy are currently enrolling patients with NSCLC, including chemotherapy-naive patients, or have completed enrollment and are awaiting study results:

- Study GO29431 (IMpower110): a randomized, Phase III, open-label study evaluating the efficacy and safety of atezolizumab compared with cisplatin/carboplatin plus pemetrexed or cisplatin/carboplatin plus gemcitabine in PD-L1–selected chemotherapy-naive patients with Stage IV non-squamous NSCLC
- Study GO29437 (IMpower 131): a randomized, Phase III, open-label study evaluating the efficacy and safety of atezolizumab in combination with carboplatin plus paclitaxel or atezolizumab in combination with carboplatin plus nab-paclitaxel versus carboplatin plus nab-paclitaxel in chemotherapy-naive patients with Stage IV squamous NSCLC
- Study GO29438 (IMpower132): a randomized, Phase III, open-label study evaluating the efficacy and safety of atezolizumab in combination with carboplatin or cisplatin plus pemetrexed compared with carboplatin or cisplatin plus pemetrexed in chemotherapy-naive patients with Stage IV non-squamous NSCLC
- Study GO29527 (IMpower010): a randomized, Phase III, open-label study of atezolizumab compared with BSC following adjuvant cisplatin-based chemotherapy in patients with completely resected Stage IB to IIIA NSCLC
- Study GO29537 (IMpower130): a randomized, Phase III, open-label study evaluating the efficacy and safety of atezolizumab plus carboplatin plus nab-paclitaxel compared with carboplatin plus nab-paclitaxel in chemotherapy-naive patients with Stage IV non-squamous NSCLC
- Study BO39610 (MORPHEUS-Lung): a randomized, Phase Ib/II, open-label umbrella study evaluating the efficacy and safety of atezolizumab plus multiple immunotherapy-based treatment combinations in chemotherapy-naive and pre-treated patients with Stage IV NSCLC

Please refer to the Atezolizumab Investigator's Brochure for full details on the clinical studies in all tumor types, including NSCLC.

1.7.2.2 Clinical Safety of Atezolizumab

As of the clinical cutoff date of 17 May *2019* of the Atezolizumab Investigator's Brochure, an estimated *21,000 patients* with solid tumor and hematologic malignancies had received atezolizumab in clinical study participation as a single agent or in combination with cytotoxic chemotherapy and/or targeted therapy.

Overall, treatment with atezolizumab is well tolerated with a manageable adverse event profile. Currently, no MTD, no DLTs, and no clear dose-related trends in the incidence of adverse events have been determined.

Immune-*mediated* 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*, myositis, and nephritis*. IRRs are another identified risk of atezolizumab.

Potential risks of atezolizumab include immune-*mediated* ocular toxicity, immune-*mediated* severe cutaneous adverse reactions, immune-*mediated* vasculitis, autoimmune hemolytic anemia, and toxicity associated with ADAs. Based on the mechanism of action, atezolizumab likely would result in fetal harm if administered to pregnant women. *In addition, immune-mediated reactions may involve any organ system and may lead to HLH and macrophage activation syndrome (MAS).*

1.7.2.2.1 Clinical Safety of Atezolizumab as a Single Agent

As of the clinical cutoff date 17 May *2019*, of the pooled *3178 patients* with NSCLC*,* urothelial carcinoma*, renal-cell carcinoma, and other tumors* who received single-agent atezolizumab, *96%* experienced an adverse event regardless of attribution to atezolizumab. The majority of these adverse events were Grade 1 or 2 in maximum severity based on NCI CTCAE v4.0.

Safety findings of single-agent atezolizumab across multiple tumor types in the clinical development program are consistent with the known mechanism of action of atezolizumab and the underlying disease. The most frequently observed adverse events occurring in ≥ 10% of treated patients included fatigue, decreased appetite, cough, nausea, dyspnea, constipation, diarrhea, pyrexia, vomiting, arthralgia, back pain, asthenia, anemia, pruritus, rash, headache, *urinary tract infection,* and peripheral edema.

Grade 3 and Grade 4 adverse events were reported in *46.5%* of patients with the most common (≥*3%* of patients) being *anemia (5.0%),* dyspnea (*3.7%*), fatigue (*3.4%*), hyponatremia (*3.1%*), and pneumonia (*3.0%*). Grade 3 and Grade 4 adverse events considered related to study drug by the investigator occurred in *15.6%* of patients.

1.7.2.2.2 Clinical Safety of Single-Agent Atezolizumab in Patients with NSCLC

Safety data for patients with metastatic NSCLC treated with single-agent atezolizumab are also derived from the following completed Phase II/III studies in NSCLC: GO28753 (POPLAR), GO28915 (OAK), and GO28754 (BIRCH). Overall, in the randomized studies (OAK and POPLAR), atezolizumab was well tolerated by patients with metastatic NSCLC, with fewer Grade 3 or Grade 4 adverse events and fewer discontinuations seen with atezolizumab versus the chemotherapy comparator arm of docetaxel. The most commonly reported adverse events (all grades) for patients treated with atezolizumab on these studies included fatigue, decreased appetite, constipation, cough, dyspnea, asthenia, diarrhea, and nausea. The adverse event profiles observed in these studies for patients with metastatic NSCLC treated with single-agent atezolizumab is consistent with that observed in Study PCD4989g (in the overall and NSCLC patient populations).

1.7.2.2.3 Immune-*Mediated* Adverse Events of Atezolizumab as a Single Agent

Immune-*mediated* 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-*mediated* adverse events are closely monitored during the atezolizumab clinical program. Although most immune-*mediated* adverse events observed with immunomodulatory agents have been mild and self-limiting, severe cases of immune-*mediated* toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

For the most recent safety data, please refer to the Atezolizumab Investigator's Brochure.

1.7.2.3 Clinical Activity of Atezolizumab

Anti-tumor activity, including RECIST-based responses (i.e., RECIST v1.1 responses), have been observed in patients with different tumor types, including NSCLC, treated with atezolizumab monotherapy in multiple Phase I, II, and III studies.

Please refer to the Atezolizumab Investigator's Brochure for details on clinical activity in all patients treated to date, regardless of tumor type.

1.7.2.3.1 Clinical Activity of Atezolizumab in Patients with NSCLC

<u>Study PCD4989g (NSCLC Cohort)</u>

As of the clinical data cutoff date of 2 December 2014, 88 patients with locally advanced or metastatic NSCLC had enrolled in the NSCLC expansion cohort of this Phase I study. The majority of these patients had received multiple prior systemic therapies. Overall, responses were observed in 20 of 88 patients (22.7%) with NSCLC and included responses in patients with non-squamous and squamous NSCLC (16 in 67 patients and 4 in 21 patients, respectively).

[redacted]

Study GO28754 (BIRCH)

This single-arm Phase II study evaluated atezolizumab monotherapy in the treatment of PD-L1–selected (defined as TC2/3 or IC2/3 by Ventana PD-L1 [SP142] IHC assay) patients with NSCLC, including chemotherapy-naive patients in Cohort 1 (1L treatment). For the primary efficacy endpoint of independent review facility-assessed ORR (confirmed responses) per RECIST v1.1, atezolizumab monotherapy resulted in a statistically significant increase in ORR compared with historical controls, ranging from

17.3% to 27.0% for TC3 or IC3. The highest level of PD-L1 expression (TC3 or IC3) showed the highest ORRs across all lines of therapy. At the time of the primary analysis on 28 May 2015, the median OS was not reached for all subgroups with the exception of TC2/3 or IC2/3 in Cohort 1 (chemotherapy-naive), where the median was 14.0 months (95% CI: 14.0–not evaluable).

An updated efficacy analysis (data cutoff date 1 August 2016) conducted for 138 patients receiving 1L treatment (Cohort 1) with a minimum follow-up of 22.5 months provided evidence of a clinically meaningful benefit of atezolizumab as 1L treatment for patients with NSCLC, as demonstrated by a median OS of 23.5 months for all patients (TC2/3 or IC2/3). ORR was 25% (95% CI: 18%, 33%) and median PFS was 7.3 months (95% CI: 5.7, 9.7 months) for all patients (TC2/3 or IC2/3); the median duration of response (DOR) was 9.8 months for all chemotherapy-naive patients (Peters et al. 2017b).

Study GO28753 (POPLAR)

This randomized Phase II study in patients with advanced or metastatic NSCLC who failed prior platinum therapy enrolled 287 patients, who were randomized to treatment with atezolizumab or docetaxel chemotherapy (Fehrenbacher et al. 2016). At the time of the primary analysis on 8 May 2015, a clinically meaningful and statistically significant improvement in OS was observed for patients treated with atezolizumab compared with docetaxel with a stratified HR of 0.73 (95% CI: 0.53, 0.99; p-value = 0.04). The median OS was 12.6 months in the atezolizumab arm versus 9.7 months in the docetaxel arm. Improvement in OS in the atezolizumab arm relative to the docetaxel arm increased with increasing PD-L1 expression. In the TC0 or IC0 subgroup, however, median OS was 9.7 months in both the atezolizumab and docetaxel arms, suggesting that atezolizumab-treated patients in this subgroup also derived clinical benefit.

Study GO28915 (OAK)

In this randomized Phase III study, patients with advanced or metastatic NSCLC who had failed prior platinum therapy were randomized to treatment with atezolizumab or docetaxel chemotherapy. The co-primary endpoints were OS in all randomized patients (intent-to-treat [ITT] population) and OS in a PD-L1–selected subgroup in the primary analysis population (TC1/2/3 or IC1/2/3 by Ventana PD-L1 [SP142] IHC assay). At the time of the primary analysis (data cutoff date 7 July 2016), which included data from the first 850 randomized patients, OS was significantly improved with atezolizumab compared with docetaxel (median OS, 13.8 vs. 9.6 months; HR = 0.73; 95% CI: 0.62, 0.87; p = 0.0003). For the TC1/2/3 or IC1/2/3 subgroups, OS was also significantly improved with atezolizumab compared with docetaxel (median OS, 15.7 vs. 10.3 months; HR = 0.74; 95% CI: 0.58, 0.93; p = 0.0102).

PFS was similar between the atezolizumab and docetaxel arms (median PFS, 2.8 vs. 4 months; HR = 0.95; 95% CI: 0.82, 1.10). Fifty-eight patients (14%) in the atezolizumab arm and 57 patients (13%) in the docetaxel arm achieved a confirmed objective

response per RECIST v1.1. Objective responses with atezolizumab were durable, with a median duration of 16.3 months (95% CI: 10 months, not estimable) in the atezolizumab arm compared with 6.2 months (95% CI: 4.9, 7.6 months) in the docetaxel arm (Rittmeyer et al. 2017).

1.7.2.3.2 Clinical Activity of Atezolizumab Plus Chemotherapy in Patients with NSCLC

Study GO29436 (IMpower150)

This Phase III study enrolled patients with chemotherapy-naive metastatic NSCLC and randomized them to receive atezolizumab or placebo combined with carboplatin plus paclitaxel with or without bevacizumab. As of the clinical data cutoff date of 15 September 2017, the safety and efficacy evaluable population included 400 patients in each arm. PFS was increased in the atezolizumab plus chemotherapy plus bevacizumab arm compared with the placebo plus chemotherapy plus bevacizumab arm (median PFS 8.3 months vs. 6.8 months; HR = 0.617, 95% CI: 0.517, 0.737). Although clinical benefit was seen across all PD-L1 subgroups, PFS was increased in the PD-L1 IHC TC1/2/3 or IC1/2/3 group compared with the PD-L1 IHC TC0 or IC0 group (median PFS 11 months and 7.1 months, respectively). The combination was well tolerated and was consistent with the known safety profile of atezolizumab, chemotherapy, and bevacizumab. OS data was not mature at the time of the data cutoff (Reck et al. 2017).

Please refer to the Atezolizumab Investigator's Brochure for the most recent information regarding clinical efficacy from the studies of atezolizumab in NSCLC.

1.7.2.4 Clinical Pharmacokinetics and Immunogenicity of Atezolizumab

Overall, atezolizumab exposures increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including the fixed dose of 1200 mg administered Q3W. The elimination half-life of atezolizumab was estimated to be 27 days, based on a Phase I population PK analysis that included 472 patients from Studies PCD4989g and JO28944. ADAs to atezolizumab have been observed in some patients at all dosing levels, but the presence of ADAs did not appear to have a clinically significant impact on pharmacokinetics, safety, or efficacy of atezolizumab at the 1200-mg dose.

Please refer to the Atezolizumab Investigator's Brochure for details on the clinical PK of atezolizumab.

1.8 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.8.1 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 NSCLC. Recent approvals by the FDA in metastatic NSCLC of the PD-1 inhibitors pembrolizumab in the 1L and 2L-plus settings, nivolumab in the 2L setting, and the PD-L1 inhibitor atezolizumab in the 2L-plus settings, as well as the observation of durable objective responses in clinical studies achieved with other anti–PD-L1/PD-1 antibodies in patients with NSCLC, validate the inhibition of the PD-L1/PD-1 pathway for achieving clinical benefit in NSCLC. Furthermore, the safety profile of these immunotherapies, including PD-L1/PD-1 antibodies, appears to be more tolerable than many of the chemotherapy doublet combinations given in the front-line setting, which are associated with substantial toxicities and are often poorly tolerated by elderly and poor-performance status patients.

Nevertheless, despite the robust activity observed with anti-PD-L1/PD-1 agents, durable clinical benefit appears limited to a minority of treated patients. Enrichment or selection strategies to identify those patients most likely to respond to PD-L1/PD-1 inhibitors are still evolving, but one area has focused on PD-L1–selection of tumors, especially in earlier lines of therapy for metastatic NSCLC. For example, nivolumab, the first PD-1 inhibitor approved for NSCLC, was approved for patients with NSCLC in the 2L setting, regardless of PD-L1 expression, although OS and PFS HRs in patients with non-squamous NSCLC trended lower with increasing PD-L1 expression (Opdivo U.S. Package Insert). Pembrolizumab was the second PD-1 inhibitor approved by the FDA for metastatic NSCLC and was approved for patients whose tumors express PD-L1 on the basis of a study that demonstrated that PD-L1 expression tends to enrich for increased efficacy (Herbst et al. 2016). Atezolizumab was the first PD-L1 inhibitor approved for 2L NSCLC irrespective of PD-L1 expression, and there was also a clinically meaningful benefit observed with atezolizumab given as 1L treatment for PD-L1–selected patients (TC2/3 or IC2/3) with NSCLC in Study GO28754 (BIRCH).

The PD-L1 expression level that is most predictive of response to PD-L1/PD-1 inhibitors remains unknown in the 1L setting for NSCLC, although current studies are focusing on a minimum level of PD-L1 expression to enroll. For example, although pembrolizumab is approved in the 1L setting for metastatic NSCLC with a TPS cutoff of $\geq$50%, pembrolizumab is currently being tested at a TPS cutoff of $\geq$1% in the KEYNOTE-042 study. Similarly, atezolizumab is being studied as a 1L treatment for patients with metastatic NSCLC whose tumors have a minimum level of PD-L1 expression ($\geq$1%) on TCs or ICs (TC1/2/3 or IC1/2/3) (Study GO29431, IMpower110).

Therefore, in the current study, in order to potentially select patients who may benefit from immunotherapy in the 1L setting, all patients, either on the experimental arm with

MTIG7192A plus atezolizumab or on the comparator arm with placebo plus atezolizumab, will need to have a minimum PD-L1 expression of TPS ≥ 1% by the PD-L1 IHC 22C3 pharmDx assay in order to enroll in the study.

Although PD-L1/PD-1 therapeutic antibodies may have a greater probability of potentially benefiting those patients whose tumors have PD-L1 expression, the majority of patients with metastatic NSCLC treated with PD-L1/PD-1 antibodies still do not experience sustained clinical benefit, despite the selection for PD-L1 expression. It is hypothesized that many of these patients with metastatic NSCLC may have intrinsic or acquired resistance to checkpoint inhibition. Thus, another strategy to increase the response to checkpoint inhibitors among patients has focused on treatment with novel immunotherapy combinations that may overcome such intrinsic or acquired resistance to PD-L1/PD-1 antibodies.

TIGIT is a novel inhibitory immunoreceptor that can limit the effector function of tumor-associated lymphocytes. Unlike other inhibitory co-receptors, TIGIT is often coordinately expressed with PD-1 on infiltrating T cells in multiple tumors, including NSCLC. Thus, the combined inhibition of the TIGIT and PD-L1/PD-1 pathways is a unique and attractive strategy to potentiate the activity of a PD-L1 antibody such as atezolizumab, due to the complementary mechanisms of action of anti-TIGIT and anti–PD-L1. In preclinical models, combined blockade of the TIGIT and PD-L1/PD-1 pathways has shown superior efficacy compared with blockade of each pathway alone.

[redacted]

Therefore, the current study is designed to evaluate whether the anti-tumor effects of atezolizumab, as measured by ORR, PFS, DOR, and OS, can be improved with the addition of the anti-TIGIT antibody MTIG7192A compared with placebo plus atezolizumab in patients with metastatic NSCLC who are selected on the basis of a minimum level of PD-L1 tumor expression (TPS ≥ 1%). The PD-L1 IHC 22C3 pharmDx assay will be used to identify patients that are positive for tumor PD-L1 expression.

1.8.2 Benefit–Risk Assessment

This study will enroll patients with locally advanced unresectable or metastatic PD–L1–selected NSCLC who are naive to chemotherapy treatment, and all patients will be administered atezolizumab, either in the experimental arm or in the placebo arm. The combination of MTIG7192A plus atezolizumab in the experimental arm can represent a potential valuable treatment option and can offer a reasonable benefit–risk balance for patients in this study.

To better understand the risks and benefits about participation on this study, patients will be fully informed of the current 1L treatment options for metastatic NSCLC, as approved in the United States by the FDA in 2017. For all patients, the standard of care in the 1L treatment of metastatic NSCLC without *EGFR* or *ALK* alterations is a chemotherapy doublet often consisting of a platinum chemotherapy agent. Although chemotherapy combinations can result in significant toxicities, such regimens are still the approved standard of care in 1L metastatic NSCLC in many countries. Furthermore, in the United States, for patients with metastatic NSCLC whose tumors have high PD-L1 expression with a TPS $\geq$ 50% by the PD-L1 IHC 22C3 pharmDx assay, pembrolizumab as a single agent is approved as a 1L treatment. Finally, in the United States, for patients with non-squamous NSCLC, the combination of pembrolizumab with pemetrexed and carboplatin chemotherapy is also approved as a 1L treatment option, irrespective of PD-L1 expression.

[redacted], atezolizumab is approved by the FDA in the 2L-plus settings for all patients with metastatic NSCLC, irrespective of PD-L1 expression, based on prolonged OS in two randomized studies (see Section 1.7.2.3). Atezolizumab has also been studied previously in 1L metastatic NSCLC in Study GO28754 (BIRCH), in which patients with PD-L1–selected NSCLC had a median OS of 23.5 months (see Section 1.7.2.1). Furthermore, multiple studies of atezolizumab as a single agent or in combination with other anti-cancer agents, including chemotherapy, are ongoing in 1L metastatic NSCLC. There is an ongoing study of single-agent atezolizumab in PD–L1–selected metastatic 1L NSCLC (Study GO29431, IMpower110) (see Section 1.7.2.1). Atezolizumab is also being studied in combination with chemotherapy in 1L NSCLC; one such study (GO29436, IMpower150) with atezolizumab in combination with carboplatin and paclitaxel with bevacizumab in non-squamous 1L NSCLC demonstrated improved PFS (Reck et al. 2017). Finally, there is an ongoing study in 1L NSCLC of atezolizumab in combination with other anti-cancer agents, including immunotherapy (Study BO39610, MORPHEUS).

Therefore, atezolizumab as a single agent has clinical efficacy in metastatic NSCLC and is generally well tolerated (see Section 1.7.2 and Section 3.3.1). Adverse events with potentially immune-*mediated* causes consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis/transaminitis, colitis, and myasthenia gravis have been observed with atezolizumab. To date, however, these events have been manageable with treatment.

[redacted]

[redacted]

Although patients will have their tumor checked for PD-L1 expression prior to being able to enroll in the study and all patients will have PD-L1–selected tumors, PD-L1 selection by itself does not ensure that the majority of patients will respond to treatment with immunotherapy, including atezolizumab. Thus, it is hypothesized that clinical activity in metastatic NSCLC may be enhanced with atezolizumab when combined with the anti-TIGIT antibody MTIG7192A (see Section 1.8.1).

[redacted]

In the current study, patients will be selected based on the PD-L1 status of their tumor, as a TPS $\geq$1% is required for enrollment. Patients will be informed that in the United States, pembrolizumab as a single agent is approved for treatment of 1L NSCLC with a PD-L1 TPS $\geq$50%; for patients whose tumors have PD-L1 TPS $<$50%, the approved therapies are chemotherapy or pembrolizumab in combination with chemotherapy. Atezolizumab as a single agent is already approved for all patients for the 2L treatment of metastatic NSCLC independent of PD-L1 IHC status, based on a Phase III study (GO28915, OAK). Additionally, there is precedent for treating patients with metastatic PD-L1–selected NSCLC in the 1L setting with atezolizumab, and there are data to suggest that pembrolizumab or atezolizumab may also have activity in 1L NSCLC in tumors having a PD-L1 TPS $\geq$1% (see Section 3.3.1). When the results of this Phase III study were analyzed by the PD-L1 IHC 22C3 pharmDx assay, atezolizumab also showed improved OS in the subset of patients who had tumors with TPS $<$1% (see Section 3.3.1). [redacted]

In summary, treatment with atezolizumab for all patients in this study offers the potential for clinical benefit in patients with chemotherapy-naive NSCLC, as patients will be required to have PD-L1 positivity in their tumors to enroll. Furthermore, the combination of MTIG7192A with atezolizumab in this study may benefit patients with PD-L1–selected tumors beyond treatment with placebo plus atezolizumab. Because the toxicities of

atezolizumab and of the combination of MTIG7192A plus atezolizumab appear to be similar, and generally mild and transient in nature, patients may not have increased toxicity with the combination of MTIG7192A and atezolizumab. As the potential toxicities of atezolizumab or MTIG7192A plus atezolizumab do not overlap with the adverse effects of chemotherapy, patients who do not respond to study treatment with atezolizumab or atezolizumab plus MTIG7192A are considered likely to be able to subsequently receive standard therapies for which they would otherwise have been eligible. In addition, PD-1 inhibitors, such as nivolumab and pembrolizumab, are also approved in 2L therapy for metastatic NSCLC. Therefore, based on the above data that patients will be selected for this study based on tumor PD-L1 expression, that all patients in the study will receive atezolizumab, and that the preclinical and clinical data suggest that patients with metatstatic NSCLC can respond to the combination of MTIG7192A plus atezolizumab without increased toxicity, the overall benefit–risk ratio is considered to be appropriate for the study population.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab in chemotherapy-naive patients with locally advanced unresectable or metastatic PD-L1–selected NSCLC, excluding patients with a sensitizing *EGFR* mutation or *ALK* translocation.

The primary population is defined as all randomized patients who are selected on the basis of a minimum level of PD-L1 expression (TPS ≥ 1%) using an FDA-approved PD-L1 IHC 22C3 pharmDx assay performed locally or centrally. Specific objectives and corresponding endpoints for the study are outlined below in Table 3.

Table 3 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab, as measured by objective response rate (ORR) and progression-free survival (PFS)	• ORR, defined as a complete response or partial response on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1 • PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab, as measured by duration of objective response (DOR) and overall survival (OS)	• DOR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first • OS, defined as the time from randomization to death from any cause

Table 3 Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety and tolerability of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab	• Incidence, nature, and severity of adverse events, graded according to the NCI CTCAE v4.0 • Clinically significant changes from baseline in vital signs, physical findings, and clinical laboratory results during and following administration of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK profile of MTIG7192A and atezolizumab	• Serum concentrations of MTIG7192A or atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to MTIG7192A and atezolizumab	• Incidence of treatment-emergent ADAs and their potential impact on safety, efficacy, and pharmacokinetics
Exploratory Patient-Reported Outcome Objective	**Corresponding Endpoints**
• To evaluate the benefit of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab, in terms of patient-relevant concepts including symptoms, daily functioning, and health-related quality of life (HRQoL)	• Clinically significant changes in symptoms, function, and HRQoL scales from the patient-completed EORTC QLQ-C30
Exploratory Biomarker Objectives	**Corresponding Endpoints**
• [redacted] • [redacted]	• [redacted] • [redacted]

ADA=anti-drug antibody; DOR=duration of response; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HRQoL=health-related quality of life; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors; TIGIT=T-cell immunoreceptor with Ig and ITIM domains.

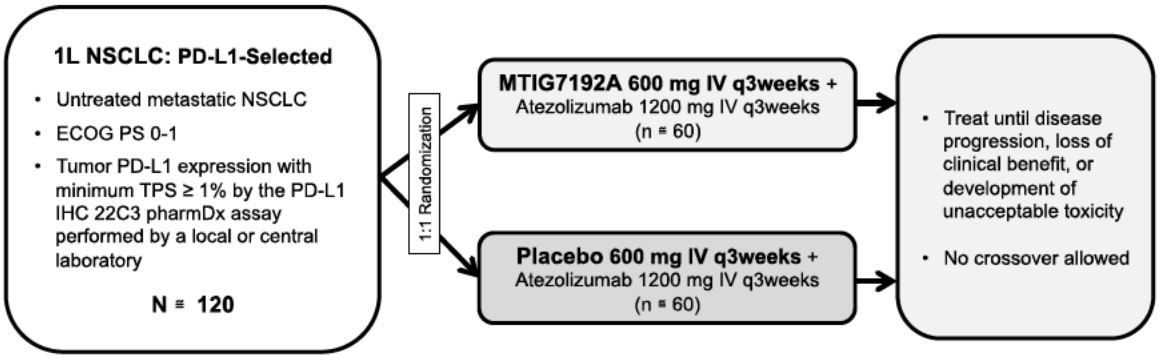
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase II, global, multicenter, randomized, blinded, placebo-controlled study, designed to evaluate the safety and efficacy of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated, locally advanced unresectable or metastatic PD-L1–selected NSCLC.

The study design is shown in Figure 2 and the schedule of activities in provided in Appendix 1.

Figure 2 Study Design



1L = first-line; ECOG = Eastern Cooperative Oncology Group; IHC = immunohistochemistry; NSCLC = non–small cell lung cancer; PD-L1 = programmed death-ligand 1; PS = Performance Status; q3weeks = every 3 weeks; TPS = tumor proportion score.

Male and female patients aged ≥18 years with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 who have previously untreated, locally advanced unresectable or metastatic PD-L1–selected NSCLC are eligible.

For the purposes of PD-L1 selection, formalin-fixed tumor samples assessed locally by the commercially available PD-L1 IHC 22C3 pharmDx assays (Dako) will be accepted. In the United States, only results from the FDA-approved Dako PD-L1 IHC 22C3 pharmDx assay will be accepted; outside of the United States, results from a health authority-approved or CE-IVD marked Dako PD-L1 IHC 22C3 pharmDx assay will be accepted. Other assays for PD-L1 expression levels will not be accepted for purposes of PD-L1 selection. PD-L1–selected tumors will be defined as tumors with a TPS ≥1% by the PD-L1 IHC 22C3 pharmDx assay.

Patients that do not have prior testing by the PD-L1 IHC 22C3 pharmDx assay will be prospectively tested for PD-L1 expression by central testing using the commercially available PD-L1 IHC 22C3 pharmDx assays (Dako) (see Section 4.5.6.2).

Patients whose tumors have a known *EGFR* mutation or *ALK* rearrangement will be excluded from this study. Patients with tumors of non-squamous histology with unknown *EGFR* or *ALK* mutational status will be required to be tested prior to enrollment (see specific inclusion criteria in Section 4.1.1). Patients with tumors of squamous histology who have an unknown *EGFR* or *ALK* mutational status will not be required to be tested at pre-screening/screening (see specific inclusion criteria in Section 4.1.1).

Eligible patients will be randomized 1:1 to receive either MTIG7192A plus atezolizumab or placebo plus atezolizumab.

Eligible patients will be stratified by the PD-L1 IHC 22C3 pharmDx assay result (TPS 1% to 49% vs. TPS ≥ 50%), tumor histology (non-squamous vs. squamous), and patient's history of tobacco use (yes vs. no).

In the experimental arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle and MTIG7192A at its recommended Phase II dose of 600 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle.

In the control arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle and placebo administered by IV infusion Q3W on Day 1 of each 21-day cycle.

Patients will undergo tumor assessments by standard RECIST v1.1 at baseline and at every 6 weeks thereafter (approximately every 2 cycles) for the first 36 weeks (approximately up to Cycle 12) following randomization (see Section 4.5.5 and Appendix 1). After 36 weeks (or after Cycle 12) from randomization, patients who have not experienced disease progression will undergo tumor assessment every 9 (±1) weeks (approximately every 3 cycles).

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 treatment (MTIG7192A plus atezolizumab or placebo plus atezolizumab) if they meet all of the criteria specified in Section 3.1.1.

Patients will undergo tumor assessments until disease progression per RECIST v.1.1 or until treatment discontinuation, whichever occurs later. In the absence of disease progression, tumor assessments should continue, if feasible, until patients start new anti-cancer therapy, consent is withdrawn, death, or study termination by the Sponsor, whichever occurs first.

Patients in whom radiographic disease progression is confirmed at a subsequent tumor assessment may be permitted to continue study treatment (MTIG7192A plus atezolizumab or placebo plus atezolizumab) at the discretion of the investigator if they show evidence of clinical benefit and continue to meet the criteria listed above and as specified in Section 3.1.1.

[redacted]

Primary imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints, if needed.

In order not to confound the OS endpoint, crossover will not be allowed from the control arm (placebo plus atezolizumab) to the experimental arm (MTIG7192A plus atezolizumab).

During the study, patients will also be asked to complete a patient-reported outcome (PRO) survey at the beginning of the study, at the same visits as tumor assessments are scheduled, and at treatment discontinuation (see Section 4.5.11 and Appendix 1).

During the study, serum samples will be collected to monitor MTIG7192A or atezolizumab PK and to detect the presence of antibodies to MTIG7192A or atezolizumab. [redacted]

Safety assessments will include the incidence, nature, and severity of adverse events, protocol-mandated vital signs, laboratory abnormalities, and other protocol-specified tests that are deemed critical to the safety evaluation of the study. Events and tests will be graded per NCI CTCAE v4.0.

After initiation of study treatment, all adverse events will be reported until *30 days* after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators should report any serious adverse events or other adverse events of *special interest until 90 days after the last dose of study* treatment *or until initiation of new systemic anti-cancer therapy, whichever occurs first.* 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 drug(s) or trial-related procedures until a final outcome can be reported.

After study treatment discontinuation, patients will be followed for survival status and subsequent anti-cancer therapies, approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first (see Sections 4.6.1 and 4.6.1.1).

3.1.1 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 after discussion with the Medical Monitor and provided that the patients meet all of the following criteria (see Figure 3):

- 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 ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing
  - Critical anatomical sites include the CNS, central airway, the great vessels, and other organs or tissues where compromised function secondary to tumor progression would be expected to result acutely in severe and/or irreversible disability or death.
- Written consent to acknowledge discussion with the treating investigator of the benefit–risk balance of continuing study treatment beyond radiographic progression, including deferring other treatment options

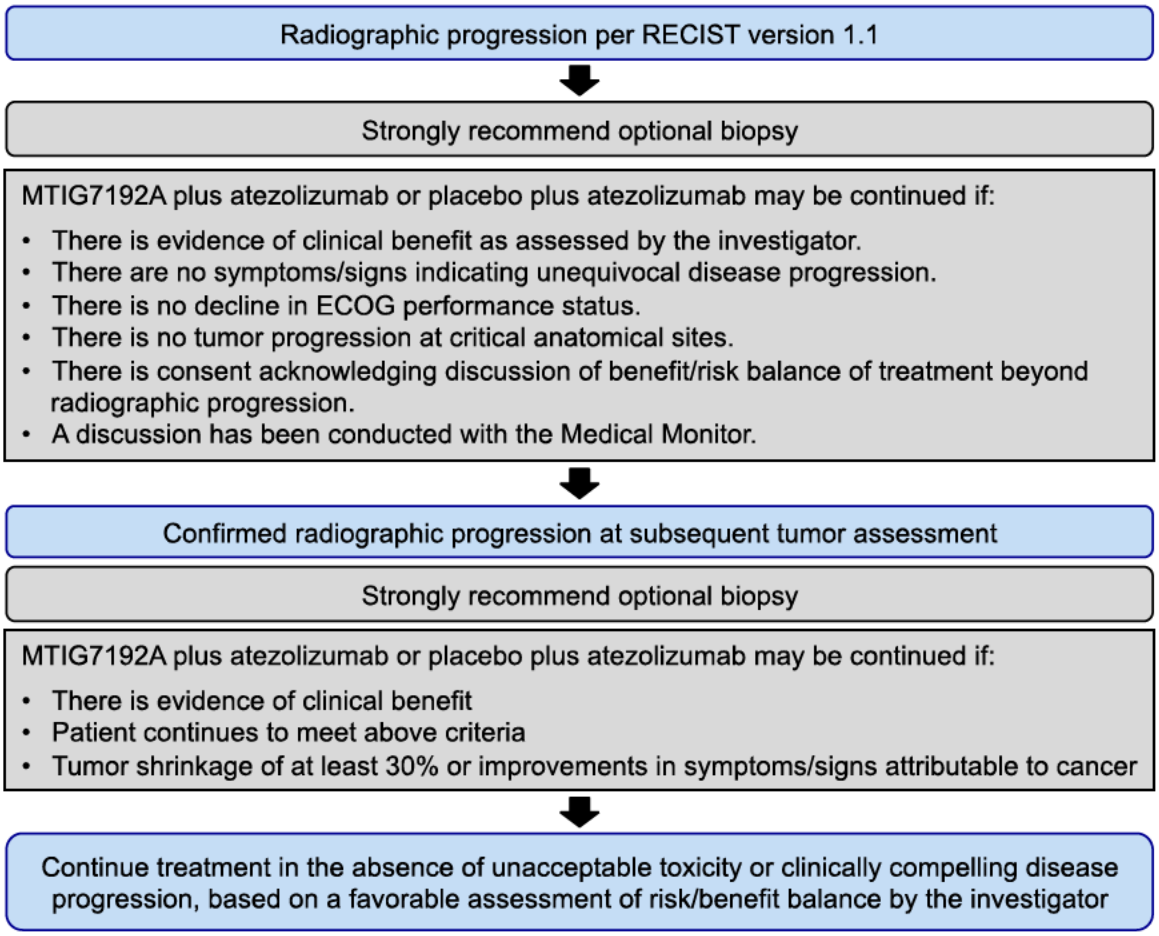
If radiographic disease progression is confirmed at a subsequent tumor assessment, patients may be considered for continued study treatment at the investigator's discretion after discussion with the Medical Monitor, if they continue to meet the above criteria and have continued clinical benefit, as evidenced by at least one of the following:

- Tumor shrinkage (at least 30% decrease in diameter from baseline) of one or more evaluable lesions, or
- Improvement in one or more symptoms or signs attributable to the underlying cancer (e.g., decreased requirement for narcotics for pain, decreased dyspnea associated with pleural effusion, or weight gain) as assessed by the investigator

For patients who consented to treatment beyond progression, new lesions should be entered in the electronic Case Report Form (eCRF). The Sponsor will derive overall

tumor assessment as per RECIST v1.1 and investigator assessment of overall tumor response at all timepoints should be *also* based on RECIST v1.1.

Figure 3 Conditions for Continuing Study Treatment Beyond Progression



ECOG = Eastern Cooperative Oncology Group; RECIST = Response Evaluation Criteria in Solid Tumors.

3.1.2 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will review available safety data periodically and make recommendations regarding study conduct to ensure the safety of patients enrolled in the study. The IMC Chair will be a medical oncologist who is not the Medical Monitor and is not associated with the study. Other IMC members may include, but are not limited to, a drug safety scientist, biostatistician, biomarker scientist, and clinical pharmacologist. The responsibility, membership, and communication flow of the IMC is further described in the IMC Charter.

[redacted]

[redacted]

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last data required for all study analysis are collected. [redacted]

In addition, the Sponsor may decide to terminate the study at any time. If the Sponsor decides to terminate the study, patients who are still receiving study treatment or undergoing survival follow-up may be enrolled in an extension study or a non-interventional study, if available.

3.3 RATIONALE FOR STUDY DESIGN

This Phase II study design is based on the hypothesis that treatment with MTIG7192A plus atezolizumab may increase ORR and/or prolong PFS and/or OS when compared with treatment with placebo plus atezolizumab in patients with locally advanced unresectable or metastatic NSCLC who are chemotherapy-naive and whose tumors are selected for PD-L1 expression.

3.3.1 Rationale for Control Arm with Placebo Plus Atezolizumab in Patients with PD-L1–Selected NSCLC

Despite recent improvements in 1L treatments, the prognosis for patients with advanced unresectable or metastatic NSCLC remains dismal, with a median OS of approximately 12.5 months (Sandler et al. 2006), with nearly all patients experiencing disease progression. Patients who receive 2L treatment for their disease have an even more limited prognosis, with median survival duration of approximately 8–9 months (Stinchcombe and Socinski 2008). Chemotherapy regimens are currently the standard of care for non–oncogene-driven 1L NSCLC, but these approved chemotherapies are associated with significant toxicities (e.g., neuropathy, febrile neutropenia,

myelosuppression, and alopecia) that negatively impact quality of life. Therefore, there is a continuing need for more efficacious, better-tolerated treatments.

Inhibition of PD-L1/PD-1 signaling has been shown to produce durable responses in some patients with metastatic NSCLC, and expression of PD-L1 by TCs and/or ICs in NSCLC correlates with response to therapy (Topalian et al. 2012; Fehrenbacher et al. 2016). Atezolizumab monotherapy has demonstrated clinical efficacy and is generally well tolerated in patients with locally advanced unresectable or metastatic squamous or non-squamous NSCLC (Spigel et al 2015; Fehrenbacher et al. 2016; Peters et al. 2017b; Rittmeyer et al. 2017). Data from the Phase Ia atezolizumab study (PCD4989g) first suggested that tumor PD-L1 status as determined by IHC in patients with metastatic NSCLC correlates with response to atezolizumab (see Section 1.7.2.3.1). In two randomized studies in NSCLC, Study GO28753 (POPLAR) and Study GO28915 (OAK), improvement in OS was observed with atezolizumab compared with docetaxel in previously treated patients with NSCLC (2L-plus), including patients with PD-L1 positive tumors categorized as TC1/2/3 or IC1/2/3 (Fehrenbacher et al. 2016; Rittmeyer et al. 2017). Data from Study GO28754 (BIRCH) demonstrated a clinically meaningful benefit of atezolizumab as 1L treatment for patients with PD-L1–selected NSCLC (TC2/3 or IC2/3), as demonstrated by a median OS of 23.5 months (Peters et al. 2017b). In addition, data from the Phase III Study GO29436 (IMpower150) demonstrated improved PFS for patients with PD-L1–selected NSCLC (TC1/2/3 or IC1/2/3) treated with 1L atezolizumab plus chemotherapy and bevacizumab compared with chemotherapy plus bevacizumab alone (Reck et al. 2017).

In this study, patients will be selected for PD-L1 status with the PD-L1 IHC 22C3 pharmDx assay (TPS $\geq$ 1%), and all patients, whether in the experimental arm or in the control arm, will receive atezolizumab. Although the PD-1 inhibitor pembrolizumab has demonstrated activity in metastatic NSCLC in a PD-L1–selected population with 22C3 IHC results of TPS $\geq$ 50% and is approved for these patients, there is accumulating data that immune checkpoint inhibitors, including atezolizumab, have activity in patients whose tumors have 22C3 IHC results of TPS $<$ 50%. Patients from the Phase III Study GO28915 (OAK) in metastatic NSCLC, were randomized to receive atezolizumab or docetaxel and PD-L1 IHC status was determined with the Ventana PD-L1 (SP142) IHC assay. These patient samples were also tested by the PD-L1 IHC 22C3 pharmDx assay (see Table 4; Gadgeel et al. 2017). As expected, atezolizumab showed improved OS in the subset of patients who had tumors with 22C3 PD-L1 TPS $\geq$ 50% versus those patients who received docetaxel (median OS 18.6 months vs. 8.4 months, OS HR = 0.49 [95% CI: 0.29, 0.80]). Furthermore, atezolizumab also showed improved OS in the PD-L1–negative patients who had tumors with TPS $<$ 1% PD-L1 by the 22C3 IHC result compared with those treated with docetaxel (median OS 12.1 months vs 7.3 months, OS HR = 0.61 [95% CI: 0.45, 0.84]). Atezolizumab monotherapy is already approved in 2L patients irrespective of PD-L1 status and is currently being tested in a population of patients with chemotherapy-naive metastatic 1L NSCLC whose tumors have a PD-L1

status similar to the 22C3 TPS ≥ 1% cutoff, as defined by the PD-L1 (SP142) IHC assay (≥ 1% on TCs or ICs, i.e., TC1/2/3 or IC1/2/3 [Study GO29431, IMpower110]). The activity of pembrolizumab is also being tested in a population of patients with chemotherapy-naive metastatic 1L NSCLC whose tumors have a PD-L1 IHC result of 22C3 TPS ≥ 1% (KEYNOTE-042). Therefore, these data and precedents provide a rationale for treating patients with metastatic NSCLC selected on the basis of tumor PD-L1 expression with atezolizumab, using a TPS ≥ 1%.

On the basis of these results, patients with metastatic NSCLC in the control group will receive atezolizumab with placebo. This control group will be instrumental in assessing the relative benefit and safety of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab in the front-line treatment setting for metastatic NSCLC.

Table 4 Overlap of the 22C3 and SP142 PD-L1 Populations in the Phase II Study GO28915 (OAK) in Metastatic NSCLC

		Ventana PD-L1 (SP142) IHC Assay [a]	
		Dx Negative	Dx Positive
PD-L1 IHC 22C3 pharmDx Assay [b]	Dx Negative	115	103
	Dx Positive	35	145

Dx = diagnostic; IHC = immunohistochemistry; TPS = tumor proportion score.

[a] For the Ventana PD-L1 (SP142) IHC assay, diagnostic negative is defined as TC0 or IC0, and diagnostic positive is defined as TC1/2/3 or IC1/2/3.

[b] For the PD-L1 IHC 22C3 pharmDx assay, diagnostic negative is defined as TPS < 1%, and diagnostic positive as TPS ≥ 1%.

Source: Modified from Gadgeel et al. 2017.

3.3.2 Rationale for Testing MTIG7192A Plus Atezolizumab in Patients with PD-L1–Selected NSCLC

While PD-L1/PD-1 inhibitors, including atezolizumab, pembrolizumab, and nivolumab, provide clinically meaningful benefit in either unselected or PD-L1–selected patients, the majority of patients either do not respond to or progress on these immunotherapies. Therefore, there is a continuing need for rational combinations with immunotherapies in order to broaden the patient population who could derive benefit and to deepen and to extend the response in the patient population that does respond.

TIGIT is a novel immune checkpoint inhibitor that is often co-expressed with PD-L1 on tumor-infiltrating lymphocytes. In preclinical models, combined blockade of both TIGIT and PD-L1/PD-1 pathways demonstrated superior efficacy over the respective single-agent treatments. Therefore, it is hypothesized that the combination of an anti-TIGIT antibody, such as MTIG7192A, with an anti–PD-L1/PD-1 antibody may result in activation of anti-tumor immune responses leading to enhanced killing of TCs and improved clinical responses. [redacted]

[redacted] The preliminary safety profile of MTIG7192A plus atezolizumab was similar to what has been reported previously for atezolizumab. Therefore, these preclinical and clinical data provide a rationale for evaluating the efficacy of MTIG7192A plus atezolizumab in patients with metastatic NSCLC selected on the basis of tumor PD-L1 expression.

3.3.3 Rationale for PD-L1 Selection of Tumor Samples

Results from atezolizumab monotherapy studies in NSCLC, including PCD4989g (NSCLC cohort), GO28753 (POPLAR), GO28754 (BIRCH), and GO28915 (OAK), suggest that PD-L1 expression is associated with an increased probability of clinical benefit with atezolizumab. Results from a clinical study in which atezolizumab is combined with chemotherapy in metastatic NSCLC, the Phase III study GO29436 (IMpower150), also suggest that PD-L1 expression is associated with increased probability of clinical benefit with the atezolizumab combination (Reck et al. 2017).

Although multiple PD-L1 IHC assays exist, there appears to be considerable overlap amongst them. [redacted]

[redacted]

Based on these data, in the current study patients will be selected for consideration of enrollment if their tumors have PD-L1 IHC 22C3 status with a TPS $\geq$ 1%. Patients will then be stratified by TPS 1% to 49% versus TPS $\geq$ 50%. [redacted]

3.3.4 Rationale for Inclusion of Patients with Squamous and Non-Squamous NSCLC

Atezolizumab has shown significant clinical benefit in patients with metastatic NSCLC independent of histology. In the Phase III OAK study, atezolizumab improved OS for

patients treated with atezolizumab compared with docetaxel, and OS was similar in patients treated with atezolizumab whose tumors had squamous histology (HR = 0.73, 95% CI: 0.54, 0.98) as compared with those patients whose tumors had non-squamous histology (HR = 0.73, 95% CI: 0.60, 0.89) (Rittmeyer et al. 2017). In the Phase II POPLAR study, atezolizumab demonstrated a statistically significant improvement in OS in unselected NSCLC patients over docetaxel, and activity was observed in patients with both squamous and non-squamous NSCLC treated with atezolizumab (median OS of 10.1 vs. 8.6 months [HR = 0.66] for squamous and 14.8 vs. 10.9 months [HR = 0.69] for non-squamous, respectively) (Fehrenbacher et al. 2016). These data suggest that atezolizumab is active in patients with metastatic NSCLC, independent of histology. Based on this data, patients with metastatic NSCLC, of either squamous or non-squamous histology, will be eligible to enroll in the current study, and all patients will receive atezolizumab.

3.3.5 Rationale for Exclusion of Patients with Sensitizing *EGFR* Mutations and *ALK* Translocations

Patients with tumors harboring sensitizing *EGFR* mutations or *ALK* translocations will not be eligible for this study. Genotype-directed therapy, rather than immunotherapy, remains the standard of care in the 1L setting for these patients. For patients with NSCLC (of mainly non-squamous histology) with an *EGFR* mutation, randomized Phase III studies of the EGFR inhibitors gefitinib, erlotinib, and afatinib showed significant improvement of PFS and ORR compared with platinum doublet chemotherapy (Fukuoka et al. 2011; Rosell et al. 2012; Yang et al. 2012). For patients with metastatic NSCLC with *ALK* rearrangements, crizotinib and alectinib have demonstrated increased efficacy (Shaw et al. 2013; Peters et al. 2017a).

When patients with metastatic NSCLC with *EGFR* mutations are treated with immunotherapy alone, there has been no increased OS benefit. In the OAK study, metastatic NSCLC patients with *EGFR* mutation-positive disease had similar OS benefit with atezolizumab or with docetaxel (median OS of 10.5 months with atezolizumab vs. 16.2 months with docetaxel [HR = 1.24]), whereas patients with *EGFR* wild-type disease had improved OS with atezolizumab compared with docetaxel (15.3 months vs. 9.5 months, HR = 0.69) (Rittmeyer et al. 2017). Similarly, in the Phase III study of nivolumab versus docetaxel in 2L NSCLC (CheckMate-057), NSCLC patients with *EGFR*-mutation-positive disease had similar OS benefit with nivolumab or docetaxel (HR = 1.18), in contrast to patients with *EGFR*-wild-type disease who had improved OS with nivolumab compared with docetaxel (HR = 0.66) (Borghaei et al. 2015). Patients with NSCLC with *EGFR*-mutation-positive disease were also excluded from the Phase III study of pembrolizumab versus chemotherapy in the 1L setting (KEYNOTE-024) (Reck et al. 2016). It is hypothesized that this subgroup of patients with *EGFR*-mutation-positive NSCLC may have decreased immunogenicity. Therefore, based on the above data, patients with known *EGFR* mutations or *ALK* translocations will be excluded from the current study.

3.3.6 Rationale for Dose and Schedule of Atezolizumab and MTIG7192A

3.3.6.1 Rationale for Dose and Schedule of Atezolizumab

Atezolizumab will be administered to all patients at a fixed dose of 1200 mg IV Q3W, on Day 1 of each 21-day cycle, which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). 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 PK, efficacy, and safety data. In the Phase I study of atezolizumab as a single agent (Study PCD4989g), the MTD of atezolizumab was not reached, and no DLTs were observed at any dose. Anti-tumor activity was observed across doses ranging from 1 mg/kg to 20 mg/kg given Q3W.

For further details, please refer to the Atezolizumab Investigator's Brochure.

3.3.6.2 Rationale for Dose and Schedule of MTIG7192A

MTIG7192A will be administered to all patients on the experimental arm at a fixed dose of 600 mg IV Q3W on Day 1 of each 21-day cycle. [redacted]

For further details, please refer to the MTIG7192A Investigator's Brochure.

3.3.7 Rationale for Biomarker Assessments

3.3.7.1 Rationale for Collection of Mandatory Archival and/or Pretreatment Biopsy Tumor Specimens

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-L1/PD-1 therapy (Topalian et al. 2012). This correlation was also observed with atezolizumab in NSCLC as a single agent in Studies PCD4989g (Herbst et al. 2014; Horn et al. 2015), GO28754 (BIRCH) (Besse et al. 2015), GO28753 (POPLAR) (Fehrenbacher et al. 2016), GO28625 (FIR) (Spigel et al. 2015), and GO28915 (OAK) (Rittmeyer et al. 2017), and in combination with chemotherapy in Study GO29436 (IMpower150) (Reck et al. 2017). Similar observations have been

reported for other PD-L1 or PD-1 inhibitors (Higgs et al. 2015; Muro et al. 2015; Seiwert et al. 2015).

In this study, archival and/or fresh tumor specimens from patients will be tested for PD-L1 expression by a local or central laboratory during the pre-screening period, and only patients with PD-L1–selected tumors (defined by expression of PD-L1 with the PD-L1 IHC 22C3 pharmDx assay as a TPS ≥ 1%) will be enrolled. [redacted]

The efficacy endpoints will be analyzed in two PD-L1–selected populations, TPS 1% to 49% and TPS ≥ 50%. [redacted]

[redacted]

[redacted]

3.3.7.2 Rationale for Collection of Blood Samples for Biomarker Analyses

[redacted]

3.3.7.3 Rationale for Collection of Optional Tumor Specimens, Including a Biopsy at the Time of Radiographic Progression

Patients agreeing to optional tumor biopsies may undergo tissue collection at any time, if clinically feasible. However, it is preferable that optional tumor biopsies be collected at the first evidence of radiographic response or at the first evidence of radiographic disease progression. Anti-tumor immune responses such as those associated with atezolizumab may result in objective responses that are delayed and can be preceded by initial apparent radiographic progression. This initial apparent progression may occur as a result of either delayed anti-tumor activity and/or robust tumor immune infiltration with a concomitant increase in tumor size. In addition, lesions that would otherwise be undetectable with conventional imaging (i.e., micrometastatic disease) may increase in size as a result of these processes and be recorded as new lesions (Hales et al. 2010).

3.3.7.4 Rationale for Next-Generation Sequencing in Tumor and/or Blood Samples

3.3.7.5 Rationale for Optional Stool Sample Collection

[redacted]

3.3.8 Rationale for Allowing Patients to Continue Study Treatment Beyond Initial Progression per RECIST v1.1

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) may not necessarily reflect therapeutic failure. Because of the potential for pseudoprogression and/or tumor immune infiltration, this study will allow patients randomized to receive either MTIG7192A plus atezolizumab or placebo plus atezolizumab to continue to receive study treatment after apparent radiographic progression, provided the benefit–risk ratio is judged to be favorable. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status (see Section 3.1).

Tumor response will be evaluated according to RECIST v1.1 for the efficacy endpoints (i.e., PFS, objective response, and DOR). Tumor assessments will be performed according to RECIST v1.1 for patients in both arms of the study.

3.3.9 Rationale for Patient-Reported Outcome Assessments

In the treatment of lung cancer, it is important to both increase survival and palliate symptoms because disease symptoms have negative impacts on health-related quality of life (HRQoL) (Hyde and Hyde 1974; Hopwood and Stephens 1995; Sarna et al. 2004).

The BR.21 study (erlotinib vs. BSC in second- or third-line NSCLC) demonstrated that longer TTD in the cough, pain, and dyspnea scales of the European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) was consistent with the superior PFS, OS, and quality-of-life benefits in the erlotinib arm compared with the placebo arm (Aaronson et al. 1993; Bergman et al. 1994; Bezjak et al. 2006). Patients in the afatinib LUX-Lung 1L study also reported a significant delay of TTD in lung cancer symptoms (cough, pain, and dyspnea) as measured by the EORTC QLQ-C30 (Yang et al. 2012).

In order to assess the clinical benefit of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab [redacted], PRO data will be collected using the validated EORTC QLQ-C30 scale (see Appendix 3).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 50–65 sites globally will participate in the study and will enroll approximately 120 patients with previously untreated, locally advanced unresectable or metastatic NSCLC that is PD-L1–selected.

4.1.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Ability to comply with the study protocol, in the judgment of the investigator
- ECOG Performance Status of 0 or 1 (see Appendix 5)
- Histologically or cytologically documented locally advanced unresectable NSCLC (i.e., Stage IIIB not eligible for definitive chemoradiotherapy), recurrent, or metastatic NSCLC (i.e., Stage IV) (per the Union Internationale Contre le Cancer/American Joint Committee on Cancer [UICC/AJCC] staging system, Detterbeck et al. 2009) of either squamous or non-squamous histology
  - [redacted]

- No prior systemic treatment for locally advanced unresectable or metastatic NSCLC
  - [redacted]
- Tumor PD-L1 expression with a TPS ≥ 1%, as determined by the PD-L1 IHC 22C3 pharmDx assay performed by a local laboratory or by a central laboratory on previously obtained archival tumor tissue or tissue obtained from a biopsy at screening
- Confirmed availability of representative tumor specimens in formalin-fixed, paraffin-embedded (FFPE) blocks (preferred) or at least [redacted] unstained serial slides, along with an associated pathology report. If central testing for *EGFR* mutations and/or *ALK* translocations are required, an additional [redacted] unstained slides need to be provided.
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Measurable disease, as defined by RECIST v1.1
  - [redacted]
- Life expectancy ≥ 12 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory results, obtained within 14 days prior to the first study treatment (Cycle 1, Day 1 [C1D1]):
  - [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

  [redacted]
- [redacted]

  [redacted]
- [redacted]

  [redacted]
- [redacted]

  [redacted]
- [redacted]
- [redacted]
- [redacted]

  [redacted]

  [redacted]
- [redacted]

- For women of childbearing potential (including women who have had a tubal ligation): Serum pregnancy test must be performed and documented as negative within 14 days prior to C1D1
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:
  - Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for at least 5 months after the last dose of study drugs. 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 has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
- Hormonal contraceptive methods must be supplemented by a barrier method plus spermicide.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as specified below:
  - With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 90 days after the last dose of study treatment 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 study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

Patients who meet any of the criteria in the following sections will be excluded from study entry.

4.1.2.1 Cancer-Specific Exclusions

Patients who meet any of the following cancer-specific criteria will be excluded from study entry:

- Patients with NSCLC known to have a sensitizing mutation in the *EGFR* gene or an *ALK* fusion oncogene are excluded from the study as follows:
  - [redacted]
  - [redacted]
  - [redacted]
- Patients with the pulmonary lymphoepithelioma-like carcinoma subtype of NSCLC

- Symptomatic, untreated, or actively progressing CNS metastases
  - [redacted]
- Spinal cord compression not definitively treated with surgery and/or radiation, and/or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥2 weeks prior to screening
- History of leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (i.e., once monthly or more frequently)
  - [redacted]
- Uncontrolled tumor-related pain
  - [redacted]
  - [redacted]
  - [redacted]
- Uncontrolled hypercalcemia (ionized calcium >1.5 mmol/L or calcium >12 mg/dL or corrected serum calcium >ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab
  - [redacted]

  - [redacted]

- Malignancies other than NSCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death and/or treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer)

4.1.2.2 General Medical Exclusions

Patients who meet any of the following general medical criteria will be excluded from study entry:

- Inability to comply with study and/or follow-up procedures
- Pregnant, lactating, or breastfeeding women
- Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results (e.g., uncontrolled major seizure disorder or superior vena cava syndrome)
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease, or current alcohol abuse

  Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction or cerebrovascular accident within 3 months prior to randomization, unstable arrhythmias, or unstable angina
- Severe infections within 4 weeks prior to initiation of study treatment, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received oral or IV antibiotics (including antifungals) within 2 weeks prior to randomization
  - [redacted]
- Major surgical procedure within 4 weeks prior to randomization, or anticipation of need for a major surgical procedure during the course of the study
- Inability to understand the local language(s) for which the EORTC QLQ-C30 is available
- Any other disease, 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, that may affect the interpretation of the results, or that may render the patient at high risk from treatment complications

4.1.2.3 Treatment-Specific Exclusions

Patients who meet any of the following treatment-specific criteria will be excluded from study entry:

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to CHO cell products or any component of the atezolizumab formulation
- Active or history of autoimmune disease [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Prior allogeneic bone marrow transplantation or prior solid organ transplantation
- History of idiopathic pulmonary fibrosis (including pneumonitis), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan
  - [redacted]
- Positive test for HIV at screening
  - [redacted]
- Patients with active HBV infection, defined as having a positive hepatitis B surface antigen (HBsAg) test at screening
  - [redacted]
  - [redacted]

- Patients with active HCV infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening
  - [redacted]
- Patients with active EBV infection and patients with known or suspected chronic active EBV infection at screening
  - [redacted]
- Active tuberculosis
- Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation that such a live attenuated vaccine will be required during the study
  - [redacted]
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone $>$10 mg/day, cyclophosphamide, azathioprine, methotrexate, thalidomide, and tumor necrosis factor [TNF-α] antagonists) within 2 weeks prior to randomization
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

After written informed consent has been obtained and eligibility has been established (including determination of tumor PD-L1 status by local or central testing), the study site will obtain the patient's identification number and blinded treatment assignment from the interactive voice or web-based response system (IxRS). Patients will be randomized to receive either MTIG7192A plus atezolizumab or placebo plus atezolizumab in a 1:1 randomization ratio using a permuted-block randomization method.

Randomization will be stratified by the following criteria:

- PD-L1 IHC 22C3 results (TPS 1% to 49% vs. TPS $\geq$50%)
- Histology of NSCLC (non-squamous vs. squamous)
- History of tobacco use (yes vs. no)

These stratification factors were chosen because of their known or suspected potential to affect prognosis in NSCLC. Prospective stratification by these factors will minimize differences in the two treatment arms due to sources other than MTIG7192A.

The investigators and the patients will be blinded to treatment assignment until the primary analysis of the primary endpoints.

Because of the size of the study, use of IxRS, randomization, blinding, and expected lack of substantial emergency unblinding, collected data will be protected from any biases that would arise from subjectivity in the reporting of the outcome measures. To further protect the integrity of the study, the results of interim safety and efficacy analyses will not be made known to the investigators.

The addition of MTIG7192A to atezolizumab is not expected to affect planned laboratory tests or adverse reactions to a degree that would significantly unblind patients or investigators. All laboratory tests or blood specimens will be performed by a local laboratory, a central laboratory, or the Sponsor, as appropriate.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this study. Laboratory personnel responsible for performing PK assays may be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed. Samples from patients assigned to the comparator arm will not be analyzed except by request (e.g., to evaluate a possible error in dosing).

If emergency unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. This emergency unblinding may occur without prior authorization from the Sponsor. However, the investigator should document and provide an explanation to the Sponsor for any premature unblinding (e.g., unblinding due to a serious adverse event or accidental unblinding). Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study drug for any other reason, the investigator should contact the Medical Monitor directly.

For regulatory reporting purposes and if required by local health authorities, the Sponsor may break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the investigator or Sponsor to be related to study drug.

If an IMC safety review is necessary, as outlined in the guidelines of the IMC Charter, the IMC may instruct the IxRS to provide the treatment assignments for those patients of interest to evaluate unbalanced toxicity.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are MTIG7192A, placebo, and atezolizumab. All patients will receive atezolizumab with either MTIG7192A or with placebo.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 MTIG7192A and Placebo

MTIG7192A and placebo will be supplied by the Sponsor.

For further information on the formulation and handling of MTIG7192A and placebo, please see the pharmacy manual and/or the MTIG7192A Investigator's Brochure.

4.3.1.2 Atezolizumab

Atezolizumab drug product will be supplied by the Sponsor.

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

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Atezolizumab and MTIG7192A/placebo should be given in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

[redacted]

Any overdose or incorrect administration of atezolizumab and/or MTIG7192A/placebo should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1 and in Appendix 7 and Appendix 8.

4.3.2.1 Atezolizumab

All patients will receive 1200 mg atezolizumab administered by IV infusion on Day 1 of each 21-day cycle (see Section 3.3.6.1). The atezolizumab dose is fixed and is not dependent on body weight.

Atezolizumab infusions will be administered per the instructions outlined [redacted]

For anaphylaxis precautions, please see Appendix 6. For management of IRRs, including premedications, please see Appendix 7 and Appendix 8.

There will be no dose reduction for atezolizumab in this study. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1. Guidance on study drug administration in the context of management of specific adverse events is provided in Section 5.1.4.

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 MTIG7192A and Placebo

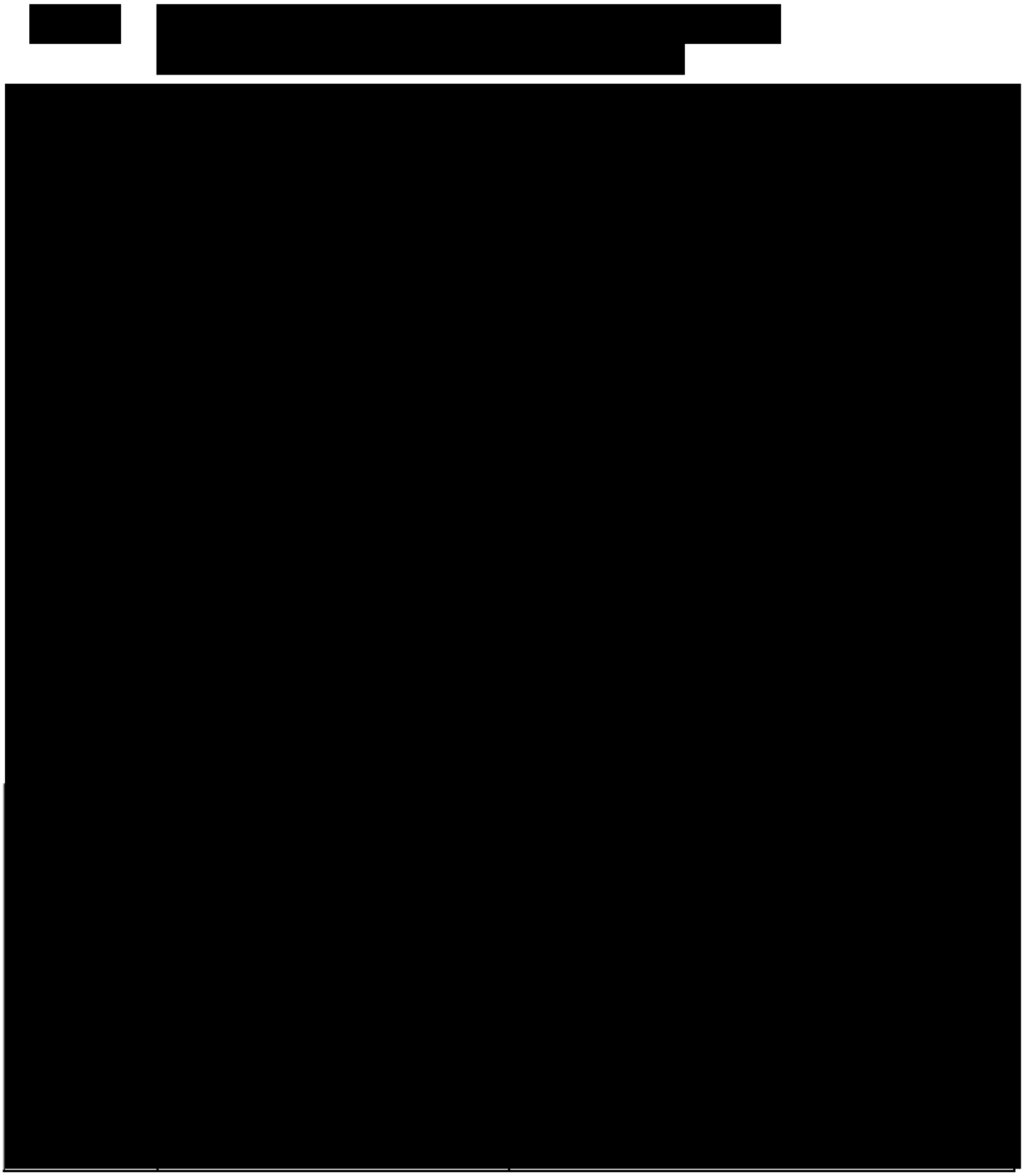
[redacted], patients will receive 600 mg MTIG7192A/placebo administered by IV infusion on Day 1 of each 21-day cycle (see Section 3.3.6.2). The MTIG7192A/placebo dose is fixed and is not dependent on body weight. MTIG7192A/placebo infusions will be administered per the instructions outlined [redacted]

For anaphylaxis precautions, please see Appendix 6. For management of IRRs, including guidance on premedication, please see Appendix 7 and Appendix 8.

There will be no dose reduction for MTIG7192A/placebo in this study. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1. Guidance on study drug administration in the context of management of specific adverse events is provided in Section 5.1.4.

[redacted]

For further details on dose preparation, storage, and administration instructions for MTIG7192A/placebo, please refer to the pharmacy manual and/or the MTIG7192A Investigator's Brochure.



[redacted]

4.3.2.3 Atezolizumab and MTIG7192A/Placebo

The following rules apply as long as neither atezolizumab nor MTIG7192A/placebo has been permanently discontinued:

- Treatment cycles will normally begin with dosing of atezolizumab and MTIG7192A/placebo on Day 1 of each 21-day cycle. [redacted]

- [redacted]

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (MTIG7192A and matching placebo, as well as atezolizumab) will be provided by the Sponsor where required by local health authority regulations. 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 (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to MTIG7192A and/or Atezolizumab

The Sponsor (Genentech, a member of the Roche Group) will offer continued access to Genentech IMPs (MTIG7192A 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.

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]

- [redacted]
- [redacted]
- [redacted]

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

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

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, or nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to screening to the 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 who experience infusion-related symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or ranitidine or another H_2 receptor antagonist, as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion-related 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 6).

Systemic corticosteroids and other immune-modulating medications may in theory attenuate the potential beneficial immunologic effects of treatment with MTIG7192A and/or atezolizumab but should be administered at the discretion of the treating physician in line with the management guidelines in Section 5.1. Premedication for MTIG7192A/placebo and/or atezolizumab may be administered for Cycles $\geq$2 at the discretion of the treating physician after consultation with the Medical Monitor. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Physiologic doses of corticosteroids for adrenal insufficiency are allowed. Megestrol administered as an appetite stimulant is acceptable while the patient is enrolled in the study. Planned use of other medications should be discussed with the Medical Monitor.

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level), or other maintenance therapy for non-malignant indications should

continue their use. Males and females of reproductive potential should follow the contraceptive guidance as outlined in the inclusion criteria for the study (see Section 4.1.1).

4.4.1.1 Cannabinoids

Cannabinoids are permitted only if obtained in accordance with local regulations.

4.4.2 Prohibited Therapy

Use of the following concomitant therapies is prohibited during the study:

- Any concomitant therapy intended for the treatment of cancer, whether health authority–approved or experimental, including but not limited to the following: chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy

  Certain forms of radiotherapy may be considered for pain palliation if patients [redacted]

- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide [redacted]

- Immunostimulatory agents, including but not limited to IFN-α, IFN-γ, or interleukin-2 [redacted]

- Traditional herbal medicines [redacted]

- Receptor activator of nuclear factor kappa B (RANK) inhibitor (i.e., denosumab). This class has the potential to alter the activity and the safety of atezolizumab (Cheng and Fong 2014).

[redacted]

- Live, attenuated vaccines (e.g., FluMist® influenza vaccine) are prohibited at any time during the study, and for 5 months following the last dose of study treatment.

[redacted]

4.5 STUDY ASSESSMENTS

Study assessments are defined in the sections below. See Appendix 1 and [redacted] for the schedule of activities to be performed during the study. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

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.

All assessments will be performed on the day of the scheduled visit date unless a time window is specified. Assessments scheduled on the days of study treatment should be performed before the infusion of study drug(s) unless otherwise noted. If the timing of a study visit coincides with a holiday, weekend, or other administrative disruption that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

Collection of any non–safety-related data or patient samples may be terminated by the Sponsor at any time if further collection of such data or samples is also not related to the study's primary objective(s). The decision to discontinue any data collection will be communicated to sites (Institutional Review Boards [IRBs] and Ethics Committees [ECs]) by means of a memorandum and will not require a protocol amendment.

4.5.1 Informed Consent Forms and Screening Log

This study requires documentation of consent for the following components of study participation, as applicable:

- Participation in Study GO40290: Written informed consent for participation in the study must be documented by signing the relevant page before any study-specific screening tests or evaluations are performed.
- Consent for Treatment Continuation after Possible Disease Worsening: This consent applies only to patients who continue study treatment beyond radiographic progression in the study (see Section 3.1.1).

[redacted]

- [redacted]
- [redacted]

[redacted]

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 in the study. 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 and Demographic Data

Medical history includes clinically significant diseases, surgeries, non-NSCLC cancer history (including prior cancer therapies and procedures), smoking history, use of alcohol and/or drugs of abuse, reproductive status and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 7 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity. Race/ethnicity is recorded because of the potential contribution of this variable to differences in observed pharmacokinetics, pharmacodynamics, toxicity, and/or response to treatment.

NSCLC cancer history will include prior cancer therapies, procedures, and an assessment of tumor mutational status (e.g., sensitizing *EGFR* mutation, *ALK* fusion status). [redacted]

4.5.3 Physical Examinations

A complete physical examination should be performed at screening and 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.

ECOG Performance Status should be assessed per the schedule of activities in Appendix 1.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. 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.

As part of tumor assessments, the physical examination should also include evaluation for lymphadenopathy, splenomegaly, hepatomegaly, and cutaneous neoplasms or metastases. All patients should be monitored for symptoms of CNS metastases, and such reported symptoms should be followed by a full neurologic examination. A brain magnetic resonance imaging (MRI) scan or a contrast-enhanced head CT should be performed as clinically indicated to confirm or rule out new or worsening brain involvement.

4.5.4 Vital Signs

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

On study treatment days, vital signs will be measured within 60 minutes before the first study drug infusion of the day [redacted]

[redacted]

Vital signs collected at the screening visit should be recorded in the eCRF. For each visit thereafter, only those vital signs that are obtained prior to study drug administration or that constitute an adverse event (e.g., temperature for event of fever) or a primary manifestation of an adverse event (e.g., blood pressure associated with an IRR or heart

rate associated with an arrhythmia) should be recorded in the eCRF. All vital signs collected per protocol should be documented in the patient's medical record.

Blood oxygen saturation will be measured at baseline by pulse oximetry and as clinically indicated thereafter.

4.5.5 Tumor and Response Evaluations

Screening and subsequent tumor assessments must include CT scans (with IV contrast unless contraindicated and oral contrast as appropriate per institutional standards) or MRI scans of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. MRI scans 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). 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 CT scan.

Patients with active or untreated CNS metastases are not eligible for this study (see Section 4.1.2 for CNS-related exclusions). At screening, a CT (with contrast) or MRI scan of the brain should be performed to document stability of all previously treated brain metastases. Brain scans should also be performed at screening to rule out the presence of untreated CNS metastases and then when clinically indicated thereafter (e.g., in patients with neurologic symptoms). In the event of an equivocal head CT scan at any tumor assessment, a brain MRI scan is required to clarify the presence or extent of suspected brain metastases. At subsequent (post-screening) tumor assessments, brain scans are not required for any patient unless clinically indicated.

Further investigations such as bone scans and CT scans of the neck should also be performed as indicated and if there is any clinical suspicion of disease at any site that may not be demonstrated by the minimum schedule of activities listed above. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

All known sites of disease, including measurable and/or nonmeasurable disease, must be documented at screening and re-assessed at each subsequent tumor evaluation. Patients with a history of irradiated brain metastases at screening are not required to undergo brain scans at subsequent tumor evaluation unless scans are clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Stable brain metastases must be evaluated with each tumor assessment with the same radiographic procedure as the baseline study. Patients without brain metastases do not need a brain scan for tumor assessment unless clinically warranted. Response will be assessed by the investigator on the

imaging modalities detailed above, using RECIST v1.1 (see Appendix 4). The investigator's assessment of overall tumor response at all timepoints should be *also* based on RECIST v1.1. The Sponsor will derive the overall tumor assessment as per *RECIST v1.1* based on entries for all target lesions, non-target lesions, and new lesions. Assessments should be performed by the same evaluator if possible to ensure internal consistency across visits.

Tumor assessments are to be performed per the schedule provided in Appendix 1, ±3 business days regardless of drug delays or interruptions (i.e., independent of treatment cycles). At the investigator's discretion, scans may be performed at any time if progressive disease or loss of clinical benefit is suspected.

Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments, if feasible, until initiation of subsequent anti-cancer therapy, disease progression, death, loss to follow-up, withdrawal of consent, or study termination, whichever occurs first. Patients who are discontinued from study treatment because of disease progression will be asked to return to the clinic for a confirmatory tumor assessment at 6 (±2) weeks later, if feasible, after experiencing disease progression unless the patient initiates another anti-cancer therapy.

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will be monitored with a follow-up scan in 6 (±2) weeks (i.e., at the next scheduled tumor assessment when the scan frequency is every 2 cycles or as an unscheduled tumor assessment when the scan frequency is every 3 cycles) or earlier if clinically indicated. Tumor assessments should be continued every 2 cycles thereafter until two consecutive scans demonstrate stability or improvement with respect to the first scan that showed radiographic disease progression, at which point the scan frequency should revert or transition to every 3 cycles if applicable. For patients who consented to treatment beyond radiographic disease progression (see Section 3.1.1), new lesions are to be assessed according to *RECIST v1.1* and applicable measurements should be entered into the eCRF. The Sponsor will derive overall tumor assessment as per RECIST v1.1 and the investigator assessment of overall tumor response at all timepoints should be *also* based on RECIST v1.1.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

4.5.6.1 Local Laboratory Tests

The following laboratory tests will be performed by the study site's local laboratory:

- Hematology [redacted]

- Serum chemistries [redacted]
- Serum ferritin and C-reactive protein (CRP)
- Coagulation [redacted]
- Pregnancy test: [redacted]
- Urinalysis [redacted]
- Thyroid function testing [redacted]
- EBV serology [redacted]
  - [redacted]
- Cytomegalovirus (CMV) serology [redacted]
- HBV serology [redacted]
  - [redacted]
- HCV serology (anti-HCV)
  - [redacted]
- All patients will be tested for HIV prior to inclusion into the study, and HIV-positive patients will be excluded from the clinical trial.

4.5.6.2 Central Laboratory Assessments

Samples for the assessments listed below will be sent to one or several central laboratories or to Genentech.

Instruction manual and supply kits will be provided for these central assessments. Please refer to the laboratory manual for additional details on sample handling.

[redacted]

- [redacted]
  - [redacted]

- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

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- [redacted]
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- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]

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.

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

4.5.7 Use and Storage of Remaining Samples from Study-Related Procedures

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and PK, immunogenicity, and biomarker assay development and validation; [redacted]
- [redacted]
- [redacted]

4.5.8 Electrocardiograms

A 12-lead ECG is required at screening, at the treatment discontinuation visit, and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

[redacted]

4.5.9 Cancer-Related Procedures

Collection of cancer-related medical, surgical, and radiation procedures will begin on Day 1 and be performed throughout the treatment period and during the survival follow-up period of the study.

4.5.10 Anti-Drug Antibody Testing

MTIG7192A and/or atezolizumab may elicit an immune response against itself. Patients with signs of any potential immune response to MTIG7192A/placebo and/or atezolizumab will be closely monitored. [redacted]

4.5.11 Patient-Reported Outcomes

PROs will be collected by the EORTC QLQ-C30 to more fully characterize the clinical profile of the study drugs. [redacted]

[redacted]

[redacted]

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 Overview of the Research Biosample Repository

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

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. [redacted]

- [redacted]
- [redacted]
- [redacted]

- [redacted]

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.12) will not be applicable at that site.

4.5.12.3 Sample Collection

[redacted]

- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
- [redacted]

[redacted]

[redacted]

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

[redacted]

4.5.12.4 Confidentiality

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

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

[redacted]

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

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

4.5.12.5 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 specimens. Patients who decline to participate will not provide a separate signature.

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

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

4.5.12.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the study is closed. A patient's withdrawal from Study GO40290 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study GO40290.

4.5.12.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Symptomatic deterioration (i.e., uncontrollable pain secondary to disease or unmanageable ascites, etc.) attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and/or clinical status
- Intolerable toxicity related to study treatment, including development of immune-mediated adverse events (see Section 5.1.1.1), 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 the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues on study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Use of a non-protocol systemic anti-cancer therapy (see Section 4.4.2)
- Pregnancy

- Radiographic disease progression per RECIST v1.1

  Exception: Patients will be permitted to continue study treatment after RECIST v1.1 criteria for progressive disease are met if they meet all of the criteria in Section 3.1.1.

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 who discontinue study treatment primarily for reasons other than disease progression will continue tumor assessments (see Section 4.5.5) if feasible, until disease progression, initiation of another systemic anti-cancer therapy, death, loss to follow-up, withdrawal of consent, or study termination, whichever occurs first. All patients who discontinue study treatment will continue to be followed for survival every 3 months unless consent is withdrawn.

4.6.1.1 Study Treatment Discontinuation Visit

Patients who discontinue study treatment will be asked to return to the clinic for a treatment discontinuation visit at ≤30 days after the last administration of study treatment.

[redacted]

See the schedule of activities provided in Appendix 1 for the respective assessments to be performed at the treatment discontinuation visit.

4.6.1.2 Survival and Subsequent Anti-Cancer Therapy Follow-Up

Following study treatment discontinuation, all patients will be followed for survival and subsequent anti-cancer therapy. [redacted]

[redacted]

4.6.2 Patient Discontinuation from Study

Patient discontinuation from the study is distinguished from discontinuation of study treatment (see Section 4.6.1) and occurs when the patient dies, is lost to follow-up, or withdraws consent to be followed. Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

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

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

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.
- Unsatisfactory patient enrollment
- Inaccurate or incomplete data recording

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 (GCP)
- 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

MTIG7192A is not approved as a single agent or in combination with atezolizumab, and clinical development is ongoing. The safety plan for patients in this study is based on anticipated mechanism of action, results from nonclinical studies, published data on similar molecules, [redacted] and the clinical safety profile of atezolizumab as a single agent. The anticipated important safety risks for MTIG7192A and atezolizumab are outlined below. Please refer to the MTIG7192A Investigator's Brochure and the Atezolizumab Investigator's Brochure for a complete summary of safety information for each respective study drug.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Administration of MTIG7192A/placebo and atezolizumab will be performed in a setting with available emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. All adverse events will be recorded during the study and for up to *30* days after the last dose of study treatment or until the initiation of another systemic anti-cancer therapy, whichever occurs first. *Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.* Guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below and in Appendix 7 and Appendix 8.

In addition to the Sponsor's routine and real-time safety monitoring, an IMC will oversee study safety (see Section 3.1.2).

5.1.1 Risks Associated with MTIG7192A

As MTIG7192A is in an early phase of clinical development, its complete risk profile is unknown at this time. [redacted]

Refer to the MTIG7192A Investigator's Brochure for further details on nonclinical and clinical safety assessments.

5.1.1.1 Infusion-Related Reactions

While clinical evaluation of MTIG7192A is limited and not all risks are known, some patients receiving either single-agent MTIG7192A or MTIG7192A plus atezolizumab, have experienced IRRs. IRRs are considered an identified risk for MTIG7192A and have been Grade 1 and 2 and have included symptoms of pyrexia, chills, nausea, and hypertension.

To minimize the risk and sequelae of IRRs, the initial dose of MTIG7192A*/placebo* will be administered over 60 minutes followed by a 60-minute observation period, and subsequent infusions as well as observation times may be shortened only if the initial dose administration is well tolerated. All infusions will be administered in an appropriate medical setting. Please see Section 4.3 for detailed guidance on administration of atezolizumab as well as MTIG7192A/placebo in this study. Please see Appendix 6 for guidance on anaphylaxis precautions, and see Appendix 7 and Appendix 8for guidance on management of IRRs and risks associated with atezolizumab, respectively.

5.1.1.2 Immune-*Mediated* Adverse Events

Nonclinical models have suggested a role of TIGIT signaling interruption in autoimmunity. In a knockout model (TIGIT–/–), loss of TIGIT signaling resulted in hyperproliferative T-cell responses and exacerbation of experimental autoimmune encephalitis (EAE). TIGIT–/– and wild-type B6 mice were immunized with myelin oligodendrocyte glycoprotein (MOG) peptide in an EAE using suboptimal doses. In contrast to the wild-type B6 mice, the majority of the TIGIT –/– mice developed severe EAE (Joller et al. 2011).

Clinical experience with therapeutics intended to enhance anti-tumor T-cell responses has demonstrated that development of autoimmune inflammatory conditions is a general risk and may therefore be considered a potential risk of MTIG7192A. Such immune-*mediated* adverse events have been described for virtually all organ systems and include, but are not limited to, colitis, hepatitis, pneumonitis, endocrinopathy, ocular toxicity, pancreatic toxicity, neurologic toxicity, myocarditis, *nephritis, myositis,* and rash. Rash and hypothyroidism have been reported in patients treated with MTIG7192A with or without atezolizumab.

Patients with a history of autoimmune disease (other than autoimmune thyroid disease managed with thyroid hormone replacement or vitiligo) will be excluded from this study (see Section 4.1.2).

Management guidelines for individual suspected immune-*mediated* adverse events are provided in Appendix 7 and Appendix 8.

5.1.1.3 Lymphopenia

Given the IgG1 backbone of MTIG7192A with intact Fc-effector function, ADCC-mediated reduction in lymphocyte count is a potential risk. In the repeat-dose toxicity study in cynomolgus monkeys, however, there were no MTIG7192A-related decreases in overall lymphocyte counts.

Transient lymphocyte count decreases without clinical sequelae have been observed in patients treated with MTIG7192A with or without atezolizumab.

Due to this potential risk of MTIG7192A to induce lymphopenia, patients with a lymphocyte count $<$500 cells/μL will be excluded from this study (see Section 4.1.1), and complete blood counts will be monitored regularly during the study (see Appendix 1).

5.1.2 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs, immune-*mediated* hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, *myositis, and nephritis. Immune-mediated adverse reactions may involve any organ system and may lead to HLH and MAS.* Please refer to Appendix 8 of this protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.3 Risks Associated with MTIG7192A Plus Atezolizumab

Based on nonclinical and/or clinical studies with each molecule as a single agent, clinical data from Study GO30103 with MTIG7192A plus atezolizumab, and data from molecules with similar mechanisms of action, there is a potential for overlapping toxicity in patients treated with MTIG7192A plus atezolizumab. Because the expected pharmacologic activity of these two molecules is to increase adaptive T-cell immune responses, there is the possibility of heightened immune responses.

The following adverse events are potential overlapping toxicities associated with combination use of MTIG7192A plus atezolizumab: immune-*mediated* pulmonary, hepatic, gastrointestinal, endocrine, ocular, pancreatic, dermatologic, neurologic adverse events, as well as immune-*mediated* myocarditis and meningoencephalitis. In addition, *HLH and MAS* (described in Appendix 8) is a potential risk when atezolizumab is given in combination with other immunomodulating agents such as MTIG7192A.

It is anticipated that immune-*mediated* adverse events following treatment with MTIG7192A and atezolizumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with immune checkpoint inhibitors to date has been incorporated into the design and safety management plan (see Section 5.1) in order to reduce the potential risks to participating patients. Patients with a history of autoimmune disease (other than autoimmune thyroid disease managed

with thyroid hormone replacement or vitiligo) will be excluded from this study (see Section 4.1.2). Patients previously treated with approved or experimental CIT will also be excluded from participation in this study. Due to the risks of active viral infection and viral reactivation (see Section 1.6.2.2.2), patients with active infection (including, but not limited to, HIV, HBV, HCV, EBV, known and/or suspected chronic active EBV infection, or tuberculosis) and/or patients with recent severe infections will be excluded from this study (see Section 4.1.2.3 and Section 4.5.6.1).

5.1.4 Management of Patients Who Experience Adverse Events

5.1.4.1 Dose Modifications

There will be no dose modifications, including dose reductions, for MTIG7192A/placebo or atezolizumab in this study.

5.1.4.2 Treatment Interruption

Study treatment may be temporarily suspended as appropriate for management of toxicity. [redacted]

[redacted]

After both MTIG7192A/placebo and atezolizumab have been permanently discontinued, the patient will be monitored for safety and efficacy as defined in Section 4.6 and Appendix 1.

5.1.4.3 Management Guidelines

General guidelines for management of patients who experience adverse events are described in Appendix 7.

Guidelines for management of patients who experience adverse events associated with MITG7192A and/or atezolizumab, including immune-*mediated* adverse events, are provided in Appendix 8.

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 Section 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 drug
- 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 drug
- 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). [redacted]

- [redacted]
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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 5.4–5.7.

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 drug, 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 drug, 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 last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 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 (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

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 the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7):

- Temporal relationship of event onset to the initiation of study drug(s)
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug(s), or reintroduction of study drug(s) (as applicable)
- Known association of the event with the study drug(s) 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 medication(s) 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 7 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug 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 the study drug(s), 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 the study drug(s); and/or the adverse event abates or resolves upon discontinuation of the study drug(s) 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 the study drug(s) (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 the study drug(s) (e.g., cancer diagnosed 2 days after first dose of study drug).

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 drug administration and are judged to be related to study drug infusion(s) should be captured as a diagnosis of "infusion-related reaction" on the Adverse Event eCRF. [redacted]

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than IRRs (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and

symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe 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. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes 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 studies, certain abnormal values may not qualify as adverse events.

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × 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 ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- [redacted]
- [redacted]

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

5.3.5.8 Deaths

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

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

be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of NSCLC

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

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

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

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

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 study. 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 drug:

- 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)
- Accidental overdoses or medication errors (see Section 5.4.4 for details on reporting requirements)

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

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor: [redacted], M.D. (Primary)
Telephone: [redacted] (USA)

[redacted] Medical Monitors: [redacted] Medical Monitor
Telephone: [redacted]
[redacted] Medical Monitor
Telephone: [redacted]

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 Drug Initiation

After informed consent has been obtained but prior to initiation of study drug(s), 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 contact information provided below:

Region	North America	EMEA/APAC
Fax	[redacted]	[redacted]
Email	[redacted]	[redacted]
24-Hour Safety Hotline (only in the event site cannot fax or email)	[redacted]	[redacted]

APAC=Asia-Pacific; EMEA=Europe, Middle East, and Africa.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug(s), serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug(s). 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 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 in Section 5.4.2.1. 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 last dose of study treatment 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 5 months after the last dose of study drug(s). 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 in Section 5.4.2.1. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue the study drug(s) 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 90 days after the last dose of study drug. 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 in Section 5.4.2.1. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug(s). 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 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug(s) or the female partner of a male patient exposed to study drug(s) 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 4.5.2).

5.4.3.4 Abortions

Any 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 4.5.2).

5.4.4 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (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
- 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.

Special situations are not in themselves adverse events, but may result in adverse events. All special situations associated with MTIG7192A and/or atezolizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- 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.

For MTIG7192A and atezolizumab, 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 MTIG7192A and atezolizumab, 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.
- 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.

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

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 drug(s) or study-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 adverse event reporting period (defined as *30 days after the last dose of study drug), serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Beyond 90 days after last dose of study treatment,* 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 drug(s), 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 using the following reference documents:

- MTIG7192A Investigator's Brochure
- Atezolizumab 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.

An IMC 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

This study will enroll approximately 120 patients that will represent the primary population (i.e., ITT) for the co-primary PFS and ORR activity objectives. Unless otherwise stated, summaries of study conduct, patient demographics, baseline characteristics, and secondary and exploratory endpoints will be assessed in the primary population.

6.1 DETERMINATION OF SAMPLE SIZE

The primary objective of this study is to obtain estimates of safety and efficacy parameters of MTIG7192A plus atezolizumab compared with placebo plus atezolizumab.

Approximately 30 months after the first patient has enrolled in the study, it is estimated that 120 patients (approximately 60 patients in each arm) [redacted]

[redacted]

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study treatment administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be listed by treatment arm and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized by treatment arm for all randomized patients. Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum, and maximum. Descriptive summaries of discrete data will present the category counts as frequencies and percentages.

6.4 EFFICACY ANALYSES

[redacted] Specifically, estimates in the difference in ORR between the two study arms and PFS HRs will be computed along with their 90% CIs. Hypothesis testing of the co-primary efficacy endpoints will also be conducted in the primary patient population. The DOR secondary endpoint in the primary population will also be analyzed at this point. [redacted]

[redacted]

All co-primary analyses of disease progression and objective response will be based on investigator review of tumor assessments using RECIST v1.1.

6.4.1 Co-Primary Efficacy Endpoints

PFS is defined as the time from randomization to the date of first documented disease progression or death, whichever occurs first. Disease progression for PFS analysis will be determined on the basis of investigator assessment using RECIST v1.1. [redacted]

Data for a patient without disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment (or at the date of randomization plus 1 day if no tumor assessment was performed after the baseline visit). Data from a patient who is lost to follow-up will be included in the analysis and censored on the last date of tumor assessment that the patient was known to be progression free.

[redacted]

ORR is defined as the percentage of patients who have experienced a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1. Objective response will be evaluated by treatment arm. Patients without postbaseline overall response assessments will be counted as non-responders.

[redacted]

6.4.2 Secondary Efficacy Endpoints

[redacted]

[redacted]

[redacted]

6.5 SAFETY ANALYSES

Safety analyses will be conducted in all randomized patients who received at least one dose of MTIG7192A/placebo or atezolizumab.

Safety analyses will be performed by treatment arm and will be based on actual treatment received. Specifically, a patient will be included in the MTIG7192A plus atezolizumab arm in the safety analyses if the patient receives any amount of MTIG7192A, regardless of the initial treatment assignment at randomization.

Safety endpoints will include incidence, nature, and severity of adverse events (using NCI CTCAE v4.0), including serious adverse events and adverse events of special interest, changes from baseline in vital signs, physical findings, and clinical laboratory results following the administration of MTIG7192A/placebo plus atezolizumab. Drug exposure will be summarized, including duration, dosage, and dose intensity. Verbatim description of adverse events will be mapped to the MedDRA thesaurus terms and graded according the NCI CTCAE v4.0. All adverse events that occur during or after the first study treatment, until 30 days after the last dose of study drug or initiation of another systemic anti-cancer therapy, whichever occurs first, will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events and adverse events leading to study treatment discontinuation or interruption will be summarized accordingly. Multiple occurrence of the same event will be counted once at the maximum severity. Laboratory data with values outside of the normal ranges will be identified. [redacted] Vital signs will also be summarized by treatment arm and visit. Deaths and causes of deaths will be summarized.

Analyses of safety endpoints will be conducted at the time of the primary efficacy analysis.

[redacted]

6.7 PHARMACOKINETIC ANALYSES

Serum concentrations, as appropriate, of MTIG7192A and atezolizumab versus time will be tabulated, and summary statistics will be computed for each scheduled sampling time.

[redacted]

6.8 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with any ADA assessments, with patients grouped according to treatment received.

[redacted]

6.9 PATIENT-REPORTED OUTCOME ANALYSES

PROs will be documented via analyses of scales from the EORTC QLQ-C30 [redacted]

6.10 INTERIM ANALYSES

Periodic analyses of cumulative safety data and one interim analysis of efficacy data are planned for this study.

[redacted]

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, and IxRS 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 subject data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, 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 study.

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 study-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

The Sponsor’s sample Informed Consent Form 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.

[redacted]

Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

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

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

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

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements,

policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

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

8.4 CONFIDENTIALITY

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.

(see Section 9.5).

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

8.5 FINANCIAL DISCLOSURE

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

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

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored by F. Hoffmann-La Roche Ltd. and will be managed by Genentech and a contract research organization (CRO). The CRO will provide clinical operations management, data management, and medical monitoring.

Approximately 50–65 sites globally will participate in the study and approximately 120 patients will be randomized. Randomization will occur through an IxRS. Central facilities will be used for study assessments throughout the study (e.g., specified laboratory tests and PK analyses). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected. Data will be recorded via an EDC system with the use of eCRFs (see Section 7.2).

An IMC will monitor and evaluate patient safety throughout the study.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following web site:

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 studies 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 study results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical studies 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 studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities

Assessment Window (Days)	Screening [a]	All Cycles	Treatment Discontinuation [b]	Post-Progressive Disease Assessment	Follow-Up
	Days –28 to –1	Day 1 (±3 Days for Cycles ≥2)	≤30 Days after Last Dose		
Signed Informed Consent Form(s) [a]	x				
Review of eligibility criteria	x				
Medical, surgical, and cancer histories, including demographic information, and *EGFR* and *ALK* mutational status [c]	x				
EBV, CMV, HIV, HBV, HCV serology [d]	x				
Concomitant medications [e]	x	x	x		
Tumor assessment [f]	x	Every 6 weeks (e.g., every 2 cycles) ±3 business days until Week 36 (e.g., up to Cycle 12), then every 9 (± 1) weeks (e.g., every 3 cycles) until confirmed disease progression, loss of clinical benefit, death, or loss of follow-up		x [g]	x [h]
Patient-reported outcomes by EORTC QLQ-C30 [i]		x [i]	x		
Complete physical examination [j]	x		x		
Limited physical examination [j]		x [k]			
ECOG Performance Status	x	x [k]	x		
Vital signs [l]	x	x	x		
Pulse oximetry, resting [m]	x				
Singleton 12-lead ECG [n]	x		x		
Weight	x	x	x		
Height	x				

Appendix 1
Schedule of Activities (cont.)

Assessment Window (Days)	Screening [a]	All Cycles	Treatment Discontinuation [b]	Post-Progressive Disease Assessment	Follow-Up
	Days –28 to –1	Day 1 (± 3 Days for Cycles ≥ 2)	≤ 30 Days after Last Dose		
Hematology [o] / Serum chemistry [p]	x	x	x		
Coagulation panel (aPTT and PT and/or INR)	x		x		
C-reactive protein, serum ferritin	x	x [k]	x [k]		
Urinalysis [q]	x	x	x		
Serum pregnancy test [s, r]	x				
TSH, free T3, free T4	x	x [t]	x		
Cancer-related procedures (medical, surgical, radiation)		x	x		x
Auto-antibody sample (central laboratory) [u]		x			
Serum sample for ADA and PK assessment (central laboratory) [v]	[redacted]				
[redacted]	[redacted]				
Adverse events [w]		x	x		x
Atezolizumab infusion [x]		x			
MTIG7192A or placebo IV infusion [y]		x			
Archival or screening FFPE tumor tissue specimen [z]	x				
[redacted]	[redacted]				

Appendix 1
Schedule of Activities (cont.)

Assessment Window (Days)	Screening [a] Days –28 to –1	All Cycles Day 1 (± 3 Days for Cycles ≥ 2)	Treatment Discontinuation [b] ≤30 Days after Last Dose	Post-Progressive Disease Assessment	Follow-Up
[redacted]					
Survival and anti-cancer therapy follow-up [cc]					x

ADA=anti-drug antibody; anti-HBc=antibody to hepatitis B core antigen; C=cycle; CMV=cytomegalovirus; CT=computed tomography; D=day; EBV=Epstein-Barr virus; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire–Core 30; FFPE=formalin fixed, paraffin embedded; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; PD=pharmacodynamic; PD-L1=programmed death–ligand 1; PET=positron emission tomography; PK=pharmacokinetic; PRO=patient-reported outcome; RECIST=Response Evaluation Criteria in Solid Tumors; TSH=thyroid-stimulating hormone.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] Written informed consent is required for performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry (except where otherwise specified) may be used for screening assessments rather than repeating such tests.

[b] Patients will be asked to return to the clinic not more than 30 days after the last dose of treatment for a treatment discontinuation visit.

[c] Cancer history includes stage, date of diagnosis, results of *EGFR* mutation and *ALK* rearrangement testing (central testing available only for sites that do not have local testing options), and prior anti-tumor treatment. Demographic information includes sex, age, and self-reported race/ethnicity.

[d] All patients will be tested for HIV prior to the inclusion into the study, and HIV-positive patients will be excluded from the clinical study. HBV DNA must be collected on or before Cycle 1, Day 1 (C1D1) in patients who have negative serology for HBsAg and positive serology for anti-HBc. An HCV-RNA test is required prior to C1D1 if the patient has positive serology for anti-HCV. Screening EBV and CMV serology samples will be collected, [redacted] Additional EBV and CMV serology tests will be performed for patients who subsequently experience an acute inflammatory event, such as systemic inflammatory response syndrome, while receiving study treatment.

[e] Concomitant medications include any prescription medications, over-the-counter medications, vaccines, herbal or homeopathic remedies, or nutritional supplements. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation will be recorded.

[f] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to randomization may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. Screening and subsequent tumor assessments should include CT scans (with IV contrast unless contraindicated and oral contrast per institutional standards) of the chest, abdomen, and pelvis. After screening, CT scans can be limited to include an evaluation of all sites of known disease. CT scans may be substituted by MRI scans, if clinically indicated. Brain imaging (either MRI or contrast-enhanced CT) is required at screening for all patients to evaluate for presence of CNS metastases, and as clinically indicated. Bone scans should also be performed, if clinically indicated. If a CT scan for tumor assessment is performed in a PET/CT scanner, the CT acquisition must be consistent with the standards of a full-contrast CT scan. The same imaging modality and radiographic procedure must be used throughout the study for each patient. Results must be reviewed by the investigator before dosing at the next cycle. Tumor assessments will be performed at baseline and every 6 weeks (approximately every 2 cycles) (± 3 business days) thereafter for 36 weeks (or approximately up to Cycle 12) following randomization. After 36 weeks (or after Cycle 12), patients who have not experienced disease progression will undergo tumor assessment every 9 (±1) weeks (approximately every 3 cycles). Additional scans should be performed as clinically indicated. If an optional biopsy is to be performed at approximately the same timepoint of a tumor assessment or as a result of the radiographic determination (e.g., response or progression), samples should be acquired after all imaging scans have been performed, if at all possible. Investigators may perform additional scans or more frequent assessments, if clinically indicated.

[g] Patients who are discontinued from study treatment because of disease progression will be asked to return for a repeat tumor assessment in 6 (±2) weeks, if feasible, after experiencing disease progression unless the patient initiates subsequent anti-cancer therapy.

[h] Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments until disease progression, initiation of subsequent anti-cancer therapy, death, loss to follow-up, withdrawal of consent, or study termination, whichever occurs first. The schedule of these tumor assessments will be approximately every 12 (± 1) weeks (as long as the patient has not started new treatment). Scans can be performed locally, if feasible.

[i] The EORTC QLQ-C30 questionnaire will be completed at baseline (prior to dosing on C1D1), and then administered and recorded prior to dosing at the first cycle visits after tumor assessments (i.e., at C3D1, C5D1, C7D1, etc.) and at the study treatment discontinuation visit at the investigational site until disease progression or treatment discontinuation, whichever occurs later (see Section 4.6.1). The EORTC QLQ C30 is required to be administered prior to administration of study drug and prior to any other study assessment(s) that might bias the answers to the questionnaire.

[j] Complete and limited physical examinations are defined in the protocol (see Section 4.5.3).

[k] ECOG Performance Status, limited physical examination, and local laboratory assessments may be obtained ≤96 hours before Day 1 of each cycle. [redacted]

Appendix 1
Schedule of Activities (cont.)

[l] Vital signs include pulse rate, respiratory rate, blood pressure, and temperature. For the first infusion, vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before and 30 (±10) minutes after the infusion. Vital signs will also be collected during the first infusion (every 15 [±5] minutes). During subsequent infusions, vital signs should be determined during each infusion only as clinically indicated and within 15 [±10] minutes after the end of each infusion. Additional vital signs should be collected during the infusion if clinically indicated or if symptoms occurred with the prior infusion.

[m] Pulse oximetry at rest is collected at baseline and as clinically indicated thereafter.

[n] For all patients, digitized, single, 12-lead ECGs will be obtained during screening and at the treatment discontinuation visit. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection, and ECGs should be performed prior to any venipuncture. Single ECG recordings may be obtained at unscheduled timepoints, as clinically indicated.

[o] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. Please see Section 4.1.1 for a list of laboratory results that are to be obtained within 14 days prior to the first study treatment.

[p] Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, ALP, lipase, amylase, LDH, total protein, and albumin. Please see Section 4.1.1 for a list of laboratory results that are to be obtained within 14 days prior to the first study treatment.

[q] Urinalysis consists of specific gravity, pH, glucose, protein, ketones, and blood.

[r] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed on C1D1 and every second cycle thereafter. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[s] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1.

[t] TSH, free T3, and free T4 are to be assessed *on C2D1 and* every second cycle *thereafter (i.e., at C4D1, C6D1, C8D1, etc.).*

[u] Baseline sample to be collected on C1D1 prior to the first dose of study treatment. On-study samples of auto antibodies only need to be collected for patients who show evidence of immune-*mediated* toxicity or if otherwise clinically indicated. All samples will be analyzed centrally.

[redacted]

[v] [redacted]

[w] After informed consent has been obtained but prior to initiation of study drug(s), only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug(s), all adverse events will be reported until *30 days* after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators should report any serious adverse events, or other adverse events of *special interest until 90 days after the last dose of study* treatment *or until initiation of new systemic anti-cancer therapy, whichever occurs first.* 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 drug(s) or study-related procedures until a final outcome can be reported. *Beyond 90 days after last dose of study treatment, all deaths, regardless of cause, should be reported through the 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 drug(s), the event should be reported through the Adverse Event eCRF, or if the EDC is unavailable, directly to the Sponsor or its designee.*

[x] [redacted] Patients will receive atezolizumab by continuous IV infusion every 21 days on Day 1 of each 21-day cycle as indicated. For atezolizumab, the initial dose will be delivered over 60 (±15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes.

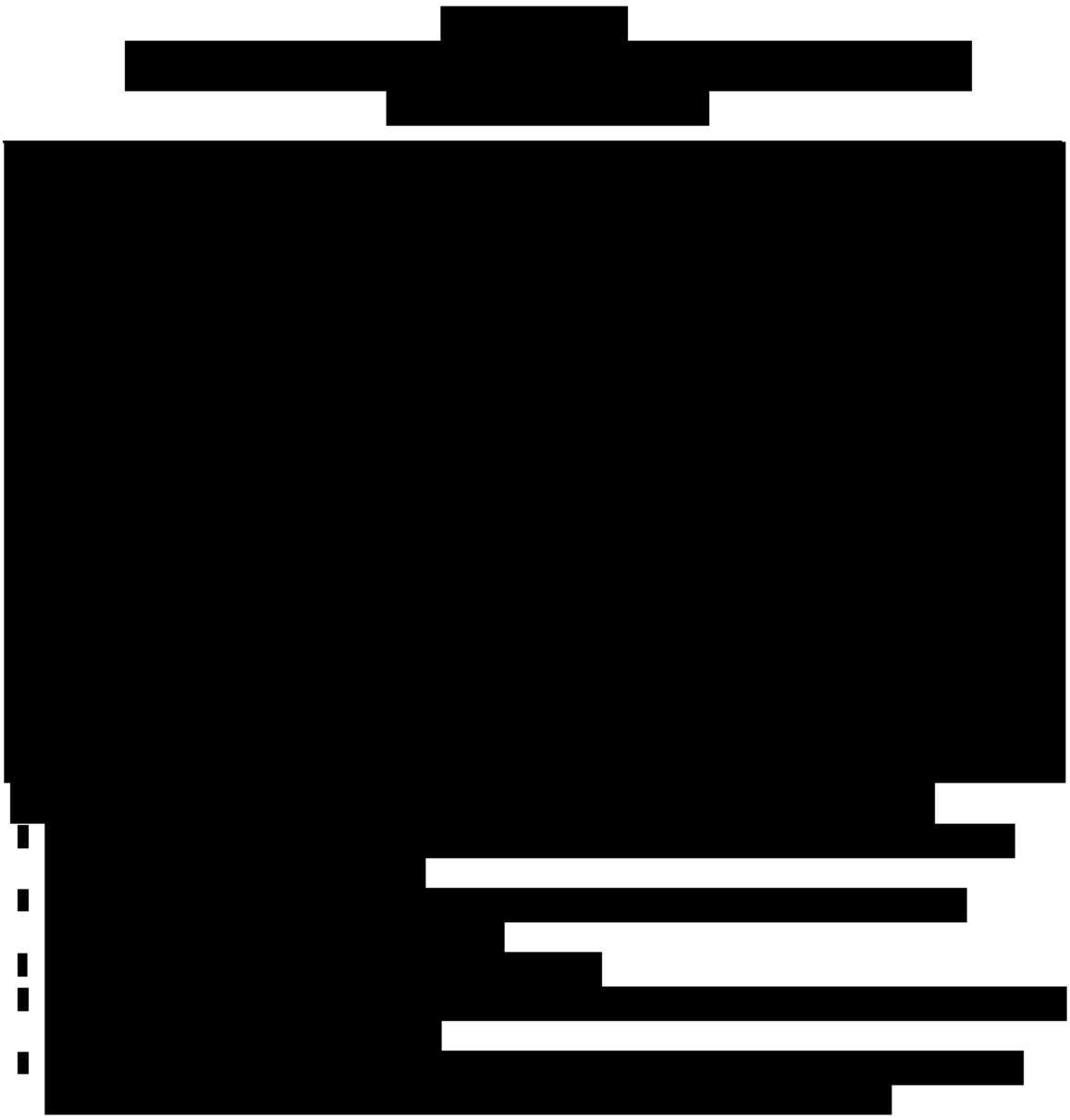
[y] [redacted], patients will receive MTIG7192A or placebo by continuous IV infusion every 21 days on Day 1 of each 21-day cycle as indicated. For MTIG7192A or placebo, the initial dose will be delivered over 60 (±15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. Dosing of both study drugs will occur only if the clinical assessment and local laboratory test results are acceptable. If a tumor assessment was performed, results must be reviewed by the investigator before dosing of study drugs.

[z] [redacted]

Appendix 1
Schedule of Activities (cont.)

[redacted]

[cc] After confirmed disease progression or loss of clinical benefit and study treatment discontinuation, survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months *(±1 week)* until death, loss to follow-up, or study termination by the Sponsor. All patients will be followed 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 study treatment but not from follow-up, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.



Appendix 3
European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Appendix 3
European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire: EORTC QLQ-C30 (cont.)

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 4
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.

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

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 unequivocal progression in the lesion and the previously irradiated lesion is not the only site of measurable disease.

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

METHODS FOR ASSESSING LESIONS

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

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

CLINICAL LESIONS

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

CHEST X-RAY

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

CT AND MRI SCANS

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

If prior to enrollment it is known that a patient is unable to undergo CT scans with 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, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, 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 $\geq$ 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,

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

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

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

CALCULATION OF SUM OF DIAMETERS

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

Measuring Lymph Nodes

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

- CR: Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- 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

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

- 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 $\geq$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.

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

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.

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

REFERENCE

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

Appendix 5
Eastern Cooperative Oncology Group Performance Status Scale

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

Appendix 6
Anaphylaxis Precautions

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

EQUIPMENT NEEDED

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

PROCEDURES

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

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observations.

Appendix 7
Overall Guidelines for Management of Patients Who Experience Adverse Events

DOSE MODIFICATIONS

There will be no dose modifications for MTIG7192A/placebo and/or atezolizumab in this study.

TREATMENT INTERRUPTION

MTIG7192A/Placebo

Study treatment may be temporarily suspended as appropriate for management of toxicity. On the basis of the available characterization of mechanism of action, MTIG7192A may cause adverse events similar to but independent of atezolizumab, may exacerbate the frequency or severity of atezolizumab-related adverse events, or may have non-overlapping toxicities with atezolizumab. Because these scenarios may not be distinguishable from each other in the clinical setting, immune-*mediated* adverse events should generally be attributed to both agents, and dose interruptions or treatment discontinuation in response to immune-*mediated* adverse events should be applied to both MTIG7192A/placebo and atezolizumab.

Appendix 7
Overall Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Atezolizumab

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >12 weeks (or 4 cycles) after event onset, the patient will be discontinued from atezolizumab. [redacted]

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A

Toxicities associated or possibly associated with atezolizumab or MITG7192A 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 and MTIG7192A 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 and/or MTIG7192A 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 and/or MTIG7192A 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. Immune-*mediated* pulmonary events are a potential risk with MTIG7192A. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. [redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

HEPATIC EVENTS

[redacted]

Eligible patients for this study must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. [redacted]

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(s).

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

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

GASTROINTESTINAL EVENTS

[redacted]

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 a diagnosis of colitis.

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

ENDOCRINE EVENTS

[redacted]

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 magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

IMMUNE-*MEDIATED* MYOCARDITIS

[redacted] 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.

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

INFUSION-RELATED REACTIONS

No premedication is indicated for the administration of Cycle 1 of MTIG7192A/placebo and atezolizumab. However, patients who experience an infusion-related reaction (IRR) with Cycle 1 of MTIG7192A/placebo and atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating MTIG7192A/placebo- and/or atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

[redacted] For subsequent cycles, IRRs should be managed according to institutional guidelines.

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

PANCREATIC EVENTS

[redacted] The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. [redacted]

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

DERMATOLOGIC EVENTS

[redacted] The majority of the 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. [redacted]

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

[redacted]

NEUROLOGIC DISORDERS

[redacted]

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. [redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

IMMUNE-*MEDIATED* MENINGOENCEPHALITIS

[redacted] 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.

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

RENAL EVENTS

[redacted] 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.

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

IMMUNE-MEDIATED MYOSITIS

[redacted]

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.

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

[redacted]

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

[redacted]

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 ×10⁹/L (100,000/μL)*
  - *ANC <1.0 ×10⁹/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*

Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

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 ≤181 ×10⁹/L (181,000/μL)*
  - *AST ≥48 U/L*
  - *Triglycerides >1.761 mmol/L (156 mg/dL)*
  - *Fibrinogen ≤3.6 g/L (360 mg/dL)*

[redacted]

REFERENCES

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Appendix 8
Risks Associated with Atezolizumab or MTIG7192A and Guidelines for Management of Adverse Events Associated with Atezolizumab or MTIG7192A (cont.)

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–9.