Official Title: **A Multistage, Phase II Study Evaluating the Safety and Efficacy of Cobimetinib plus Paclitaxel, Cobimetinib plus Atezolizumab plus Paclitaxel, or Cobimetinib plus Atezolizumab plus Nab-Paclitaxel as First-Line Treatment for Patients with Metastatic Triple-Negative Breast Cancer**

NCT Number: **NCT02322814**

Document Date: Protocol Version 8: 25-Oct-2018

PROTOCOL

TITLE: **A MULTISTAGE, PHASE II STUDY EVALUATING THE SAFETY AND EFFICACY OF COBIMETINIB PLUS PACLITAXEL, COBIMETINIB PLUS ATEZOLIZUMAB PLUS PACLITAXEL, OR COBIMETINIB PLUS ATEZOLIZUMAB PLUS NAB-PACLITAXEL AS FIRST-LINE TREATMENT FOR PATIENTS WITH METASTATIC TRIPLE-NEGATIVE BREAST CANCER**

PROTOCOL NUMBER: WO29479

VERSION NUMBER: 8

EUDRACT NUMBER: 2014-002230-32

IND NUMBER: (GDC-0973/RO5514041/XL518): 122878

TEST PRODUCTS: Cobimetinib (RO5514041), atezolizumab (MPDL3280A; RO5541267), nab-paclitaxel

MEDICAL MONITOR: [redacted], Ph.D., MRPharmS

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: Version 1: 17 July 2014

DATES AMENDED: Version 2: 4 September 2014
Version 3: 31 March 2015
Version 4: 20 June 2016
Version 5: 3 December 2016
Version 6: 26 December 2016
Version 7: 6 December 2017
Version 8: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	25-Oct-2018 21:44:24

PROTOCOL AMENDMENT, VERSION 8:
RATIONALE

Protocol WO29479 has been amended to update the lists of risks for atezolizumab and guidelines for managing patients who experience atezolizumab-associated adverse events including nephritis. Changes to the protocol, along with a rationale for each change, are summarized below:

- Subsequent reviews of the triplet treatment combinations for Cohorts II and III have been updated to take place as needed instead of every 6 months (Section 3.1.1.2)
- The inclusion criterion that addresses female contraception has been modified to specify when women must refrain from donating eggs (Section 4.1.1).
- The flexible wording that paclitaxel "may also be considered an IMP in this study, depending on local legislation" has been removed to align with Roche standard operating procedures (Section 4.3.3).
- Guidelines for managing patients who experience atezolizumab-associated adverse events have been revised to include guidelines for nephritis. Those guidelines have been provided in an appendix so there is no longer a need to consult the Atezolizumab Investigator's Brochure for management guidelines (Section 5.1.2 and Appendix 12).
- The reporting of the term "sudden death" has been updated to also require the presumed cause of death (Section 5.3.5.8).
- Adverse event reporting for hospitalization has been clarified (Section 5.3.5.10).
- The reporting timeframe for serious adverse events and adverse events of special interest has been updated for Cohorts II and III (Section 5.4.2.2).
- Language has been revised to account for the fact that some sites may not allow follow-up on partner pregnancies (Section 5.4.3.2).
- Language has been updated to indicate that therapeutic or elective abortions are not considered adverse events unless performed because of an underlying maternal or embryofetal toxicity. In such cases, the underlying toxicity should be reported as a serious adverse event. Language has also been added to clarify that all abortions are to be reported on the paper Clinical Trial Pregnancy Reporting Form (Section 5.4.3.3).
- Language has been added for consistency with Roche's current data retention policy and to accommodate more stringent local requirements (if applicable) (Section 7.5).
- The process for reviewing and handling protocol deviations has been updated per internal standard operating procedures (Section 9.1).
- Clarification has been made that the predose atezolizumab serum PK [redacted] will be done on Day 1 of the visit cycle for Cycles 2, 4, 8, and every 8 cycles thereafter (Appendix 2, Table 6).

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A MULTISTAGE, PHASE II STUDY EVALUATING THE SAFETY AND EFFICACY OF COBIMETINIB PLUS PACLITAXEL, COBIMETINIB PLUS ATEZOLIZUMAB PLUS PACLITAXEL, OR COBIMETINIB PLUS ATEZOLIZUMAB PLUS NAB-PACLITAXEL AS FIRST-LINE TREATMENT FOR PATIENTS WITH METASTATIC TRIPLE-NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	WO29479
VERSION NUMBER:	8
EUDRACT NUMBER:	2014-002230-32
IND NUMBER:	(GDC-0973/RO5514041/XL518): 122878
TEST PRODUCT:	Cobimetinib (RO5514041), atezolizumab (MPDL3280A; RO5541267), nab-paclitaxel
MEDICAL MONITOR:	[redacted] Ph.D., MRPharmS
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A MULTISTAGE, PHASE II STUDY EVALUATING THE SAFETY AND EFFICACY OF COBIMETINIB PLUS PACLITAXEL, COBIMETINIB PLUS ATEZOLIZUMAB PLUS PACLITAXEL, OR COBIMETINIB PLUS ATEZOLIZUMAB PLUS NAB-PACLITAXEL AS FIRST-LINE TREATMENT FOR PATIENTS WITH METASTATIC TRIPLE-NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	WO29479
VERSION NUMBER:	8
EUDRACT NUMBER:	2014-002230-32
IND NUMBER:	(GDC-0973/RO5514041/XL518): 122878
TEST PRODUCT:	Cobimetinib (RO5514041), atezolizumab (MPDL3280A; RO5541267), nab-paclitaxel
PHASE:	II
INDICATION:	Metastatic triple-negative breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

This three-cohort study in patients with metastatic triple negative breast cancer (mTNBC) will evaluate the efficacy, safety, and pharmacokinetics of cobimetinib plus paclitaxel in Cohort I, of cobimetinib plus atezolizumab plus paclitaxel in Cohort II, and of cobimetinib plus atezolizumab plus nab-paclitaxel in Cohort III. Objectives and corresponding endpoints are presented for each cohort in the tables below.

Table S1 Objectives and Corresponding Endpoints for Cohort I

Objectives	Corresponding Endpoints
Primary efficacy objective:	
• To estimate the clinical benefit of cobimetinib plus paclitaxel relative to placebo plus paclitaxel, as measured by investigator-assessed PFS	• PFS, defined as the time from randomization to the first occurrence of disease progression or relapse as determined by the investigator using RECIST v1.1
Secondary efficacy objectives:	
• To determine the ORR, ORR uc, and DOR of cobimetinib plus paclitaxel and placebo plus paclitaxel • To evaluate the OS benefit of cobimetinib plus paclitaxel and placebo plus paclitaxel	• OS, defined as the time from randomization to death from any cause • ORR, defined as the rate of a PR or CR occurring after randomization and confirmed ≥ 28 days later as determined by the investigator using RECIST v1.1 • DOR, defined as the time from the first occurrence of a documented objective response to the time of relapse, as determined by the investigator using RECIST v1.1 or death from any cause during the study, whichever occurs first. • ORR uc (ORR confirmation not required), defined as the rate of a PR or CR occurring after randomization as determined by the investigator using RECIST v1.1, confirmation not required
Safety objective:	
• To evaluate the safety and tolerability of cobimetinib administered in combination with paclitaxel	• Nature, frequency, and severity of adverse events as graded using NCI CTCAE v4.0 • Changes in vital signs and clinical laboratory results during and following cobimetinib and paclitaxel administration
PK objectives:	
• To characterize the pharmacokinetics of cobimetinib and paclitaxel when administered in combination (safety run-in) • To characterize the pharmacokinetics of cobimetinib and to investigate the relationship between cobimetinib exposure and efficacy and safety outcomes using population approaches (expansion stage)	The goal of PK sampling in the safety run-in stages is to check for any differences in cobimetinib and paclitaxel pharmacokinetics when these drugs are co-administered, relative to their PK when administrated alone (historic PK data). For cobimetinib and paclitaxel, the following PK parameters will be estimated using data from the safety run-in stage: • C_{max} • C_{min} • Additionally, AUC_{0-t} will be estimated for cobimetinib, paclitaxel, and nab-paclitaxel

Table S1 Objectives and Corresponding Endpoints for Cohort I (cont.)

AUC_{0-T} = total exposure; C_{max} = maximum concentration; C_{min} = minimum concentration; CR = complete response; DOR = duration of response; [redacted]; mTNBC = metastatic triple negative breast cancer; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = overall response rate; ORR_uc = unconfirmed overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; [redacted] RECIST = Response Evaluation Criteria in Solid Tumors.

Table S2 Objectives and Corresponding Endpoints for Cohort II

Objectives	Corresponding Endpoints
Primary efficacy objective:	
• To estimate the clinical benefit of cobimetinib plus atezolizumab plus paclitaxel, as measured by ORR	• ORR, as defined in Table S1
Secondary efficacy objectives:	
• To determine the ORR_uc and DOR of cobimetinib plus atezolizumab plus paclitaxel • To evaluate the OS and PFS	• PFS, as defined in Table S1 • OS, as defined in Table S1 • DOR as defined in Table S1 • ORR_uc, as defined in Table S1
Safety objective:	
• To evaluate the safety and tolerability of cobimetinib and atezolizumab administered with paclitaxel	• Nature, frequency, and severity of adverse events as graded using NCI CTCAE v4.0 • Changes in vital signs and clinical laboratory results during and following cobimetinib, atezolizumab, and paclitaxel administration
PK objectives:	
• To characterize the pharmacokinetics of cobimetinib, atezolizumab, and paclitaxel when administered together (safety run-in) • To characterize the pharmacokinetics of cobimetinib and to investigate the relationship between cobimetinib exposure and efficacy and safety outcomes using population approaches (expansion stage)	The goal of PK sampling in the safety run-in stages is to check for any differences in cobimetinib, atezolizumab, and paclitaxel pharmacokinetics when these drugs are co-administered, relative to their PK when administrated alone (historic PK data). For cobimetinib, atezolizumab, and paclitaxel, the following PK parameters will be estimated using data from the safety run-in stage: • C_{max} • C_{min} • Additionally, AUC_{0-t} will be estimated for cobimetinib, atezolizumab, and paclitaxel
[redacted]	
[redacted]	[redacted]

Table S2 Objectives and Corresponding Endpoints for Cohort II (cont.)

[redacted]	[redacted]
[redacted]	[redacted]

AUC_{0-T} = total exposure; C_{max} = maximum concentration; C_{min} = minimum concentration; CR = complete response; DOR = duration of response; [redacted] mTNBC = metastatic triple negative breast cancer; [redacted]; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = overall response rate; ORR_uc = unconfirmed overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; [redacted] RECIST = Response Evaluation Criteria in Solid Tumors.

Table S3 Objectives and Corresponding Endpoints for Cohort III

Objectives	Corresponding Endpoints
Primary efficacy objective:	
• To estimate the clinical benefit of cobimetinib plus atezolizumab plus nab-paclitaxel, as measured by ORR	• ORR, as defined in Table S1
Secondary efficacy objectives:	
• To determine the ORR_uc and DOR of cobimetinib plus atezolizumab plus nab-paclitaxel • To evaluate the OS PFS	• PFS, as defined in Table S1 • OS, as defined in Table S1 • ORR_uc as defined in Table S1 • DOR as defined in Table S1

Table S3 Objectives and Corresponding Endpoints for Cohort III (cont.)

Safety objective:	
• To evaluate the safety and tolerability of cobimetinib and atezolizumab administered with nab-paclitaxel	• Nature, frequency, and severity of adverse events as graded using NCI CTCAE v4.0 • Changes in vital signs and clinical laboratory results during and following cobimetinib, atezolizumab, and nab-paclitaxel administration
PK objectives:	
• To characterize the pharmacokinetics of cobimetinib, atezolizumab, and nab-paclitaxel when administered in combination (safety run-in) • To characterize the pharmacokinetics of cobimetinib and to investigate the relationship between cobimetinib exposure and efficacy and safety outcomes using population approaches (expansion stage)	The goal of PK sampling in the safety run-in stages is to check for any differences in cobimetinib, atezolizumab, and nab-paclitaxel pharmacokinetics when these drugs are co-administered, relative to their PK when administrated alone (historic PK data). For cobimetinib, atezolizumab, and nab-paclitaxel, the following PK parameters will be estimated using data from the safety run-in stage: • Maximum plasma concentrations (C_{max}) • Minimum plasma concentration (C_{min}) • Additionally, total exposure (AUC_{0-t}) will be estimated for cobimetinib, atezolizumab, and nab-paclitaxel.
[redacted]	[redacted]
[redacted]	[redacted]

Table S3 Objectives and Corresponding Endpoints for Cohort III (cont.)

[redacted]	[redacted]

AUC_{0-T} = total exposure; C_{max} = maximum concentration; C_{min} = minimum concentration; CR = complete response; DOR = duration of response [redacted]; mTNBC = metastatic triple negative breast cancer; [redacted]; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = overall response rate; ORR_uc = unconfirmed overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response [redacted]; RECIST = Response Evaluation Criteria in Solid Tumors.

Study Design

Description of Study

This is a three-cohort, multistage, randomized, Phase II, multicenter trial designed to evaluate the safety and tolerability and estimate the efficacy of cobimetinib plus paclitaxel versus placebo plus paclitaxel, and that of cobimetinib plus atezolizumab plus paclitaxel/nab-paclitaxel in patients with metastatic or locally advanced, triple-negative adenocarcinoma of the breast who have not received prior systemic therapy for metastatic breast cancer (MBC). Locally advanced disease must not be amenable to resection with curative intent.

The study will commence with Cohort I, which includes an initial safety run-in stage followed by a randomized (expansion) stage. The initial safety run-in stage will comprise approximately 12 patients receiving cobimetinib plus paclitaxel followed by an expansion stage where approximately 90 patients will be randomized (1:1) to receive either cobimetinib plus paclitaxel or placebo plus paclitaxel.

Following completion of Cohort I, enrollment into Cohorts II and III will begin. Patients will be randomized (1:1) into either Cohort II or III. In Cohort II, patients will receive cobimetinib plus atezolizumab plus paclitaxel. In Cohort III, patients will receive cobimetinib plus atezolizumab plus nab-paclitaxel.

Number of Patients

In Cohort I, the initial safety run-in stage will comprise approximately 12 patients receiving cobimetinib plus paclitaxel followed by an expansion stage where approximately 90 patients will be randomized (1:1) to receive either cobimetinib plus paclitaxel or placebo plus paclitaxel.

Each of Cohorts II and III will comprise a safety run-in stage of approximately 15 patients followed by an expansion stage of approximately 15 patients.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Women and men, age ≥ 18 years
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Histologically confirmed estrogen receptor (ER)-negative, progesterone receptor (PR) negative, and human epidermal growth factor 2 (HER2)-negative adenocarcinoma of the breast with measurable metastatic or locally advanced disease

The determination of triple negative breast cancer (TNBC) status should, whenever possible, utilize tissue from a metastatic or recurrent lesion and where more than one biopsy source is available, priority should be given to the most recent sample.

Patients who have not had HER2, ER, or PR testing, and thus, the HER2, ER, and PR status of the breast adenocarcinoma is unknown, are not eligible.

- Locally advanced disease must not be amenable to resection with curative intent
- Measurable disease, according to Response Evaluation Criteria in Solid Tumors (RECIST), v1.1
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to first dose of study drug treatment:

  ANC $\geq 1.5 \times 10^9$/L

  Platelet count $\geq 100 \times 10^9$/L

  Hemoglobin ≥ 9 g/dL

  Albumin ≥ 2.5 g/dL

  Bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN)

  AST, ALT, and alkaline phosphatase $\leq 3 \times$ ULN, with the following exceptions:

  Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN

  Patients with documented liver or bone metastases: alkaline phosphatase $\leq 5 \times$ ULN

  Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance (CrCl) ≥ 40 mL/min on the basis of measured CrCl from a 24-hour urine collection or Cockcroft-Gault* glomerular filtration rate estimation:

  * The Modification of Diet in Renal Disease (Levey et al. 2006) and the Chronic Kidney Disease Epidemiology Collaboration (Levey et al. 2009) formulas for estimation of glomerular filtration rate are also acceptable.

  (140-age) $\times$ (weight in kg) $\times$ (0.85 if female)

  72 $\times$ (serum creatinine in mg/dL)
- Ability and capacity to comply with the study and follow-up procedure
- For female patients (and female partners of male patients) who are not postmenopausal ($\geq$ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 6 months after the last dose of paclitaxel/nab-paclitaxel, at least 5 months after the last dose of atezolizumab, and 3 months after the last dose of cobimetinib. *Women must refrain from donating eggs during this same period.*
  - Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
  - Post-ovulation methods and withdrawal are not acceptable methods of contraception.
- Men must agree not to donate sperm or have intercourse with a female partner without using appropriate barrier contraception during the treatment period and for 6 months after the last dose of paclitaxel/nab-paclitaxel and 3 months after the last dose of cobimetinib. Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Abraxane® (paclitaxel protein-bound particles for injectable suspension) (albumin bound) or lower fertility with paclitaxel.

Exclusion Criteria

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

A. Disease-Specific Exclusion Criteria

- Known HER2-, ER-, or PR-positive breast cancer by local laboratory assessment (if more than one test result is available and not all results meet the eligibility criterion definition for TNBC, all results should be discussed with the Medical Monitor to establish eligibility of the patient)

  HER2 positivity is defined as one of the following: immunohistochemistry 3 positive or in situ hybridization (ISH) positive using either a single-probe ISH (average HER2 gene copy number ≥ 6 signals/cell) or dual-probe ISH (ratio of HER2 to CEP17 ≥ 2.0; if HER2/CEP17 < 2.0 then average HER2 copy number ≥ 6.0 signals/cell).

  ER and PR positivity is defined positive for ER or PR if a finding of ≥ 1% of tumor cell nuclei are immunoreactive.
- Any prior chemotherapy, hormonal, or targeted therapy, for inoperable locally advanced or mTNBC

  Prior chemotherapy (including taxanes) and/or radiation in the neoadjuvant or adjuvant setting is allowable if treatment occurred ≥ 6 months prior to initiation of study treatment (Cycle, 1 Day1)
- Any systemic anticancer therapy within 3 weeks prior to Cycle 1, Day 1
- Any radiation treatment to metastatic site within 28 days of Cycle 1, Day 1
- Major surgical procedure, open biopsy, or significant traumatic injury within 30 days prior to Cycle 1, Day 1 or anticipation of need for major surgical procedure during the course of the study
- Prior therapy with bevacizumab, sorafenib, sunitinib, or other putative vascular endothelial growth factor pathway–targeted therapy within 2 years of start of study treatment
- Prior exposure to experimental treatment targeting Raf, MEK, or the MAPK pathway
- Previous therapy with Akt, PI3K, and/or mTOR inhibitors
- Prior therapy with trastuzumab
- Grade ≥ 2 peripheral neuropathy
- Brain metastases (symptomatic or nonsymptomatic) that have not been treated previously, are progressive, or require any type of therapy (e.g., radiation, surgery, or steroids) to control symptoms from brain metastases within 60 days prior to first study treatment dose

B. Cobimetinib-Specific Exclusion Criteria

- History of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment/central serous chorioretinopathy, retinal vein occlusion (RVO), or neovascular macular degeneration
- Patients will be excluded if they currently have the following risk factors for RVO:

  Uncontrolled glaucoma with intra-ocular pressures ≥ 21 mmHg

  Serum cholesterol ≥ Grade 2

  Hypertriglyceridemia ≥ Grade 2

  Hyperglycemia (fasting) ≥ Grade 2
- Cobimetinib is metabolized by the hepatic cytochrome CYP3A4 enzyme. The drugs listed below should be avoided. If use of one of these drugs is necessary, the risks and benefits and potential alternatives should be discussed with the Medical Monitor prior to its concomitant use with cobimetinib.

  Strong CYP3A4/5 inhibitors such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, and voriconazole

Strong CYP3A4/5 inducers such as, but not limited to, rifampin, carbamazepine, rifapentine, phenytoin, and phenobarbital

- The following foods/supplements are prohibited at least 7 days prior to initiation of and during study treatment:

  St. John's wort or hyperforin (potent CYP3A4 enzyme inducer)

  Grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor)

C. Atezolizumab-Specific Exclusion Criteria (Cohorts II and III Only)

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

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

  Patients with controlled Type 1 diabetes mellitus on a stable insulin dosing regimen may be eligible for this study.

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

  Rash must cover less than 10% of body surface area (BSA).

  Disease is well controlled at baseline and only requiring low potency topical steroids

  No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive test for human immunodeficiency virus (HIV)
- Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test or positive HBV DNA at screening) or hepatitis C

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen antibody test) are eligible.

  Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Active tuberculosis
- Receipt of a live, attenuated vaccine within 4 weeks prior to randomization or anticipation that such a live, attenuated vaccine will be required during the study
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–programmed death-1, or anti–programmed death ligand-1 therapeutic antibodies

- Treatment with systemic immunostimulatory agents (including but not limited to interferons or IL-2) within 4 weeks or five half-lives of the drug (whichever is shorter) prior to randomization
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor agents) within 2 weeks prior to randomization, or anticipated requirement for systemic immunosuppressive medications during the trial

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study

  The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

D. Cardiac Exclusion Criteria

- History of clinically significant cardiac dysfunction, including the following:
  - Significant cardiovascular disease, such as symptomatic congestive heart failure, defined as New York Heart Association Class II or higher
  - Unstable angina, or new-onset angina within 3 months prior to initiation of study treatment
  - Myocardial infarction within 3 months prior to initiation of study treatment
  - Unstable arrhythmia
  - History of congenital long QT syndrome
- Corrected QT interval at screening > 480 ms (average of triplicate screening measurements)
- Left ventricular ejection fraction below the institutional lower limit of normal or below 50%, whichever is lower

E. General Exclusion Criteria

- Pregnancy (positive serum pregnancy test) or lactation
- Uncontrolled serious medical or psychiatric illness
- Active infection requiring intravenous (IV) antibiotics on Cycle 1, Day 1
- Patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor® EL (polyoxyethylated castor oil)

Length of Study

The enrollment period for Cohort I of the study is estimated to be approximately 18 months and the enrollment period for Cohort II and II is estimated to be approximately 11 months, including the halt for internal safety review. The progression-free survival (PFS) final analysis for Cohort I will be done when approximately 60 progression events are observed in the intent-to-treat population, which will happen approximately 20 months after first patient first visit (in the safety run-in stage). The overall response rate (ORR) analysis for Cohorts II and III will be done when the last patient in the expansion stage has completed their first on study tumor assessment. All patients will be followed until the final analysis for overall survival.

End of Study

The study will end when all patients enrolled have been followed until death, withdrawal of consent, lost to follow-up, or the Sponsor decides to end the study, whichever occurs first.

Patients may continue on study treatment until the development of progressive disease or the loss of clinical benefit, unacceptable toxicity, and/or consent withdrawal. Patients who discontinue study treatment for any reason will be followed for disease progression and followed for survival until death, withdrawal of consent, or they are lost to follow-up.

Investigational Medicinal Products

Cobimetinib, placebo, atezolizumab, and nab-paclitaxel are investigational medicinal products (IMPs) in this study and will be provided by the Sponsor. Paclitaxel may also be considered an IMP in this study, depending on local legislation, and may be provided by the Sponsor or sourced locally. Paclitaxel and nab-paclitaxel will be locally sourced in the United States. Dose administration should be performed according to the drugs' national prescribing guidelines. Refer to the appropriate Package Insert as needed for details.

Cobimetinib (all cohorts) will each be orally administered at a dose of 60 mg/day, once a day, on Day 3 through Day 23 of each 28 day treatment cycle. Cobimetinib should be taken at approximately the same time each morning no later than 12 hours after the scheduled time.

Cobimetinib can be taken with or without a meal. Cobimetinib or placebo tablets should never be chewed, cut, or crushed.

Placebo (patients in the Cohort I expansion only) should be taken as cobimetinib.

Patients in Cohorts II and III will receive atezolizumab 840 mg administered by IV infusion q2w (every 14 [±3] days). On days of scheduled infusions of atezolizumab and paclitaxel or nab-paclitaxel, all study treatment is to be administered after infusion of atezolizumab.

For more detailed information on drug preparation, storage, and administration, refer to the atezolizumab Investigator's Brochure and Pharmacy Manual.

Paclitaxel will be administered at a dose of 80 mg/m^2 by IV infusion on Day 1, Day 8, and Day 15 of each 28 day cycle for patients in Cohorts I and II. Calculation of BSA for the purposes of dosing of paclitaxel should be made according to the prescribing information.

Nab-paclitaxel will be administered according to the local prescribing information. The starting dose level of nab-paclitaxel in this study will be 100 mg/m^2 administered intravenously over 30 minutes on Days 1, 8, and 15 of each 28-day cycle (3-weeks-on/1-week-off schedule).

Non-Investigational Medicinal Products

Paclitaxel

Because of the known potential for allergic reactions to paclitaxel, patients in Cohorts I and II will be premedicated with dexamethasone, diphenhydramine, and an H2 blocker 30 to 60 minutes prior to the paclitaxel administration and according to the paclitaxel Package Insert and institutional guidelines.

Nab-Paclitaxel

Granulocyte-colony stimulating factor (G-CSF) treatment is permitted for patients receiving nab-paclitaxel. The primary prophylaxis should be administered per the American Society of Clinical Oncology, European Organization for Research and Treatment of Cancer, and European Society for Molecular Oncology guidelines; namely, in patients who are ≥60 years of age and/or with comorbidities.

Evidence supporting the use of long-acting (pegylated) forms of G-CSF in patients receiving weekly chemotherapy is limited, and investigators should consider giving preference to conventional formulations of G-CSF.

Antiemetics, anti-allergic measures, and other treatments for concomitant nab-paclitaxel toxicities may be used at the discretion of the investigator, taking into account precautions from the Package Insert.

Refer to the Package Insert for nab-paclitaxel for all boxed warnings and contraindications.

Permitted Therapy

Patients who use oral contraceptives, hormone-replacement therapy, or maintenance therapy should continue their use as outlined in the eligibility criteria.

Pain medications may be administered according to local standard practice guidelines while the patient is in the study.

Antiemetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drugs. At the discretion of the investigator, prophylactic antihistamine, antiemetic, and anti-diarrheal medication(s) may be used before subsequent doses of study drugs per standard clinical practice.

Hematopoietic growth factors should not be administered prophylactically before initial treatment with study drugs. Hematopoietic growth factors may be administered according to local guidelines if indicated during the course of the study.

Inactive influenza vaccinations are permitted.

Statistical Methods

Primary Analysis for Cohort I

The primary efficacy endpoint for Cohort I is PFS, defined as the time from randomization to the first occurrence of disease progression as determined by investigator per RECIST v1.1, or death from any cause, whichever occurs first.

Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm and Kaplan-Meier curves will be produced. Stratified log-rank tests will be used to compare cobimetinib plus paclitaxel with placebo plus paclitaxel. The hazard ratio (HR) estimates and their 95% CI will be determined by the stratified Cox proportional hazards model. The stratification factors include prior neoadjuvant/adjuvant taxane therapy (yes or no) and disease-free interval from last dose of chemotherapy ($\leq$ 12 months vs. $>$ 12 months/no prior chemotherapy) and will be determined by the Electronic Case Report Form (eCRF) data, unless the eCRF data are missing, in which case data collected by the Interactive Response System at the time of randomization will be used. Data for randomized patients without disease progression or death will be censored at the last tumor assessment date. If no tumor assessment was performed after randomization, data will be censored at the randomization date. Results from an unstratified log-rank test will also be prepared.

Primary Analysis for Cohorts II and III

The primary efficacy endpoint for Cohorts II and III is ORR, defined as the rate of a partial response or complete response occurring after randomization and confirmed $\geq$ 28 days later as determined by the investigator using RECIST v1.1. An estimate of the ORR and its 95% CIs will be calculated for each treatment arm (Clopper and Pearson 1934). CIs for the difference in ORR will be calculated as well.

Determination of Sample Size

This study is designed to evaluate the safety and to provide preliminary evidence of activity for:

- Cohort I: cobimetinib plus paclitaxel versus placebo plus paclitaxel
- Cohort II: cobimetinib plus atezolizumab plus paclitaxel
- Cohort III: cobimetinib plus atezolizumab plus nab-paclitaxel

Cohort I Safety Run-In Stage

The number of patients enrolled during the safety run-in stage in Cohort I (n = 12) allows for a reasonable likelihood of observing a given adverse event in at least 1 patient even when the incidence of the specific adverse event is low.

Cohort I Expansion Stage

The study will randomize approximately 90 patients in the Cohort I randomized stage. For the evaluation of the primary efficacy endpoint of PFS in this cohort, patients will be followed until approximately 60 investigator-assessed PFS events have occurred among the 90 randomized patients.

One of the purposes of this study is to estimate the effect of the addition of cobimetinib on duration of PFS relative to the current standard of care in patients with metastatic or locally advanced, triple-negative adenocarcinoma of the breast who have not received prior systemic therapy for MBC. Point and interval estimates of the true underlying HR will be obtained. It is assumed that the median duration of PFS in the control arm is 6 months.

This study is able to detect only a large benefit of combination therapy with cobimetinib and paclitaxel, and will not have adequate power to detect minimum clinically meaningful differences between treatment arms at a statistically significant α (type 1) error level of 5%. For example, with 60 events in the 2 comparator arms, there is an 80% power to detect a HR of 0.48 at a 2-sided significance level of 0.05. However, there is only a 51% power to detect a HR of 0.60. Thus, a statistically negative outcome on the primary PFS does not necessarily rule out a clinically meaningful outcome.

Cohorts II and III Safety Run-In Stage

The number of patients enrolled into Cohort II and III during the safety run-in stage (n = 15 per cohort) allows for a reasonable likelihood of observing a given adverse event in at least 1 patient even when the incidence of the specific adverse event is low.

Cohorts II and III Expansion Stage

The study is also designed to estimate the effect of cobimetinib plus atezolizumab plus paclitaxel and cobimetinib plus atezolizumab plus nab-paclitaxel (indirectly relative to cobimetinib plus paclitaxel in mTNBC).

To evaluate the primary endpoint of overall response rate, the analyses will be performed after the last recruited patient in each cohort (combining both safety run-in and expansion stages) has completed two cycles of study treatment and a post-baseline tumor assessment.

Number of Responders	ORR (%)	95% CI
6	20	7.7–38.6
9	30	14.7–49.4
12	40	22.7–59.4
15	50	31.3–68.7
18	60	40.6–77.3
21	70	50.6–85.3
24	80	61.4–92.3
27	90	73.5–97.9

ORR = overall response rate.

No formal statistical hypothesis testing is planned in this Phase II study. Instead, the analysis here is for hypothesis generation and the emphasis is on estimation.

Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may conduct up to two interim analyses of efficacy. The decision to conduct such an interim analysis and its timing will be documented in the Sponsor's study master file prior to the conduct of the interim analysis. The clinical study report will also document that such an interim analysis occurred. The interim analysis, should it occur, will be performed and interpreted by members of the Sponsor study team and management who would then be unblinded at the treatment-group level.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
14/14	14 days on/14 days off
21/7	21 days on/7 days off
[redacted]	[redacted]
$AUC_{0-\infty}$	area under curve baseline-infinity
AUC_{0-T}	total exposure
BSA	body surface area
C_{max}	maximum plasma concentrations
C_{min}	minimum plasma concentrations
CRC	colorectal cancer
CrCl	creatinine clearance
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DDI	drug-drug interaction
DOR	duration of response
EC	Ethics Committee
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
[redacted]	[redacted]
ER	estrogen receptor
ERK	extracellular signal responsive kinase
ESMO	European Society for Molecular Oncology
EU	European Union

[redacted]	[redacted]
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
G-CSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
HER2	human epidermal growth factor 2
HIPAA	Health Insurance Portability and Accountability Act
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	hazard ratio
IB	investigator brochure
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
[redacted]	[redacted]
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ISH	in situ hybridization
ITT	intent-to-treat
IxRS	interactive voice or web response system
IV	Intravenous
LVEF	left ventricular ejection fraction
MBC	metastatic breast cancer
MEK	MAP kinase/ERK kinase
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
mTNBC	metastatic triple-negative breast cancer
MUGA	multiple-gated acquisition

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next-generation sequencing
NSCLC	non–small cell lung cancer
OCT	optical coherence tomography
OS	overall survival
ORR	overall response rate
ORR_uc	unconfirmed overall response rate
PARP	poly ADP-ribose polymerase
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed T-cell death ligand-1
PFS	progression-free survival
PK	Pharmacokinetic
PPI	proton pump inhibitor
PR	partial response
PR	progesterone receptor
PRO	patient-reported outcome
PTEN	phosphatase and tensin homolog
PUVA	psoralen plus ultraviolet A radiation
q2w	every 2 weeks
q3w	every 3 weeks
QD	once a day
[redacted]	[redacted]
[redacted]	[redacted]
QTcF	QT interval corrected using Fridericia's formula
RVO	retinal vein occlusion
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
TNF	tumor necrosis factor

TNBC	triple-negative breast cancer
ULN	upper limit of normal

1. BACKGROUND

1.1 METASTATIC BREAST CANCER

Globally, breast cancer is the most common invasive malignancy and the most common cause of cancer-related mortality in women (Siegel et al. 2012) with 5-year survival following metastatic diagnosis of approximately 15%. According to the Surveillance, Epidemiology, and End Results (SEER) database, over 230,000 women were diagnosed with breast cancer and approximately 40,000 women died of breast cancer in 2013 in the United States (U.S.; SEER 2013). The lifetime probability of developing invasive breast cancer in the United States and Europe is one in eight (Sasieni et al. 2011).

Although metastatic breast cancer (MBC) is generally considered incurable, there are a number of therapies available that can extend life and palliate symptoms to preserve quality of life for these patients. The treatment algorithm for patients with MBC is based on several factors that include clinical considerations such as prior treatment, response to therapy, number and specific sites of metastatic disease, and histologic characteristics, such as hormone receptor status and human epidermal growth factor receptor 2 (HER2) amplification. Numerous cytotoxic chemotherapy agents have shown activity in MBC, including anthracyclines, taxanes, gemcitabine, capecitabine, vinorelbine, eribulin, and ixabepilone. The response rates and progression-free intervals seen with these agents vary depending on the extent and type of prior therapy and the extent of metastatic disease.

Taxanes and anthracyclines are among the most active chemotherapy agents for the treatment of HER2-negative MBC in terms of response rates or survival and are commonly used in the neoadjuvant, adjuvant, and metastatic settings. A meta-analysis of three randomized trials in HER2-negative MBC comparing single-agent taxane (paclitaxel or docetaxel) with single-agent anthracycline showed similar overall survival (OS) (19.5 months taxane vs. 18.6 months anthracycline) and response rates (33% taxane vs. 38% anthracycline) (Piccart-Gebhart et al. 2008). Another meta-analysis of bevacizumab versus chemotherapy in patients receiving first-line treatment for metastatic triple-negative breast cancer (mTNBC) found the ORR to be 23% with median progression-free survival (PFS) and OS of 5.4 and 17.5 months, respectively (Miles et al. 2013). Because anthracyclines are often used in neoadjuvant/adjuvant treatment and are associated with a high risk of cardiotoxicity (particularly with cumulative exposure), taxanes are more commonly used in patients with locally advanced or metastatic disease, particularly in the front-line setting.

1.1.1 Molecular Classification of Breast Cancer, Including Triple-Negative Breast Cancer

Breast cancer is a genetically heterogeneous and biologically diverse disease that can be clinically subdivided into subgroups that guide therapeutic intervention, which is based on the expression of estrogen receptor (ER), progesterone receptor (PR), and

HER2. The ER-positive subgroup is the most common, representing almost three fourths of all breast cancers (Anderson et al. 2002). HER2-positive cancers represent approximately 15% of all breast cancers (Choritz et al. 2011). Cancers that lack expression of all three of these critical markers are classified as triple-negative breast cancer (TNBC) and represent 10%–17% of all breast cancers (Dent et al. 2007; Rakha et al. 2007).

While the three-marker (ER/PR/HER2) classification system has been a useful clinical tool for determining appropriate treatment for breast cancer patients, there is enough variability of response to treatment to suggest that this system does not capture the true heterogeneity among breast cancers. These long recognized clinical and phenotypic differences in breast cancers have been shown to correlate with differences at the gene expression level (van't Veer et al. 2002). Molecular profiling of breast cancers using array technology has shown that the biological and clinical heterogeneity of breast cancer is explained by differences in genetic composition (Perou et al. 2000). Five distinct breast cancer subtypes that have been defined by hierarchical cluster analyses of array gene expression data include the following: two ER–positive groups referred to as luminal subtypes A and B (because of features shared with luminal epithelial cells arising from the inner layer of the duct lining), a group with HER2/neu overexpression, a normal breast gene expression group, and a group with the basal-like subtype of cancers (Sorlie et al. 2001). Understanding the importance of the estrogen pathway (in luminal subtypes A and B) and the HER2 pathway in HER2-expressing tumors in the pathogenesis of breast cancer has led to effective targeted therapies for these respective subtypes. The molecular pathogenesis of the basal-like subtype is less understood.

The basal-like subtype was so named because the expression pattern of this subtype mimics that of basal epithelial cells of other parts of the body and normal breast myo-epithelial cells. Although the gold standard for classifying a tumor as basal-like is gene expression array, it is not feasible at most centers to perform gene expression and cluster analysis on formalin-fixed tissue. The patterns of protein expression of a few biomarkers such as ER, PR, HER2, epidermal growth factor receptor (EGFR), and cytokeratins can be used to stratify breast cancers into distinct subtypes. The basal-like subtype is characterized by low expression of hormone receptor–related genes and HER2-related genes and the presence of cytokeratins and EGFR expression. Approximately 80% of basal–like breast cancers lack staining for hormone receptors and HER2 and are thus referred to as "triple-negative" breast cancer. Accordingly, all basal-like breast cancer trials presently registered with the National Cancer Institute (NCI) typically use the biomarker triplet of ER, PR, and HER2 to identify eligible patients.

Overall, patients with TNBC exhibit a poor clinical outcome, with neoadjuvant TNBC patients showing rapid progression and significantly shorter median survival than non-TNBC breast cancer patients (Harris et al. 2006; Dent et al. 2007;

Liedtke et al. 2008). Unlike the ER-positive and HER2-positive subgroups there are no targeted therapies available for TNBC patients and treatment is limited to chemotherapy, typically anthracyclines and taxanes, although there is no established standard. The lack of actionable targets and the rapid development of resistance to chemotherapy highlight the need for new therapies for this aggressive cancer.

1.2 BACKGROUND ON COBIMETINIB

Cobimetinib (Cotellic®) is a reversible, potent, and highly selective inhibitor of MEK1 and MEK2, a central kinase in the RAS/RAF/MEK/ERK (MAPK) pathway that activates extracellular signal responsive kinase 1/2 (ERK1/2). Cobimetinib is approved in the United States, European Union, Switzerland, and in multiple other countries across the world for use with vemurafenib for the treatment of advanced BRAF-mutated melanoma.

The MAPK pathway plays a central role in normal cellular processes, including the response to mitogens, oncogenes, stress, and inflammation, as well as the regulation of proliferation, differentiation, and survival in particular cell types (Cargnello and Roux 2011). Abnormal regulation of this signaling pathway can lead to tumorigenesis by contributing to uncontrolled proliferation, invasion, metastasis, and angiogenesis, as well as diminished apoptosis (Downward 2003).

First–generation MEK inhibitors such as PD0325901 (PD901; Pfizer) exhibited a significant occurrence of adverse events in the CNS that may be mechanistically related to the MAPK signaling pathway in the brain (Menon et al. 2005). To avoid these serious toxicities, cobimetinib was specifically selected for its inability to cross the blood-brain barrier.

1.2.1 Summary of Nonclinical Studies with Cobimetinib

Cobimetinib inhibits proliferation of a variety of human tumor-cell lines by inhibiting MEK1 and MEK2. In addition, cobimetinib inhibits ERK phosphorylation in xenograft tumor models (i.e., breast, lung, colon, and melanoma) and stimulates apoptosis. Cobimetinib accumulates in tumor xenografts and remains at high concentrations in the tumor after plasma concentrations have declined. The activity of cobimetinib to inhibit ERK1 phosphorylation is more closely correlated with its concentrations in tumor tissue than in plasma; in general, there is a good correlation between reduced ERK1 phosphorylation and efficacy in tumor xenograft models. Tumor regression has been observed in several human tumor xenograft models. This tumor regression was dose dependent with up to 100% regression at the highest doses tested. The models studied included colorectal cancer (CRC), malignant melanoma, breast carcinoma (including TNBC), and anaplastic lung carcinoma.

1.2.2 Nonclinical Metabolism and Pharmacokinetics of Cobimetinib

A characterization of the pharmacologic and pharmacokinetic (PK) properties of cobimetinib was performed in a series of nonclinical studies that are summarized in the cobimetinib Investigator's Brochure (IB).

1.2.3 Nonclinical Safety of Cobimetinib

The nonclinical toxicity of cobimetinib was characterized in single-dose and repeat-dose general toxicity studies in rats and dogs, in vitro genotoxicity studies, rat embryolethality/teratogenicity studies, and in cardiovascular, neurobehavioral, and respiratory safety pharmacology studies. These studies are summarized in the cobimetinib IB.

1.2.4 Clinical Pharmacology of Cobimetinib

Cobimetinib pharmacokinetics have been characterized in cancer patients following oral administration after single and multiple dosing in the Phase Ia dose-escalation study (MEK4592g). Additionally, clinical pharmacology studies have been conducted in healthy subjects to determine absolute bioavailability, effect of food, and proton-pump inhibitor (PPI) on cobimetinib pharmacokinetics. The overall PK findings were as follows:

- Cobimetinib has a moderate rate of absorption (median time to maximum concentration [t_{max}] of 1–3 hours).
- Cobimetinib has linear pharmacokinetics in the dose range of 0.05 mg/kg (approximately 3.5 mg/kg for 70 kg adult) to 80 mg.
- Mean terminal half-life ($t_{1/2}$) of cobimetinib was 48.8 hours (range: 23.1 to 80 hours).
- The absolute bioavailability of cobimetinib was 45.9% (90% CI: 39.74%, 53.06%) as determined in Study MEK4952g in healthy subjects.
- Cobimetinib pharmacokinetics are not altered when administered in the fed state compared with administration in the fasted state in healthy subjects (Study MEK4593g). Since food does not alter cobimetinib pharmacokinetics, cobimetinib can be administered with or without food.
- The PPI rabeprazole appears to have a minimal effect on cobimetinib pharmacokinetics, whether administered in the presence or absence of a high-fat meal compared with cobimetinib administration alone in the fasted state (Study MEK4594g). Thus, increase in gastric pH does not affect cobimetinib pharmacokinetics, indicating it is not sensitive to alterations in gastric pH.
- Cobimetinib does not alter the pharmacokinetics of either midazolam or dextromethorphan in patients with cancer administered at 60 mg on a 21-days on/7-days off (21/7) schedule (Study MEK4592g). Therefore cobimetinib can be co-administered with CYP3A and CYP2D6 substrates in patients.
- Preliminary results from a drug interaction study in healthy subjects showed an approximate 7-fold increase in cobimetinib area under curve baseline-infinity ($AUC_{0-\infty}$) in the presence of itraconazole, a potent CYP3A inhibitor (Study GP28620). It is likely that exposures of cobimetinib will be significantly lowered in presence of

CYP3A inducers, and hence, concomitant administration of potent CYP3A inducers and inhibitors with cobimetinib is not permitted.

- A human mass balance study was conducted in healthy subjects [redacted], and showed that cobimetinib was extensively metabolized and eliminated in feces. The fraction absorbed was approximately 88% indicating that there is significant first pass metabolism. Cobimetinib was the predominant moiety in plasma as no metabolites were circulating at greater than 10% of total radioactivity, and therefore no additional analytes need to be monitored in clinical studies.

Detailed information on the clinical pharmacokinetics of cobimetinib is described in the cobimetinib IB.

1.2.5 Summary of Clinical Studies with Cobimetinib

1.2.5.1 Summary of Clinical Studies with Cobimetinib Monotherapy

As of October 2015, cobimetinib had been administered alone or with other agents to more than 1000 adult cancer patients and approximately 120 healthy volunteers in 18 clinical trials; the vast majority of patients had been treated with cobimetinib plus other agents, such as vemurafenib. These include one trial of cobimetinib as a single agent (Study MEK4592g), seven clinical pharmacology studies, and nine trials of cobimetinib with other agents.

Study MEK4592g was a Phase I, non-randomized, open-label, safety, and PK dose-escalation study. The study was conducted in patients with metastatic or unresectable solid tumors for which standard curative or palliative measures did not exist or were no longer effective. A total of 115 patients were treated, and the study has since been completed.

The study consisted of five treatment stages:

- Stage I: Dose-escalation cohorts; patients were treated on a 21/7 schedule to determine the maximum-tolerated dose (MTD).
- Stage IA: Dose-escalation cohorts; patients were treated on a 14-days-on, 14-days-off (14/14) schedule to determine the MTD on an alternate dosing regimen.
- Stage II: Expansion cohort with the MTD determined in Stage I (60 mg once a day [QD] 21/7) in patients who harbored a BRAF, NRAS, or KRAS mutation.
- Stage IIA: Expansion cohort with the MTD determined in Stage IA (100 mg QD 14/14) in patients who harbored a BRAF, NRAS, or KRAS mutation.
- Stage III: A dedicated drug-drug interaction (DDI) study at the MTD determined in Stage I (60 mg QD 21/7) in approximately 20 patients with solid tumors.

Adverse Events

All patients in Study MEK4592g experienced an adverse event. The most frequent adverse events were diarrhea (67.0%), fatigue (50.4%), rash (49.6%), nausea and vomiting (33.9% each), and edema peripheral (28.7%). Other events that occurred

in ≥10% of patients included anemia, abdominal pain, constipation, hypokalemia, decreased appetite, headache, dizziness, back pain, increased AST, dermatitis acneiform, pruritus, and dry skin. Among the patients who received cobimetinib 60 mg 21/7, the most frequent treatment-emergent adverse events were diarrhea (64.4%), rash (53.3%), fatigue (48.9%), nausea and edema peripheral (31.1% each), and vomiting (28.9%).

Grade≥3 Adverse Events

Among all cobimetinib-treated patients, 5 patients (4.3%) experienced a Grade 4 adverse event, and 53 patients (46.1%) experienced a Grade 3 adverse event. The most frequent Grade 3 and Grade 4 adverse events were hyponatremia (9.6%), fatigue (8.7%), anemia (7.8%), and diarrhea and hypokalemia (6.1% each).

Serious Adverse Events

A total of 49 patients (42.6%) experienced a serious adverse event. The most common types of serious adverse events were gastrointestinal disorders (n=17), but there were no trends in specific preferred terms. The gastrointestinal serious adverse events, such as intestinal obstructions and gastrointestinal hemorrhages, occurred in patients with gastrointestinal malignancies. Serious adverse events reported for more than 2 patients among all patients in the study were anemia, bile duct obstruction, dehydration, syncope, and respiratory arrest (3 patients each [2.6%]).

Efficacy

Best overall response was assessed for 74 of 97 patients in Stages I, IA, II, and IIA. Overall 6 patients (all of whom had melanoma; 6.2%) had a confirmed partial response (PR), 28 patients (28.9%) had stable disease (SD), and 40 patients (41.2%) had progressive disease. Out of the 14 CRC patients, all patients experienced progressive disease (PD). In Stage III of Study MEK4592g, 18 patients were accrued, and best overall response was assessed for 14 of 18 patients. Four patients (22.2%) had SD as their best overall response, and 2 patients (11.1%) had unconfirmed tumor responses.

For further clinical information on cobimetinib as monotherapy or with other anti-cancer agents, please see the cobimetinib IB.

1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (Tecentriq®, MPDL3280A) is a humanized IgG1 monoclonal antibody against programmed death ligand-1 (PD-L1). Atezolizumab was engineered with a modified Fc domain to eliminate the antibody-dependent cellular cytotoxicity at clinically relevant doses, which prevents the depletion of activated T cells (Herbst et al. 2014).

Atezolizumab targets human PD-L1, an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors: programmed death-1 (PD-1) and B7.1. Many human tumors have been found to overexpress PD-L1 (Blank et al. 2005, 2007; Thompson et al. 2006). PD-1 is an

inhibitory receptor expressed on T cells following chronic stimulation such as in chronic infection or cancer (Blank et al. 2005, 2007; Keir et al. 2008). Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen-presenting cells can mediate downregulation of immune responses, including inhibition of T-cell activation and cytokine production (Butte et al. 2007; Yang et al. 2011).

1.3.1 Nonclinical Safety of Atezolizumab

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

Overall, the nonclinical pharmacokinetics 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 down modulating the PD-L1/PD-1 pathway and supported entry into clinical trials in patients.

Refer to the atezolizumab IB for details on the nonclinical studies.

1.3.2 Clinical Experience with Atezolizumab

1.3.2.1 Ongoing Clinical Studies

In the United States, atezolizumab is approved for the treatment of locally advanced or metastatic urothelial bladder cancer who have progressed during or following platinum-containing chemotherapy and for metastatic non–small cell lung cancer (mNSCLC) who have progressed during or following platinum-containing chemotherapy and if harboring an EGFR or ALK aberration have progressed on U.S. Food and Drug Administration (FDA)-approved therapy for these aberrations. Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies (see the atezolizumab IB for study descriptions).

1.3.2.2 Clinical Safety of Atezolizumab as a Single Agent

The safety data for atezolizumab have been derived mainly from the treatment of patients in Study [redacted]. As of [redacted], there were [redacted] safety-evaluable patients from the Phase Ia study. The median duration of treatment was [redacted], and the median number of atezolizumab cycles administered was [redacted]. To date, no MTD, DLTs, or clear dose-related trends in the incidence of adverse events have been determined.

Adverse Events

Of the [redacted] treated patients in Study [redacted] patients experienced an adverse event regardless of attribution to atezolizumab. Treatment–related adverse events (per investigator's assessment of causality) were reported in [redacted] patients [redacted]. Approximately [redacted] patients experienced an adverse event of Grade 3–4 severity, based on the NCI Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

The most frequently observed adverse events [redacted] included fatigue, decreased appetite, nausea, pyrexia, constipation, cough, dyspnea, diarrhea, headache, back pain, vomiting, anemia, arthralgia, rash, insomnia, asthenia, abdominal pain, chills, pruritus, generalized pain, and peripheral edema.

Most of the Grade 3–4 adverse events occurred in [redacted] patients. Those that were reported in [redacted] patients included dyspnea [redacted]; anemia [redacted]; hyponatremia [redacted]; fatigue [redacted]; asthenia [redacted]; dehydration [redacted]; hyperglycemia, AST increased, and abdominal pain [redacted] each; ALT increased [redacted]; and urinary tract infection [redacted]. Related Grade 3–4 events were reported in [redacted] of patients, with fatigue and asthenia [redacted], AST increased and dyspnea [redacted], and hyponatremia [redacted] as the most frequently occurring [redacted]

Overall, atezolizumab as a single agent was well tolerated, with low rates of treatment related Grade 3–4 events, Grade 5 events, treatment-related serious adverse events, and adverse events leading to treatment withdrawals.

Refer to the atezolizumab IB for additional details regarding clinical safety.

Immune–Mediated Adverse Events

Immune related adverse events are consistent with the role of the PD L1/PD 1 pathway in regulating peripheral tolerance. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune–mediated adverse events are closely monitored during the atezolizumab clinical program. Immune-related adverse events associated with atezolizumab include dermatologic, hepatic, endocrine, gastrointestinal, respiratory, and neurological events (see Section 5.2.3 for reportable adverse events of special interest).

Refer to the atezolizumab IB for additional details regarding immune-related adverse events observed in patients treated with atezolizumab.

1.3.2.3 Clinical Safety of Atezolizumab in Combination with Chemotherapy

Study [redacted] is a Phase Ib trial of the safety and pharmacology of atezolizumab administered with bevacizumab and/or chemotherapy in patients with advanced solid tumors.

This multi-arm study is evaluating several chemotherapy regimens.

As of [redacted], preliminary safety data were available from [redacted] patients in Study [redacted]. Of these patients, [redacted] patients received cytotoxic chemotherapy in combination with atezolizumab, and [redacted] of patients reported 1 or more adverse effects. The most frequently reported adverse effects [redacted], regardless of attribution to study treatment, included fatigue, nausea, diarrhea, neutropenia, peripheral neuropathy, constipation, vomiting, cough, anemia, arthralgia, headache, alopecia, pyrexia, and decreased appetite. The most frequently reported adverse effects were mainly assessed as Grade 1 or 2 in maximum severity (excluding neutropenia).

[redacted] patients [redacted] discontinued a study treatment (i.e., chemotherapy or atezolizumab) due to an adverse effect, including [redacted] patients [redacted] who discontinued atezolizumab due to an adverse effect. The most commonly reported adverse effects leading to discontinuation of a study treatment were bone marrow suppression (neutropenia [redacted] and thrombocytopenia [redacted]), peripheral neuropathy [redacted], and fatigue [redacted].

Safety data from [redacted] patients with TNBC [redacted] in Study [redacted] indicates that the combination appears to be well tolerated and is consistent with the known risks of nab-paclitaxel and atezolizumab (Adams et al. 2016). [redacted] of patients [redacted] experienced adverse events leading to discontinuation of nab-paclitaxel and [redacted] discontinued atezolizumab after prolonged asymptomatic Grade 2 AST elevation. The most frequent adverse events attributed to atezolizumab [redacted] included fatigue, pyrexia, diarrhea, nausea, alopecia, headache, peripheral neuropathy and peripheral sensory neuropathy, and decreased neutrophil count.

The safety data to date suggest that atezolizumab can be safely combined with standard chemotherapy treatments. Several combinations have been evaluated and have been generally well-tolerated. The adverse events observed for atezolizumab in combination with chemotherapy are consistent with the known risks of each study treatment.

Refer to the atezolizumab IB for additional details regarding clinical safety.

1.3.3 Clinical Safety of Atezolizumab in Combination with Cobimetinib

Study [redacted] is a Phase Ib, open-label, multicenter study designed to assess the safety, tolerability, and pharmacokinetics of cobimetinib plus atezolizumab in patients with advanced solid tumors.

As of [redacted], a total of [redacted] patients were accrued and evaluable for safety. The most common adverse events reported were diarrhea [redacted], fatigue [redacted], nausea [redacted], rash [redacted], vomiting [redacted], decreased appetite [redacted],

constipation [redacted], pruritus [redacted], dermatitis acneiform [redacted], and blood CPK increased [redacted]. The most common Grade 3 or higher adverse events reported were anemia [redacted], diarrhea [redacted], fatigue [redacted], dyspnea [redacted], rash [redacted], and blood CPK increased [redacted].

[redacted] patients experienced Grade 5 (fatal) adverse events. These included disease progression in [redacted] patients and large intestine perforation, asthenia, dyspnea, pneumonia, sepsis, and road traffic accident [redacted]. The safety of cobimetinib plus atezolizumab appeared similar to the known single-agent safety profiles of each drug; no new safety signals were noted.

Refer to the atezolizumab IB for additional details regarding clinical safety.

1.3.4 Clinical Activity of Atezolizumab

1.3.4.1 Clinical Activity of Atezolizumab Monotherapy in Triple Negative Breast Cancer

As of [redacted], clinical activity analyses have been performed on [redacted] patients with PD-L1-selected (IC2/3) TNBC in Study [redacted] who received atezolizumab treatment [redacted].

Unconfirmed responses were recorded [redacted]. [redacted] patients experienced a complete response (CR) and [redacted] patients experienced a PR. As of [redacted] patients were still responding and [redacted] experienced disease progression. The median DOR has not been reached. The Kaplan-Meier estimated overall 24-week progression-free survival (PFS) rate was [redacted]

1.3.4.2 Clinical Activity of Atezolizumab plus Chemotherapy in Triple Negative Breast Cancer

Study [redacted] is a multi-arm Phase Ib study evaluating the safety and preliminary efficacy of a number of combinations of atezolizumab and chemotherapy with or without bevacizumab in patients with locally advanced or metastatic solid tumors. [redacted] of the study is testing the combination of atezolizumab and nab-paclitaxel in female patients with metatstatic TNBC. Patients receive [redacted] atezolizumab on Days [redacted] of every [redacted] cycle plus nab-paclitaxel [redacted] on Days [redacted] of every [redacted] cycle. Up to two prior cytotoxic regimens for metastatic disease are allowed.

On the basis of a clinical cutoff of [redacted], safety and preliminary efficacy data were available for [redacted] patients [redacted] Of the efficacy-evaluable patients [redacted] received the treatment combination as first-line therapy, and [redacted] had received ≥ 1 prior cytotoxic regimen(s) for metastatic disease. [redacted] had previously received taxanes. In the overall efficacy-evaluable population, [redacted] patients [redacted] achieved confirmed RECIST v1.1 responses. CRs were observed in patients with PD-L1IC1/2/3 tumors as well as in those with PD-L1IC0. [redacted] patients

[redacted] who received atezolizumab plus nab-paclitaxel as first-line therapy achieved investigator-assessed confirmed responses, comprising [redacted]

1.3.5 Clinical Pharmacokinetics and Immunogenicity

The pharmacokinetics of atezolizumab monotherapy have been characterized in patients at doses 0.01 mg/kg to 20 mg/kg q3w, including the approved dose of 1200 mg (equivalent to 15 mg/kg). Exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg. While a subset of anti-therapeutic antibodies (ATA)-positive patients receiving 0.3 mg/kg to 3 mg/kg atezolizumab q3w experienced a reduction of atezolizumab minimum serum concentration (C_{min}) to below the pharmacokinetic (PK) assay lower limit of quantification, patients receiving 10–20 mg/kg atezolizumab, including the approved 1200 mg dose, maintained geometric mean C_{min} that was in excess of both the limit of quantification and the target serum concentration of 6 μg/mL. A Phase I population PK analysis indicated that atezolizumab clearance was 0.20 L/day, volume of distribution at steady state was 6.91 L, and the half-life was 27 days in the typical patient. Steady state was obtained after 6–9 weeks (2–3 cycles) of repeated dosing.

The development of anti-therapeutic antibodies (ATAs) has been observed in patients in all dose cohorts and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses from 10 to 20 mg/kg. Patients dosed at the 10, 15, and 20 mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between detection of ATAs and adverse events or infusion reactions has been observed.

Refer to the atezolizumab IB for details regarding nonclinical and clinical pharmacology of atezolizumab.

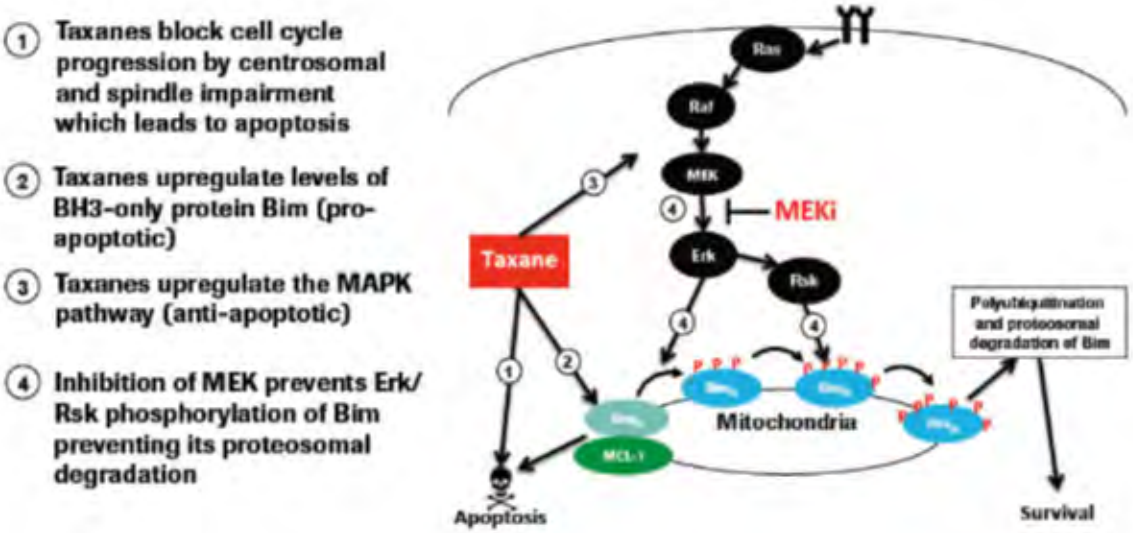
1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.4.1 Rationale of Cobimetinib and Taxane in Triple Negative Breast Cancer

Upregulation of the MAPK pathway is an effect of taxane treatment that has been described in multiple tumor types (McDaid and Horwitz 2001; Okano and Rustgi 2001; Haass et al. 2008). Activation of this pro-growth and survival pathway can act as a resistance mechanism in response to taxane treatment. In vitro and xenograft experiments in breast cancer models (MacKeigan et al. 2000; Balko et al. 2012) and other tumor types (Davies et al. 2007; Holt et al. 2012) have shown that the addition of a MEK inhibitor to taxane treatment can increase sensitivity of cancer cells to taxane therapy and overcome this resistance.

Recent experiments have shown that a potential mechanism for how inhibition of the MAPK pathway can overcome taxane-resistance is through modulation of pro-apoptotic BH3-only proteins such as Bim (Tan et al. 2005; Meng et al. 2010), BAD (Bonni et al. 1999), and PUMA (Wang et al. 2006; refer to Figure 1). In normal cells the levels of pro-apoptotic and anti-apoptotic proteins are tightly regulated. The MAPK pathway plays a critical role in this regulation by phosphorylating pro-apoptotic BH3-only proteins such as Bim, which results in Bim's degradation. Loss of these pro-apoptotic BH3-only proteins causes an overall shift in the apoptotic balance of the cell towards cell survival as BH3-only proteins can no longer sequester pro-survival proteins like MCL and BCL-2 and prevent them from inhibiting the apoptosis effector proteins BAX and BAK (Cragg et al. 2009). Taxane treatment increases the levels of these BH3-only pro-apoptotic proteins (Tan et al. 2005) but the upregulation of the MAPK pathway can effectively limit the cytotoxic effect of the chemotherapy. The addition of a MAPK pathway inhibitor like cobimetinib can prevent this resistance by preventing the phosphorylation of the pro-apoptotic BH3-only proteins, allowing a shift in the apoptotic balance towards cell death and maximizing the effectiveness of the taxane.

Figure 1 Proposed Mechanism of Action for Paclitaxel+Cobimetinib



Clinically, the addition of a MEK inhibitor to taxane therapy has been shown to significantly enhance the anti-tumor effect compared to taxane monotherapy. In a randomized Phase II study of selumetinib plus docetaxel versus docetaxel in patients with second-line KRAS mutation NSCLC (Janne et al. 2013), the combination of the MEK inhibitor selumetinib and docetaxel showed a response rate of 28% with a significant improvement in PFS (hazard ratio [HR] = 0.58) compared to docetaxel alone. This represents a major improvement over the activity seen with standard docetaxel monotherapy, which has shown a response rate of <10% in this disease setting (Fossella et al. 2000; Shepard et al. 2000). Additionally a similar result was observed in a recent Phase I study where the combination of the MEK inhibitor trametinib plus

docetaxel showed a response rate of 28% in a similar population of patients with NSCLC (Gandara et al. 2013). This significant enhancement of anti-tumor activity demonstrates that MEK inhibition can significantly improve the effectiveness of taxane-based chemotherapy and offers the potential for even greater gains in cancers that are more taxane-sensitive.

In contrast to the limited activity of taxanes seen in second-line NSCLC, response rates for paclitaxel monotherapy are substantially higher in patients with MBC at approximately 25%–42% in the first-line setting (Wilson et al. 1994; Seidman et al. 1995; Nabholtz et al. 1996; Seidman et al. 2008). Paclitaxel activity for the TNBC subgroup in the metastatic setting appears comparable to overall MBC; Study CALGB 9342 reported a 26% response rate in the TNBC subgroup (Harris et al. 2006). This taxane sensitivity extends to the neoadjuvant setting, where it has been observed that taxanes are more effective than anthracyclines in the triple-negative/basal-like subtype of patients when given as monotherapy (Martin et al. 2011). If MEK inhibition can prevent taxane resistance in NSCLC, the increased taxane sensitivity of MBC and TNBC could translate into even greater gains when paclitaxel is combined with a MEK inhibitor like cobimetinib.

Interestingly, when compared with other breast cancer subgroups, TNBC tumors show more upregulation of the MAPK pathway and increased sensitivity to MEK inhibition (Hoeflich et al. 2009; Jing et al. 2012). This suggests that patients with TNBC may have some intrinsic resistance to taxane treatment. If true, patients with TNBC should benefit more from a cobimetinib/paclitaxel combination and provides rationale for focusing initially on the triple-negative patients.

More interestingly, data generated in the open-label safety run-in cohort of this study is promising with unconfirmed response rates of 50%for the cobimetinib plus paclitaxel combination in first line mTNBC and no new or unexpected safety signals noted (Brufsky et al. 2016).

Further rationale for the addition of paclitaxel as a comparator and for the selected dose of paclitaxel is provided in Section 3.3.3.

1.4.2 Rationale for Cobimetinib, Taxane, and Atezolizumab Combination Treatment in Triple Negative Breast Cancer

There are robust nonclinical and clinical data for enhancement of anti-tumor activity of MEK inhibitors with PD1/PDL1 inhibitors and with taxanes. Treatment with cobimetinib, atezolizumab, and paclitaxel/nab-paclitaxel may offer the potential for substantial clinical benefit in patients with mTNBC.

Single-agent activity has been observed for cobimetinib in Phase I melanoma setting. Atezolizumab single-agent activity has been observed, both in vivo and Phase I trials in diseases such as NSCLC, melanoma, and CRC, which has provided support for development of these drugs with various targeted agents.

1.4.2.1 Atezolizumab and Taxane

Conventional chemotherapies may have immunogenic effects (Zitvogel et al. 2008) and clinical evidence suggests that T-cell and natural killer-cell functions are enhanced in breast cancer (Stage II/III) patients treated with taxanes compared with patients who did not receive taxanes (Carson et al. 2004). In addition, cytotoxic chemotherapy can be expected to expose the immune system to high levels of tumor antigens, and invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling resulting in deep and durable responses.

Furthermore, observations that high CD8-positive T-cell density in primary breast tumors is correlated with improved OS and that mTNBC tumors have fewer tumor-infiltrating lymphocytes than their matched primary tumors, suggest that the immune system is able to partially restrain human breast cancer but that immune suppression becomes more prevalent with increasing growth and metastasis (Cimino-Mathews et al. 2013; Adams et al. 2014; Loi 2014). The identification of immune-enriched subtypes of TNBC underscores the potential to harness preexisting host anti-tumor immunity in this disease (Lehmann et al. 2011). In this setting, invigorating T-cell activity with atezolizumab may be an effective treatment strategy.

Atezolizumab has been tested in combination with nab-paclitaxel in TNBC in Study [redacted] (refer to the atezolizumab IB for details and Section 1.3.2.3). The safety data to date suggest that atezolizumab can be safely combined with standard chemotherapy treatments. Safety data from [redacted] patients with TNBC [redacted] in Study [redacted] indicates that the combination appears to be well tolerated and is consistent with the known risks of nab-paclitaxel and atezolizumab (Adams et al. 2016). The most frequent adverse events attributed to atezolizumab [redacted] included fatigue, pyrexia, diarrhea, nausea, alopecia, headache, peripheral neuropathy and peripheral sensory neuropathy, and decreased neutrophil count.

1.4.2.2 MEK and PD-L1/PD-1

MAPK pathway activation has been shown to enhance tumor immune evasion (Loi et al. 2016; Ebert et al. 2016). MEK inhibition results in an increased number of tumor-infiltrating CD8-positive T lymphocytes and PD-L1 and MHC expression, thereby enhancing anti-tumor immune responses by PD1/PDL1 inhibitors (Loi et al. 2016; Ebert et al. 2016). These nonclinical observations were further supported by clinical results of the Phase Ib Study [redacted] (cobimetinib plus atezolizumab) showing promising evidence of enhanced activity in patients with metastatic colorectal cancer, advanced melanoma and advanced non-small cell lung cancer.

Further rationale for the addition of atezolizumab and nab-paclitaxel including the selected dose and schedule is provided in Sections 3.3.4 and 3.3.5.

1.4.3 Benefit Risk

1.4.3.1 Unmet Need in Metastatic Triple Negative Breast Cancer

mTNBC remains an incurable disease for which no targeted therapies are available and chemotherapy is the only active treatment. Most patients develop rapid resistance to chemotherapy, which leads to fast relapse of disease and short OS. This is a population with a high unmet need.

1.4.3.2 Profile of Cobimetinib plus Paclitaxel

Clinical proof of concept for the combination of MEK inhibitor and a taxane has been demonstrated in second-line NSCLC in several clinical studies (Gandara et al. 2013; Janne et al. 2013), where the combination showed significant increases in activity when compared to single agent taxane. It is reasonable to expect that a similar enhancement in taxane activity may be seen in MBC and TNBC with this combination.

The addition of MEK inhibitors to docetaxel could result in worsened neutropenia, which has been shown to be the major limitation for this combination in second-line patients with NSCLC (Janne et al. 2013). To mitigate the potential for MEKi enhancement of taxane-related neutropenia, this study will use paclitaxel dosed weekly, where the risk of neutropenia is significantly lower than that of docetaxel (Perez et al. 2001). In addition, the previously untreated metastatic TNBC patients should be better able to tolerate chemo-related toxicities than patients with NSCLC in second-line who have already had extensive exposure to chemotherapy, thereby further reducing the risk of serious neutropenia.

The safety profile of cobimetinib at 60 mg on the 21/7 schedule has been well characterized at the proposed dose and schedule. Paclitaxel, as an approved agent, has extensive safety data available and has been shown to be a safe and active treatment for metastatic breast cancer, particularly when administered on a weekly schedule (Perez et al. 2001). In comparing the safety data of both cobimetinib and paclitaxel dosed on the weekly regimen, there is no evidence of significant overlapping toxicities, which suggests that this combination should be well tolerated using established dose and schedules for both drugs.

The potential for significant improvement in disease outcome balanced with the reasonable anticipated tolerability of cobimetinib plus paclitaxel provides a favorable benefit risk proposition.

1.4.3.3 Profile of Cobimetinib and Atezolizumab plus Taxane

The study regimen combines three agents that target three hallmarks of cancer: proliferative signaling, cell cycle progression and immune evasion (Hanahan and Weinberg 2000; Schiff et al. 1979). Treatment with cobimetinib, atezolizumab, and paclitaxel/nab-paclitaxel may offer the potential for substantial clinical benefit in patients with mTNBC.

Atezolizumab monotherapy and in combination with cobimetinib has been shown to be safe and well tolerated (see Section 1.3.2.2 and 1.3.2.3, respectively).

Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis/transaminitis, colitis, and myasthenia gravis, have been observed in ongoing studies of atezolizumab. To date, the majority of these events have been manageable without requiring treatment discontinuation.

Evidence suggests that combination treatment with atezolizumab and chemotherapy may offer the potential for clinical benefit in patients with metastatic breast cancer, as discussed in Section 1.4.2.1. However, as cobimetinib has not previously been studied in combination with paclitaxel/nab-paclitaxel and atezolizumab, the study design incorporates an initial safety run-in stage in each cohort to determine whether cobimetinib can potentiate paclitaxel/nab-paclitaxel or atezolizumab toxicities and to identify any unforeseen tolerability issues with the proposed combinations. For each cohort, the study team and steering committee will review the safety data from this stage to confirm that there are no new risks associated with this combination before exposing further patients in the expansion stage of the study.

The study design also ensures that all patients in the safety run in stage and expansion stage will receive paclitaxel therapy as a minimum, ensuring that all patients enrolled in the study will be getting active therapy for their disease.

The potential for significant improvement in disease outcome balanced with the reasonable anticipated tolerability of the proposed regimens of the doublet (cobimetinib plus paclitaxel) and the triplet (cobimetinib plus atezolizumab plus paclitaxel/nab-paclitaxel) provides justification for participation in the study.

2. OBJECTIVES AND ENDPOINTS

This three-cohort study in patients with mTNBC will evaluate the efficacy, safety, and pharmacokinetics of cobimetinib plus paclitaxel in Cohort I, of cobimetinib plus atezolizumab plus paclitaxel in Cohort II and of cobimetinib plus atezolizumab plus nab-paclitaxel in Cohort III. Analyses of the following objectives (refer to Table 2, Table 3, and Table 4 for Cohort I, II, and III objectives, respectively) will be performed in the population of patients with metastatic or locally advanced triple-negative adenocarcinoma of the breast who have not received prior systemic therapy for MBC. Prior chemotherapy (including taxanes) and/or radiation in the neoadjuvant or adjuvant setting is allowable if treatment occurred ≥6 months prior to initiation of study treatment (Cycle 1 Day 1) (Section 4.1.2).

Patients will be enrolled into the following treatment cohorts shown in Table 1.

Table 1 Study Cohorts and Treatments

Cohort	Treatment
I (safety run-in)	Cobimetinib + paclitaxel
I (expansion)	Cobimetinib (or placebo) + paclitaxel
II (safety run-in and expansion)	Cobimetinib + atezolizumab + paclitaxel
III (safety run-in and expansion)	Cobimetinib + atezolizumab + nab-paclitaxel

Note: The complete definitions for each treatment cohort are provided in Section 3.1.1.

Table 2 Objectives and Corresponding Endpoints for Cohort I

Objectives	Corresponding Endpoints
Primary efficacy objective:	
• To estimate the clinical benefit of cobimetinib plus paclitaxel relative to placebo plus paclitaxel, as measured by investigator-assessed PFS	• PFS, defined as the time from randomization to the first occurrence of disease progression or relapse as determined by the investigator using RECIST v1.1
Secondary efficacy objectives:	
• To determine the ORR, ORR_uc, and DOR of cobimetinib plus paclitaxel and placebo plus paclitaxel • To evaluate the OS benefit of cobimetinib plus paclitaxel and placebo plus paclitaxel	• OS, defined as the time from randomization to death from any cause • ORR, defined as the rate of a PR or CR occurring after randomization and confirmed ≥28 days later as determined by the investigator using RECIST v1.1 • DOR, defined as the time from the first occurrence of a documented objective response to the time of relapse, as determined by the investigator using RECIST v1.1 or death from any cause during the study, whichever occurs first. • ORR_uc (ORR confirmation not required), defined as the rate of a PR or CR occurring after randomization as determined by the investigator using RECIST v1.1, confirmation not required
Safety objective:	
• To evaluate the safety and tolerability of cobimetinib administered in combination with paclitaxel	• Nature, frequency, and severity of adverse events as graded using NCI CTCAE v4.0 • Changes in vital signs and clinical laboratory results during and following cobimetinib and paclitaxel administration

Table 2 Objectives and Corresponding Endpoints for Cohort I (cont.)

PK objectives:	
• To characterize the pharmacokinetics of cobimetinib and paclitaxel when administered in combination (safety run-in) • To characterize the pharmacokinetics of cobimetinib and to investigate the relationship between cobimetinib exposure and efficacy and safety outcomes using population approaches (expansion stage)	The goal of PK sampling in the safety run-in stages is to check for any differences in cobimetinib and paclitaxel pharmacokinetics when these drugs are co-administered, relative to their PK when administrated alone (historic PK data). For cobimetinib and paclitaxel, the following PK parameters will be estimated using data from the safety run-in stage: • Maximum plasma concentrations (C_{max}) • Minimum plasma concentration (C_{min}) • Additionally, total exposure (AUC_{0-t}) will be estimated for cobimetinib, paclitaxel, and nab-paclitaxel.
[redacted]	

Table 2 Objectives and Corresponding Endpoints for Cohort I (cont.)

[redacted]	[redacted]

AUC_{0-T} = total exposure; C_{max} = maximum concentration; C_{min} = minimum concentration; CR = complete response; DOR = duration of response; [redacted] mTNBC = metastatic triple negative breast cancer; [redacted] NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = overall response rate; ORR_uc = unconfirmed overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response [redacted] RECIST = Response Evaluation Criteria in Solid Tumors.

Table 3 Objectives and Corresponding Endpoints for Cohort II

Objectives	Corresponding Endpoints
Primary efficacy objective:	
• To estimate the clinical benefit of cobimetinib plus atezolizumab plus paclitaxel, as measured by ORR	• ORR, as defined in Table 2
Secondary efficacy objectives:	
• To determine the ORR_uc and DOR of cobimetinib plus atezolizumab plus paclitaxel • To evaluate the OS and PFS	• PFS, as defined in Table 2 • OS, as defined in Table 2 • DOR as defined in Table 2 • ORR_uc, as defined in Table 2
Safety objective:	
• To evaluate the safety and tolerability of cobimetinib and atezolizumab administered with paclitaxel	• Nature, frequency, and severity of adverse events as graded using NCI CTCAE v4.0 • Changes in vital signs and clinical laboratory results during and following cobimetinib, atezolizumab, and paclitaxel administration

Table 3 Objectives and Corresponding Endpoints for Cohort II (cont.)

PK objectives:	
• To characterize the pharmacokinetics of cobimetinib, atezolizumab, and paclitaxel when administered together (safety run-in) • To characterize the pharmacokinetics of cobimetinib and to investigate the relationship between cobimetinib exposure and efficacy and safety outcomes using population approaches (expansion stage)	The goal of PK sampling in the safety run-in stages is to check for any differences in cobimetinib, atezolizumab, and paclitaxel pharmacokinetics when these drugs are co-administered, relative to their PK when administrated alone (historic PK data). For cobimetinib, atezolizumab, and paclitaxel, the following PK parameters will be estimated using data from the safety run-in stage: • Maximum plasma concentrations (C_{max}) • Minimum plasma concentration (C_{min}) • Additionally, total exposure ($AUC_{0-\tau}$) will be estimated for cobimetinib, atezolizumab, and paclitaxel
[redacted]	[redacted]
[redacted]	[redacted]

Table 3 Objectives and Corresponding Endpoints for Cohort II (cont.)

[redacted]	[redacted]

AUC_{0-T} = total exposure; C_{max} = maximum concentration; C_{min} = minimum concentration; CR = complete response; DOR = duration of response [redacted] mTNBC = metastatic triple negative breast cancer; [redacted]; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = overall response rate; ORR_uc = unconfirmed overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response [redacted]; RECIST = Response Evaluation Criteria in Solid Tumors.

Table 4 Objectives and Corresponding Endpoints for Cohort III

Objectives	Corresponding Endpoints
Primary efficacy objective:	
• To estimate the clinical benefit of cobimetinib plus atezolizumab plus nab-paclitaxel, as measured by ORR	• ORR, as defined in Table 2
Secondary efficacy objectives:	
• To determine the ORR_uc and DOR of cobimetinib plus atezolizumab plus nab-paclitaxel • To evaluate the OS PFS	• PFS, as defined in Table 2 • OS, as defined in Table 2 • ORR_uc as defined in Table 2 • DOR as defined in Table 2
Safety objective:	
• To evaluate the safety and tolerability of cobimetinib and atezolizumab administered with nab-paclitaxel	• Nature, frequency, and severity of adverse events as graded using NCI CTCAE v4.0 • Changes in vital signs and clinical laboratory results during and following cobimetinib, atezolizumab, and nab-paclitaxel administration

Table 4 Objectives and Corresponding Endpoints for Cohort III (cont.)

PK objectives:	
• To characterize the pharmacokinetics of cobimetinib, atezolizumab, and nab-paclitaxel when administered in combination (safety run-in) • To characterize the pharmacokinetics of cobimetinib and to investigate the relationship between cobimetinib ex posure and efficacy and safety outcomes using population approaches (expansion stage)	The goal of PK sampling in the safety run-in stages is to check for any differences in cobimetinib, atezolizumab, and nab-paclitaxel pharmacokinetics when these drugs are co-administered, relative to their PK when administrated alone (historic PK data). For cobimetinib, atezolizumab, and nab-paclitaxel, the following PK parameters will be estimated using data from the safety run-in stage: • Maximum plasma concentrations (C_{max}) • Minimum plasma concentration (C_{min}) • Additionally, total exposure (AUC_{0-t}) will be estimated for cobimetinib, atezolizumab, and nab-paclitaxel
[redacted]	[redacted]
[redacted]	[redacted]

Table 4 Objectives and Corresponding Endpoints for Cohort III (cont.)

[redacted]	[redacted]

AUC_{0-T} = total exposure; C_{max} = maximum concentration; C_{min} = minimum concentration; CR = complete response; DOR = duration of response; [redacted] mTNBC = metastatic triple negative breast cancer; [redacted]; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = overall response rate; ORR_uc = unconfirmed overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; [redacted]; RECIST = Response Evaluation Criteria in Solid Tumors.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

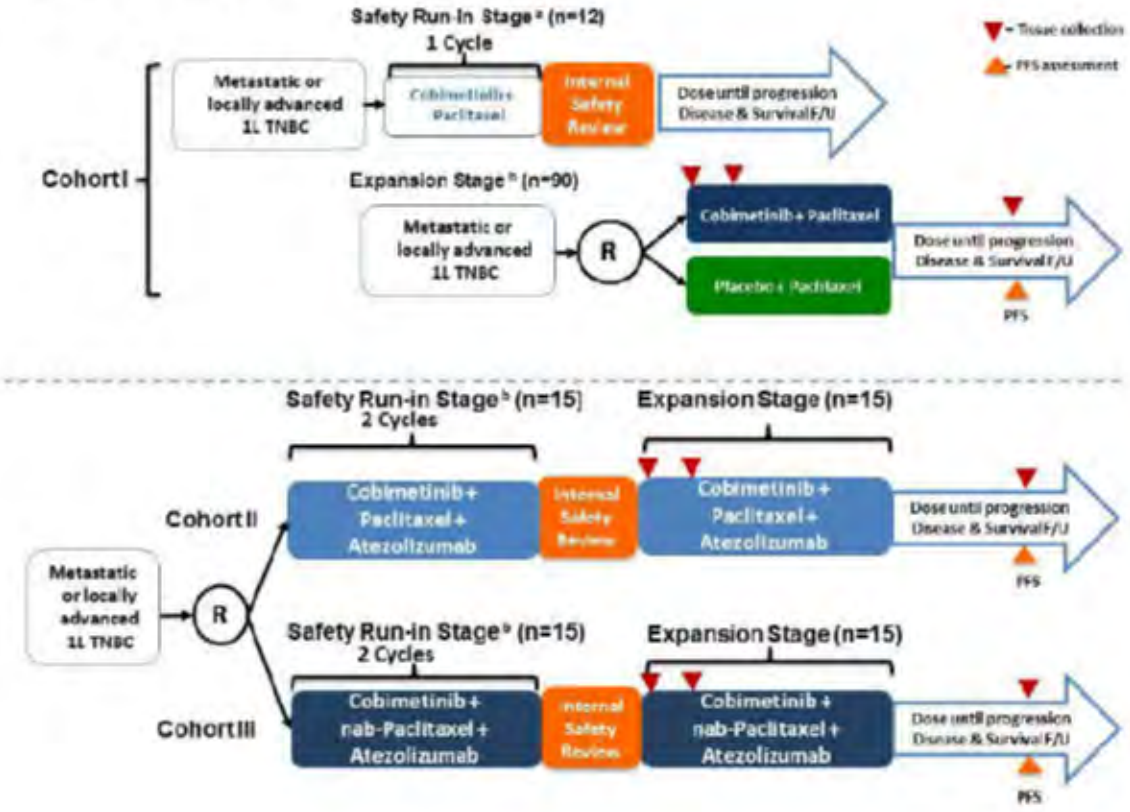
3.1.1 Overview of Study Design

This is a three-cohort, multi-stage, randomized, Phase II, multicenter, trial designed to evaluate the safety and tolerability and estimate the efficacy of cobimetinib plus paclitaxel versus placebo plus paclitaxel, and that of cobimetinib plus atezolizumab plus paclitaxel/nab-paclitaxel in patients with metastatic or locally advanced, triple-negative adenocarcinoma of the breast who have not received prior systemic therapy for MBC. Locally advanced disease must not be amenable to resection with curative intent. Figure 2 shows the study schema and treatment cohorts.

The study will commence with Cohort I that includes an initial safety run-in stage followed by a randomized (expansion) stage. The initial safety run-in stage will comprise approximately 12 patients receiving cobimetinib plus paclitaxel followed by an expansion stage where approximately 90 patients will be randomized (1:1) to receive either cobimetinib plus paclitaxel or placebo plus paclitaxel.

Following completion of Cohort I, enrollment into Cohort II and III will begin. Patients will be randomized (1:1) into either Cohort II or III. In Cohort II, patients will receive cobimetinib plus atezolizumab plus paclitaxel. In Cohort III patients will receive cobimetinib plus atezolizumab plus nab-paclitaxel. Each of Cohorts II and III will comprise a safety run-in stage of approximately 15 patients followed by an expansion stage of approximately 15 patients (see Figure 2).

Figure 2 Study Schema



F/U = follow-up; R = randomization; TNBC = triple – negative breast cancer.

[a] Safety run-in patients will continue dosing until progression and will be followed for long-term safety.

[b] Stratified on the basis of prior neoadjuvant/adjuvant taxane therapy (yes or no) and disease-free interval from last dose of chemotherapy (≤ 12 months vs. > 12 months/no prior chemotherapy).

Approximately 75 sites in the U.S., Asia, and Europe will participate in the study. Randomization for the Cohort I expansion stage and for Cohorts II and III will be stratified on the basis of prior neoadjuvant/adjuvant taxane therapy (yes or no) and disease-free interval from last dose of chemotherapy (≤ 12 months vs. > 12 months/no prior chemotherapy).

All patients must have histologically confirmed triple-negative adenocarcinoma of the breast, with measurable metastatic or locally advanced disease. Locally advanced disease must not be amenable to resection with curative intent. Patients who have a known ER-positive, PR-positive, or HER2-positive status are not eligible to participate in the study. Patients who have an unknown ER, PR, or HER2 status, and for whom determination of status is not possible, are also not eligible for this study. All enrolled patients must consent to provide a baseline tissue sample for confirmation of TNBC

diagnosis and molecular subtyping analysis and a post-progression sample to assess mechanisms of resistance.

The dosing regimens for all three cohorts are presented in Table 5.

Table 5 Dosing Scheme

	Dosing by Cohort for Each 28-Day Cycle		
Drug	Cohort I	Cohort II	Cohort III
Cobimetinib 60 mg po QD × 21 days/placebo [a]	Days 3–23	Days 3–23	Days 3–23
Paclitaxel 80 mg/m^2 IV QW	Days 1, 8, and 15	Days 1, 8, and 15	NA
Nab-paclitaxel 100 mg/m^2 IV QW	NA	NA	Days 1, 8, and 15
Atezolizumab 840 mg IV q2w	NA	Days 1 and 15	Days 1 and 15

IV = intravenous; NA = not applicable; po = orally; QW = every week; q2w = every 2 weeks; QD = once daily.

[a] Placebo is only applicable to Cohort I, expansion stage.

Cohort I

Patients in the safety run-in stage will continue to receive the combination of cobimetinib plus paclitaxel until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study. These patients will continue to be followed for long-term safety.

Once the 12 patients in the safety run-in stage have completed at least one cycle of treatment, the study team will review all clinical data to determine if the expansion stage can be initiated. As it is estimated that it will take at least several months to complete enrollment of this group, the safety review should contain data covering patients who have been on treatment with the combination for several cycles at the time of the safety evaluation for this group.

If the 60 mg cobimetinib dose is not tolerable in this combination, the study team may decide to enroll an additional cohort of 12 patients at a reduced cobimetinib dose of 40 mg QD (21/7). Once this second cohort has completed one cycle of treatment, the study team will conduct a review of clinical data and determine if the expansion stage can initiate with this lower dose of cobimetinib.

Cohorts II and III

Cohorts II and III recruitment will begin after Cohort I recruitment is complete.

Once 15 patients are recruited into each cohort for the safety run-in stage in Cohort II and III, recruitment will halt until all patients have received at least two cycles of study treatment (including a study tumor assessment) and the safety review is complete. Patients will not be replaced if they discontinue the study after receiving study treatment. As it is estimated that it will take at least several months to complete enrollment of the safety run-in groups, some patients may have data beyond two treatment cycles. The safety review will contain all data for the patients who have been on treatment with the triple regimen and will determine if the expansion stage can be opened to enroll an additional 15 patients in the corresponding cohort. The safety review will be performed by the Sponsor and the Steering Committee.

Patients in the safety run-in stages of Cohort II and III will continue to receive cobimetinib plus atezolizumab plus paclitaxel/nab-paclitaxel until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

In all treatment cohorts in both the safety run-in and the expansion stages, treatment will be continued until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study, whichever occurs first. Because cobimetinib and atezolizumab are investigational agents, for which benefit in this population has not been established, crossover will not be allowed. Tumor measurement for disease evaluation will be performed every two cycles (approximately every 8 weeks). Patients will be monitored throughout the study for adverse events, changes in laboratory values, and physical examination findings. Upon treatment discontinuation, all patients will be followed every 3 months for safety and survival.

A schedule of assessments is provided in Appendix 1.

3.1.1.1 Safety Plan

All enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. All patients (in both in the safety run-in stages and expansion stages) will be followed for safety until 30 days after the last dose of study treatment.

Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, ECG recordings, echocardiogram (ECHO) recordings/multiple gated ejection acquisition (MUGA) scans, ophthalmologic exams, and laboratory measurements. Patients will be evaluated for adverse events (all grades), serious adverse events, and any adverse events requiring drug interruption or discontinuation throughout the course of the study.

Any toxicity associated with, or possibly associated with cobimetinib administration should be managed with symptomatic treatment and/or dose interruptions (maximum allowable length of treatment interruption is 28 days) or reductions. Any toxicity associated with, or possibly associated with atezolizumab administration should be managed with symptomatic treatment. No dose reductions are allowed for atezolizumab. Toxicity due to paclitaxel or nab-paclitaxel administration will be managed by symptomatic treatment and/or dose interruptions or reductions. There will be no dose escalations allowed during this study. See Section 5.1.6 for detailed guidance for management of toxicities.

See Section 5 and Appendix 1 for complete details of the safety evaluation for this study.

3.1.1.2 Steering Committee

Since the majority of the study is open-label (except for the Cohort I expansion stage), an independent data safety monitoring board is not planned. However, safety data will be reviewed at regular intervals by the study Steering Committee, which will include representatives of the Sponsor and select study investigators. The external steering committee members will provide their recommendation to the Sponsor for opening the expansion stages of the study, in addition to any other ongoing concerns.

The first review for cobimetinib plus paclitaxel treatment (Cohort I safety run-in stage) was performed after 12 patients had completed at least one cycle of treatment. The Steering Committee will continue to review all safety data at approximately 6 monthly intervals including Cohort I expansion stage data which will remain blinded.

The first review for the triple combination for Cohorts II and III will occur when 15 patients have been recruited and have received at least two cycles of study treatment. The reviews will focus on patient safety and the adverse event profile of the triplet treatment combinations. Subsequent reviews will take place *as needed*.

3.2 END OF STUDY

The study will end when all patients enrolled have been followed until death, withdrawal of consent, lost to follow-up, or the Sponsor decides to end the trial, whichever occurs first.

Patients may continue on study treatment until the development of PD or the loss of clinical benefit (refer to Section 3.3.9), unacceptable toxicity, and/or consent withdrawal. Patients who discontinue study treatment for any reason other than disease progression will be followed until disease progression and followed for survival until death, withdrawal of consent, or they are lost to follow-up.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Cobimetinib Dosage and Schedule

Cobimetinib will be dosed at 60 mg QD using the 21/7 schedule (dosing from Day 3 through Day 23 out of a 28-day cycle). Cobimetinib 60 mg on a 21/7 schedule is the approved dose and schedule of cobimetinib.

The single-agent safety profile for cobimetinib has been established in the MEK4592g study, where cobimetinib dosed at 60 mg was established as the MTD on the 21/7 schedule. In this study the cobimetinib 60 mg QD 21/7 regimen was shown to be well tolerated with 48 patients with cancer having been treated on this schedule during the first two phases of the study. Review of the safety profiles of cobimetinib and paclitaxel shows no obvious overlapping toxicities so using the MTD dose maximizes the efficacy potential of the combination.

As the differential cell cycle effects of MEKi and taxane treatment can potentially limit the activity of taxane chemotherapy (Holt et al. 2012) this study will use a staggered dosing strategy where cobimetinib dosing will start on study Day 3 of each cycle.

In the event that unforeseen toxicities are identified with this combination during the safety run-in stage at the 60 mg cobimetinib dose level the study allows for exploration of the 40 mg level if the study team feels it is appropriate.

3.3.2 Rationale for Atezolizumab Dosage and Schedule

Atezolizumab will be administered at a fixed-dose of 840 mg on Days 1 and 15 of every cycle in Cohorts II and III only. The dose and schedule were selected on the basis of both nonclinical studies and available clinical data from Study [redacted] (see Section 1.3.2) and are consistent with the currently ongoing Phase III Study [redacted] in first-line mTNBC.

The atezolizumab dose and schedule is also informed by available clinical activity, safety and PK data:

- Anti-tumor activity has been observed across doses from 1 to 20 mg/kg.
- Overall atezolizumab exhibits pharmacokinetics that are both linear and consistent with typical IgG1 antibodies for doses ≥ 1 mg/kg q3w. PK data (Bai et al. 2012) does not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight. A fixed dose of atezolizumab 800 mg q2w (equivalent to a body weight–based dose of 10 mg/kg q2w) results in equivalent exposure to the Phase III dose of 1200 mg administered q3w.
- Atezolizumab is formulated at concentration of 60 mg/mL and in the interest of simplifying administration; 840mg corresponds to a volume of 14 mL, which can be accurately administered with a single syringe. The 840-mg dose is not expected to result in meaningfully different exposures compared with an 800-mg dose and is expected to maintain concentrations above the target atezolizumab exposure.

- The atezolizumab dosing schedule of q3w and q2w have been tested. The q3w schedule is being used in multiple Phase III studies of atezolizumab monotherapy across multiple tumor types and the q2w predominantly used in combination with chemotherapy regimens.
- The MTD of atezolizumab was not reached, and no DLTs have been observed at any dose in Study [redacted].
- In Study [redacted] in mTNBC, atezolizumab dosed q2w concurrently with nab-paclitaxel 125mg/m^2 q1w has been well tolerated with promising efficacy (Adams et al. 2016).
- In Phase Ib Study [redacted], atezolizumab dosed q2w concurrently with cobimetinib schedule has been well tolerated.

On the basis of this evidence, the fixed dose of 840 mg q2w was selected for this study, and allows for a simplified dose administration for a convenient integration with the current cobimetinib 21/7 and taxane q1w dosing schedule, and maintains the consistency across the TNBC atezolizumab trials.

3.3.3 Rationale for Weekly Paclitaxel as Control Group

While there are no approved treatments for mTNBC, single–agent taxane chemotherapy is generally considered an appropriate treatment choice given its status as a primary treatment of choice for patients with MBC in the front-line setting. Taxanes are among the most active of such chemotherapy agents for the treatment of MBC in terms of response rates and survival, as shown in a recent meta-analysis of three randomized trials comparing a taxane with an anthracycline (Piccart-Gebhart et al. 2008). In fact both the Guidelines from the European Society for Molecular Oncology (ESMO) and from the National Comprehensive Cancer Network (NCCN) state that for patients without directly life-threatening or severely symptomatic disease, single-agent chemotherapy (including taxanes) is the preferred option (Cardoso et al. 2012; NCCN 2014).

In MBC, combination chemotherapy regimens have been shown to offer slightly better response rates and comparable time to progression compared with single-agent chemotherapy, but they have not demonstrated improved survival and are associated with significantly greater toxicity (Carrick et al. 2005; Gennari et al. 2011). Regarding TNBC specifically, the ESMO guidelines note that although combination therapy is an available option for triple-negative disease, "triple-negative biopsy on its own, however, is not a sufficient reason to give combination chemotherapy." Rather, the selection of best treatment/regimen should balance several disease-specific and patient-specific factors (Cardoso et al. 2012). As this study will focus on metastatic patients in the first-line setting, exposure to the greater toxicities associated with combination chemotherapy is not appropriate as it does not offer the chance for improved survival.

The use of single-agent paclitaxel as the control for the study in Cohort I (expansion stage) also allows the most precise means for determining the efficacy potential of the

cobimetinib plus paclitaxel combination. In Cohort II, atezolizumab will be used with cobimetinib plus paclitaxel, and thus will allow the incremental benefit of atezolizumab to be assessed [redacted]

Paclitaxel dosed on a weekly schedule at 80 mg/m^2 has been shown to have comparable activity but better tolerability compared to other taxanes dosed q3w (Perez et al. 2001; Seidman et al. 2008). In the adjuvant setting, weekly paclitaxel (90 mg/m^2) has also shown an increased trend for disease free survival when compared the q3w regimen (Cardoso et al. 2012).

3.3.4 Rationale for Nab-Paclitaxel Dosage and Regimen

Nab-paclitaxel (260 mg/m^2) delivered every 3 weeks (q3w) is the FDA approved dose for metastatic breast cancer established in the Phase III study comparing paclitaxel with nab-paclitaxel (Gradishar et al. 2005). However, the q3w regimen is not generally used in current clinical practice as the weekly schedule of nab-paclitaxel has been shown to be better tolerated and potentially more efficacious in MBC (Gradishar et al. 2009).

In a randomized Phase II study in patients MBC using schedules of nab-paclitaxel, weekly nab-paclitaxel 150 mg/m^2 (3-weeks-on/1-week-off schedule) attained the highest response rates (49%) compared to 37% with q3w nab-paclitaxel, 45% with weekly nab-paclitaxel 100 mg/m^2 (3-weeks-on/1-week-off schedule) (Gradishar et al. 2009). Other studies have also shown that higher doses of nab-paclitaxel are associated with greater toxicities (Blum et al. 2007) and without improvements in PFS (Rugo et al. 2015).

To date, 100 mg/m^2 of nab-paclitaxel weekly on a 3-weeks-on/1-week-off schedule is a commonly used dosing schedule, with potentially superior efficacy and decreased toxicities in MBC. Therefore, patients on this study will receive nab-paclitaxel 100 mg/m^2 via IV infusion on Days 1, 8, and 15 of each 28-day cycle. This dose and schedule is consistent with the Phase III [redacted] study.

3.3.5 Rationale for Dose and Schedule for Cobimetinib plus Atezolizumab plus Paclitaxel/Nab-Paclitaxel

Atezolizumab plus cobimetinib was studied in the Phase Ib Study [redacted] which used the approved dose and schedule of cobimetinib (cobimetinib 60 mg on a 21/7 days on/off schedule) with atezolizumab 800 mg IV q2w. Atezolizumab and nab-paclitaxel was studied in the Phase Ib Study [redacted], which evaluated atezolizumab at 800mg q2w concurrently with nab-paclitaxel 125mg/m^2 q1w.

In Cohort II (cobimetinib plus atezolizumab plus paclitaxel) and Cohort III (cobimetinib plus atezolizumab plus nab-paclitaxel), cobimetinib will be dosed at the approved dose and schedule (cobimetinib 60 mg on a 21/7 days on/off schedule) concurrently with atezolizumab at 840mg q2w. The 840 mg dose is expected to be similar to the 800 mg dose of atezolizumab dose and selected in this study to simplify dose administration (see Section 3.3.2).

Cohorts II and III will utilize doses and schedules of paclitaxel or nab-paclitaxel that have been widely used in clinical practice (Gradishar et al. 2009; Rugo et al. 2015).

Additional rationale to support the exploration of chemoimmunotherapy combination in mTNBC is outlined in more detail in Section 1.4.2.

3.3.6 Rationale for Cobimetinib, Atezolizumab, and Paclitaxel/Nab-Paclitaxel Pharmacokinetic Assessments

Paclitaxel is mainly metabolized by CYP2C8 and CYP3A4 with minimal renal excretion. Cobimetinib is also extensively metabolized and this is mainly by CYP3A4. Though in vitro studies indicated the cobimetinib may be an inhibitor of CYP3A4, in a clinical study, cobimetinib did not affect the PK of midazolam, a sensitive CYP3A4 substrate. Considering the in vitro metabolism and DDI data for cobimetinib and paclitaxel, it is unlikely that there may be a PK interaction between them when administered concurrently. However, since the PK of cobimetinib has not been studied in patients with breast cancer and in combination with paclitaxel which is also a substrate of CYP3A4, a detailed assessment of the PK of the individual agents will be performed in the safety run-in stage. A much more sparse collection strategy will be implemented in the expansion stage, for continued assessment of a potential DDI and also to help generate individual specific PK parameters for cobimetinib for exposure-efficacy and exposure-safety analyses.

PK data from the cobimetinib single-agent Phase I study (MEK4592g), show that cobimetinib median t_{max} at steady-state ranges from 1 to 6 hours and the $t_{1/2}$ ranges from 21 to 69 hours. Paclitaxel will be infused over 1 hour, and the $t_{1/2}$ ranges from 13 to 20 hours after a 3-hour infusion.

Based on these PK characteristics and the regimens of cobimetinib, paclitaxel, nab-paclitaxel, and atezolizumab blood samples for the determination of plasma (or serum for atezolizumab) concentrations of the drugs will be collected as outlined in Appendix 2 for the safety run-in stage and the expansion stage. The sampling schedule following the dose of cobimetinib on Day 15 in the run-in stage is designed to capture sufficient timepoints to adequately describe the steady state profile of the individual agents. This will allow a comparison of single-agent data (from Phase I studies for cobimetinib and historical data for paclitaxel) with the combination data collected here. It is unlikely that atezolizumab will affect the pharmacokinetics of cobimetinib, paclitaxel or nab-paclitaxel, and vice-versa. As such, sparse sample collection for atezolizumab will be carried out to meet PK [redacted] objectives.

The sparse sampling schedule during the expansion stage will help generate individual PK parameters that may be used for exposure-efficacy and exposure-safety analyses for cobimetinib and atezolizumab, leveraging the already-developed population PK model based on prior PK data, as warranted by the data.

3.3.7 [redacted]

[redacted]

[redacted]

3.3.8 Rationale for Collection of Blood and Plasma Samples for Noninvasive Disease Monitoring

Circulating tumor DNA (ctDNA) can be detected in the blood of cancer patients with epithelial cancers and may have diagnostic and therapeutic significance (Schwarzenbach et al. 2011). For example, the mutational status of tumor cells may be obtained through the isolation of ctDNA (Maheswaran et al. 2008), and ctDNA has been used to monitor treatment effectiveness in melanoma (Shinozaki et al. 2007). In this study plasma samples will be assessed for genetic alterations in the MAPK pathway, because this may help predict which patients may benefit from cobimetinib and may also help identify potential causes of acquired resistance to cobimetinib. Analysis and correlation of oncogenic mutations in plasma will help to further evaluate the option of using plasma for the detection and monitoring of mutations during the course of treatment.

3.3.9 Rationale for Allowing Patients to Continue Treatment until Loss of Clinical Benefit in Cohorts II and III

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents as increase in tumor size does not consistently reflect therapeutic failure (Wolchok et al. 2009). The phenomena of pseudo progression or infiltration of tumor by immune cells may mimic tumor progression. Therefore, as this study is evaluating an immunotherapy, patients will be allowed to continue to receive study treatment after documented RECIST v1.1–defined radiographic disease progression, provided that the benefit-risk ratio for the patient remains favorable as assessed by the physician and Medical Monitor (see Section 4.3.2.5).

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients with metastatic or locally advanced, triple-negative adenocarcinoma of the breast that have not received prior systemic therapy for MBC may be eligible for this study. Locally advanced disease must not be amenable to resection with curative intent. Patients may have received prior chemotherapy in the neoadjuvant/adjuvant setting if treatment was ≥ 6 months prior to initiation of study treatment (Cycle 1 Day 1). Patients for both the safety run-in and expansion stages must comply with all applicable eligibility criteria to be enrolled.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Women and men, age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Histologically confirmed ER-negative, PR-negative, and HER2-negative (see definitions Section 4.1.2) adenocarcinoma of the breast with measurable metastatic or locally advanced disease
  - The determination of TNBC status should, whenever possible, utilize tissue from a metastatic or recurrent lesion and where more than one biopsy source is available, priority should be given to the most recent sample.
  - Patients who have not had HER2, ER, or PR testing, and thus, the HER2, ER, and PR status of the breast adenocarcinoma is unknown, are not eligible.
- Locally advanced disease must not be amenable to resection with curative intent
- Measurable disease, according to RECIST, v1.1 (see Appendix 3)
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to first dose of study drug treatment:
  - ANC ≥ 1.5×10^9/L
  - Platelet count ≥ 100×10^9/L
  - Hemoglobin ≥ 9 g/dL
  - Albumin ≥ 2.5 g/dL
  - Bilirubin ≤ 1.5 × the upper limit of normal (ULN)
  - AST, ALT, and alkaline phosphatase ≤ 3 × ULN, with the following exceptions:
    - Patients with documented liver metastases: AST and/or ALT ≤ 5 × ULN
    - Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN

- Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min on the basis of measured CrCl from a 24-hour urine collection or Cockcroft-Gault* glomerular filtration rate estimation:

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

* The Modification of Diet in Renal Disease (Levey et al. 2006) and the Chronic Kidney Disease Epidemiology Collaboration (Levey et al. 2009) formulas for estimation of glomerular filtration rate are also acceptable.

- Ability and capacity to comply with the study and follow-up procedure
- For female patients (and female partners of male patients) who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 6 months after the last dose of paclitaxel/nab-paclitaxel, at least 5 months after the last dose of atezolizumab, and 3 months after the last dose of cobimetinib. *Women must refrain from donating eggs during this same period.*
  - Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
  - Post-ovulation methods and withdrawal are not acceptable methods of contraception.
- Men must agree not to donate sperm or have intercourse with a female partner without using appropriate barrier contraception during the treatment period and for 6 months after the last dose of paclitaxel/nab-paclitaxel and 3 months after the last dose of cobimetinib. Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Abraxane® (paclitaxel protein-bound particles for injectable suspension) (albumin bound) or lower fertility with paclitaxel.

4.1.2 Exclusion Criteria

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

A. Disease-Specific Exclusion Criteria

- Known HER2-positive, ER-positive, or PR-positive breast cancer by local laboratory assessment (if more than one test result is available and not all results meet the eligibility criterion definition for TNBC, all results should be discussed with the Medical Monitor to establish eligibility of the patient)
  - HER2 positivity is defined as one of the following: IHC 3 positive or in situ hybridization (ISH) positive using either a single-probe ISH (average HER2 gene copy number ≥ 6 signals/cell) or dual-probe ISH (ratio of HER2 to CEP17 ≥ 2.0; if HER2/CEP17 < 2.0 then average HER2 copy number ≥ 6.0 signals/cell) (Wolff et al. 2013).

- ER and PR positivity is defined positive for ER or PR if a finding of ≥ 1% of tumor cell nuclei are immunoreactive (Hammond et al. 2010).

- Any prior chemotherapy, hormonal, or targeted therapy, for inoperable locally advanced or metastatic TNBC
  - Prior chemotherapy (including taxanes) and/or radiation in the neoadjuvant or adjuvant setting is allowable if treatment occurred ≥ 6 months prior to initiation of study treatment (Cycle 1, Day1)
- Any systemic anticancer therapy within 3 weeks prior to Cycle 1, Day 1
- Any radiation treatment to metastatic site within 28 days of Cycle 1, Day 1
- Major surgical procedure, open biopsy, or significant traumatic injury within 30 days prior to Cycle 1, Day 1 or anticipation of need for major surgical procedure during the course of the study
- Prior therapy with bevacizumab, sorafenib, sunitinib, or other putative vascular endothelial growth factor pathway–targeted therapy within 2 years of start of study treatment
- Prior exposure to experimental treatment targeting Raf, MEK, or the MAPK pathway
- Previous therapy with Akt, PI3K, and/or mTOR inhibitors
- Prior therapy with trastuzumab
- Grade ≥ 2 peripheral neuropathy
- Brain metastases (symptomatic or nonsymptomatic) that have not been treated previously, are progressive or require any type of therapy (e.g., radiation, surgery, or steroids) to control symptoms from brain metastases within 30 days prior to first study treatment dose

B. Cobimetinib-Specific Exclusion Criteria

- History of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment/central serous chorioretinopathy, retinal vein occlusion (RVO), or neovascular macular degeneration
- Patients will be excluded if they currently have the following risk factors for RVO:
  - Uncontrolled glaucoma with intra-ocular pressures ≥ 21 mmHg
  - Serum cholesterol ≥ Grade 2
  - Hypertriglyceridemia ≥ Grade 2
  - Hyperglycemia (fasting) ≥ Grade 2
- Cobimetinib is metabolized by the hepatic cytochrome CYP3A4 enzyme. The drugs listed below should be avoided. If use of one of these drugs is necessary, the risks and benefits and potential alternatives should be discussed with the Medical Monitor prior to its concomitant use with cobimetinib.

- Strong CYP3A4/5 inhibitors such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, and voriconazole
- Strong CYP3A4/5 inducers such as, but not limited to, rifampin, carbamazepine, rifapentine, phenytoin, and phenobarbital

- The following foods/supplements are prohibited at least 7 days prior to initiation of and during study treatment:
  - St. John's wort or hyperforin (potent CYP3A4 enzyme inducer)
  - Grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor)

C. Atezolizumab-Specific Exclusion Criteria (Cohorts II and III Only)

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 11 for a more comprehensive list of autoimmune diseases)

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

  Patients with controlled Type 1 diabetes mellitus on a stable insulin dosing regimen may be eligible for this study.

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

  Rash must cover less than 10% of body surface area (BSA).

  Disease is well controlled at baseline and only requiring low potency topical steroids

  No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan

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

- Positive test for HIV
- Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test or positive HBV DNA at screening) or hepatitis C

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.

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

- Active tuberculosis
- Receipt of a live, attenuated vaccine within 4 weeks prior to randomization or anticipation that such a live, attenuated vaccine will be required during the study
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, or anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or IL-2) within 4 weeks or five half-lives of the drug (whichever is shorter) prior to randomization
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [TNF] agents) within 2 weeks prior to randomization, or anticipated requirement for systemic immunosuppressive medications during the trial

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study

  The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

D. Cardiac Exclusion Criteria

- History of clinically significant cardiac dysfunction, including the following:
  - Significant cardiovascular disease, such as symptomatic congestive heart failure, defined as New York Heart Association Class II or higher; see Appendix 8
  - Unstable angina, or new-onset angina within 3 months prior to initiation of study treatment
  - Myocardial infarction within 3 months prior to initiation of study treatment
  - Unstable arrhythmia

- History of congenital long QT syndrome

- Corrected QT interval at screening >480 ms (average of triplicate screening measurements)
- Left ventricular ejection fraction (LVEF) below the institutional lower limit of normal or below 50%, whichever is lower

E. General Exclusion Criteria

- Pregnancy (positive serum pregnancy test) or lactation
- Uncontrolled serious medical or psychiatric illness
- Active infection requiring IV antibiotics on Cycle 1, Day 1
- Patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor® EL (polyoxyethylated castor oil) or to nab-paclitaxel and any of the excipients
- No other history of or ongoing malignancy that would potentially interfere with the interpretation of the PD or efficacy assays

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The run-in stage of Cohort I and all of Cohorts II and III are open label. The expansion (randomized) stage of Cohort I is double-blind and placebo-controlled. After written informed consent has been obtained, all screening procedures and assessments have been completed, eligibility has been established and entered into the interactive voice or web response system (IxRS), each patient will be assigned an identification number from the IxRS.

The randomization scheme is designed to ensure that an approximately equal number of patients will be enrolled in each treatment arm within the baseline characteristics of the following criteria:

- Prior neoadjuvant/adjuvant taxane therapy (Yes or No)
- Disease-free interval from last dose of chemotherapy (≤12 months vs. >12 months/no prior chemotherapy).

Cohort I

During the safety run-in stage, the study is open-label. Once 12 patients have successfully completed the first cycle of study treatment in the safety run-in stage, screening for the expansion stage will not be opened until the study team has completed their evaluation of clinical safety data to determine if the expansion stage can begin.

The expansion stage is double blind and placebo controlled. In the expansion stage, once the patient has been enrolled into the study, the IxRS will be used to assign the batch numbers for study drug(s) to be dispensed at each treatment visit. It is important that the study drug(s) dispensed for each visit are the correct batch number as assigned

by the IxRS. This will ensure drug use by dates and automatic study drug resupply to sites are managed appropriately via the IxRS.

In Cohort I expansion stage, patients will be randomized in a 1:1 ratio to one of two treatment arms:

- Arm A: cobimetinib plus paclitaxel
- Arm B: placebo plus paclitaxel

Patients should receive their first dose of assigned study treatment no later than 72 hours after randomization. Roche, the contract research organization (CRO), investigators, and patients will be blinded to treatment assignment of cobimetinib or placebo. 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 trial. Sponsor personnel responsible for performing PK assays will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed. Samples from patients assigned to the placebo plus paclitaxel arm will not be analyzed except by request (i.e., to evaluate a possible error in dosing).

If 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. 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, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug.

Cohorts II and III

Patients will be randomized in a 1:1 ratio to:

- Cohort II: cobimetinib plus paclitaxel plus atezolizumab
- Cohort III: cobimetinib plus nab-paclitaxel plus atezolizumab

As described in the expansion stage above, a similar approach will be applied for Cohorts II and III. Once the 15 safety run-in patients have been randomized into each cohort and the 15th patient has completed at least two cycles of treatment (including a tumor assessment) the study team will review all clinical data to determine if the expansion stage can be initiated to enroll additional 15 patients in the corresponding

cohort. Patients should receive their first dose of assigned study treatment no later than 72 hours after randomization.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

Cobimetinib, placebo, atezolizumab, nab-paclitaxel, and paclitaxel packaging may be overseen by the Roche clinical trial supplies department and will bear a label with the identification required by local law as well as the protocol number. Paclitaxel and nab-paclitaxel will be locally sourced in the United States. The packaging and labeling of the study drugs will be in accordance with the Sponsor's standards and local regulations. Local packaging and labeling requirements may differ in some countries.

Upon delivery of the investigational products to the site, site personnel should check for damage and verify proper identity, quantity, integrity of seals, and temperature conditions. Site personnel should report any deviations or product complaints to the study monitor upon discovery.

Cobimetinib, placebo, atezolizumab, nab-paclitaxel, and paclitaxel will be stored at the clinical site under the required storage conditions as indicated on the study drug labels. Patients will be asked to store cobimetinib or placebo at the required storage conditions noted on the label, out of the reach of children or other co-inhabitants.

4.3.1.1 Cobimetinib

The 20 mg cobimetinib drug product is a film-coated, white, round, immediate release tablet. Cobimetinib will be packaged in blister packs.

The inactive ingredients in cobimetinib are as follows: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate for the tablet core. The tablet coating consists of polyvinyl alcohol-part hydrolyzed, titanium dioxide, polyethylene glycol 3350, and talc.

Cobimetinib should not be stored above 25°C (77°F).

If study drug is stored outside of the permitted temperature ranges, quarantine the affected supply and contact the monitor.

4.3.1.2 Placebo

Cobimetinib placebo tablets have been manufactured to match the size, shape, and color of the cobimetinib active tablets and consist of the same inactive ingredients used in the corresponding active drug product as well as the same storage requirements (see Section 4.3.1.1). Placebo will be packaged in blister packs.

4.3.1.3 Atezolizumab

The atezolizumab drug product is provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution. Extraction of 14 mL of atezolizumab solution from a 1200-mg per vial contains an 840 mg dose. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

Atezolizumab must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until use. Vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Discard any unused portion of drug left in a vial. Vial contents should not be frozen or shaken and should be protected from light.

For further details on the storage and preparation of atezolizumab see the Pharmacy Manual and the Investigator's Brochure.

Atezolizumab will be supplied by the Sponsor for use in Cohorts II and III.

4.3.1.4 Paclitaxel

Refer to the paclitaxel Package Insert for details on the formulation and storage.

Paclitaxel will be used in Cohorts I and II.

4.3.1.5 Nab-Paclitaxel

Refer to the nab-paclitaxel (Abraxane) Package Insert for details on formulation and storage.

Nab-paclitaxel will be supplied by the Sponsor for use in Cohort III only.

4.3.2 Dosage, Administration, and Compliance

Patients must record the time and date they take each dose of cobimetinib in a medication diary. Missed doses should also be recorded. Patients will be instructed to bring all unused study drugs and their study drug diaries to each study visit for assessments of compliance.

If a dose of cobimetinib is missed (i.e., not taken within 12 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

If a patient's study treatment (i.e., all drugs) has been interrupted for more than 28 days for whatever reason, the patient will be considered to have discontinued from study treatment and will enter the follow-up after treatment discontinuation portion of the study.

Each study cycle is defined by the 28-day dosing cycle of paclitaxel/nab-paclitaxel.

Guidelines for interruption, dose modification, and permanent discontinuation of study drugs are provided in Section 5.1.

4.3.2.1 Cobimetinib

Cobimetinib (or placebo for patients in the Cohort I expansion stage only) should be taken orally once daily on Day 3 through Day 23 of each 28-day treatment cycle. Cobimetinib should be taken at approximately the same time each morning no later than 12 hours after the scheduled time. On clinic days where cobimetinib should be administered (Day 8 and Day 15 of each 28-day cycle), cobimetinib should be taken in the clinic prior to administration of paclitaxel /nab-paclitaxel.

Cobimetinib can be taken with or without a meal. Cobimetinib tablets should never be chewed, cut, or crushed.

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

4.3.2.2 Atezolizumab

Patients will receive atezolizumab 840 mg administered by IV infusion q2w (every 14 [±3] days). On days of scheduled infusions of atezolizumab and paclitaxel or nab-paclitaxel, all study treatment is to be administered after infusion of atezolizumab, as described in Section 4.3.2.3 and 4.3.2.4.

Atezolizumab will be administered in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions (see Appendix 10).

For more detailed information on drug preparation, storage, and administration, refer to the atezolizumab Investigator's Brochure and Pharmacy Manual.

Atezolizumab infusions will be administered per the instructions outlined in Table 6.

Table 6 Administration of First and Subsequent Infusions of Atezolizumab

First Infusion	Subsequent Infusions
• No premedication is administered. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • Infuse 14 mL atezolizumab (840 mg) in 250 mL NaCl) over 60 (± 15) minutes. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during and after the infusion if clinically indicated • Patients will be informed about the possibility of delayed symptoms following infusion and instructed to contact their study physician if they develop such symptoms.	• If patient experienced infusion-related reaction during any previous infusion, premedication with antihistamines may be administered for Cycles ≥2 at the discretion of the treating physician. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • If the patient tolerated the first infusion well without infusion-associated adverse events, the second infusion may be administered over 30 (± 10) minutes. • If no reaction occurs, subsequent infusions may be administered over 30 (± 10) minutes • Continue to record vital signs within 60 minutes before starting infusion and during or after the infusion if clinically indicated. • If the patient had an infusion-related reaction during the previous infusion, the subsequent infusion must be administered over 60 (± 15) minutes. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during and after the infusion if clinically indicated.

Dose reduction of atezolizumab is not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events associated with atezolizumab and cobimetinib are provided in Section 5.1.6. For information regarding management of atezolizumab-associated adverse events, please refer to *Appendix 12*.

4.3.2.3 Paclitaxel

Paclitaxel will be administered at a dose of 80 mg/m^2 on Day 1, Day 8, and Day 15 of each 28-day cycle. Calculation of body surface area for the purposes of dosing of paclitaxel should be made according to the prescribing information.

Paclitaxel will be administered as an infusion over a period of approximately 1 hour per standard practice or institutional guidelines. Because of the known potential for allergic reactions to paclitaxel, patients will be premedicated with dexamethasone, diphenhydramine, and an H2 blocker 30–60 minutes prior to the paclitaxel administration and according to the paclitaxel Package Insert and institutional guidelines. Paclitaxel infusions may be slowed or interrupted for patients experiencing infusion-associated

symptoms. If infusion-related symptoms occur, patients should be treated according to best medical practice and patients will be monitored until adequate resolution of signs and symptoms.

Paclitaxel should be continued until disease progression, unacceptable paclitaxel-related toxicity, investigator decision, death, or completion of study, whichever occurs first.

Alteration to the initial starting dose of paclitaxel is not permitted unless the modification is specifically addressed by a guideline in the paclitaxel Package Insert. Paclitaxel dose modifications in subsequent cycles are allowed if consistent with standard practice or institutional guidelines. If a cycle of cobimetinib or placebo is delayed, paclitaxel may continue. If paclitaxel is discontinued in the absence of disease progression, treatment with cobimetinib/placebo should continue. If a patient discontinues treatment with cobimetinib/placebo, paclitaxel should continue and the patient followed for survival.

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

4.3.2.4 Nab-Paclitaxel

Nab-paclitaxel will be administered according to the local prescribing information. The starting dose level of nab-paclitaxel in this study will be 100 mg/m^2 administered intravenously over 30 minutes on Days 1, 8, and 15 of each 28-day cycle (3-weeks-on/1-week-off schedule). Dose modifications should be performed according to Section 5.1.6.

Sites should follow their institutional standard of care for determining the nab-paclitaxel dose for patients who are obese and for dose adjustments in the event of patient weight changes. The infusion site should be closely monitored for possible infiltration during drug administration.

Nab-paclitaxel should be continued until disease progression, unacceptable nab-paclitaxel–related toxicity, investigator decision, death, or completion of study, whichever occurs first.

4.3.2.5 Dosing of Study Treatment Beyond Disease Progression in Cohorts II and III

Dosing of study treatment beyond RECIST v1.1–defined disease progression is allowed for patients in Cohort II and III only. Patients must meet all of the following criteria to be allowed to receive study treatment beyond disease progression:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs indicating unequivocal progression of disease. Patients may continue to receive treatment beyond disease progression in the absence of clinical signs or symptoms of progression despite a rising CEA level.

- No decline in Eastern Cooperative Oncology Group (ECOG) performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol–allowed medical interventions
- Patients must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of RECIST v1.1-defined disease progression
- Approval by the study Medical Monitor

4.3.3 Investigational Medicinal Product Accountability

Cobimetinib/placebo, atezolizumab, and nab-paclitaxel are investigational medicinal products (IMPs) in this study and will be provided by the Sponsor. Paclitaxel *is* also an IMP in this study and may be provided by the Sponsor or sourced locally. Even though nab-paclitaxel is an IMP in this protocol, it will be locally sourced in the United States. Dose administration should be performed according to the drugs' national prescribing guidelines. Refer to the appropriate Package Insert as needed for details.

The study site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced.

Investigational medicinal products will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any 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 Post-Trial Access to Study Drugs

The Sponsor will offer post-trial access to the study drugs (cobimetinib, atezolizumab, and nab-paclitaxel [where applicable]) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

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

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for TNBC
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for TNBC
- Provision of study drug is not permitted under the laws and regulations of the patient's country

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

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

4.4 CONCOMITANT THERAPY AND FOOD

4.4.1 Permitted Therapy

Concomitant medication includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, or nutritional supplements) used by a patient from 7 days prior to Cycle 1 Day 1 through the end-of study treatment visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients who use oral contraceptives, hormone-replacement therapy, or maintenance therapy should continue their use as outlined in the eligibility criteria.

Pain medications may be administered according to local standard practice guidelines while the patient is in the study.

Antiemetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drugs. At the discretion of the investigator, prophylactic antihistamine, antiemetic, and anti-diarrheal medication(s) may be used before subsequent doses of study drugs per standard clinical practice.

Hematopoietic growth factors should not be administered prophylactically before initial treatment with study drugs. Hematopoietic growth factors may be administered according to local guidelines if indicated during the course of the study.

Inactive influenza vaccinations are permitted.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study (all cohorts) and for at least 14 days prior to initiation of study treatment, unless otherwise specified below:

- Any prior or concomitant therapy intended for the treatment of metastatic breast cancer, either approved by health authorities or experimental, including chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy, or investigational agents is prohibited.
- Palliative radiotherapy within 28 days of first dose of study treatment is prohibited. Major surgery within 30 days of first dose of study treatment is prohibited.
- Concomitant use of strong inhibitors of CYP3A4 (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) should be avoided. Cobimetinib exposures were increased 6.6-fold in presence of itraconazole in healthy subjects. Cobimetinib exposures may be increased in presence of these agents, though to a lesser extent in patients with cancer compared to that observed in healthy subjects. Caution should be exercised when co-administering with moderate inhibitors of CYP3A.
- Avoid strong and moderate CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's wort) as they increase the metabolism of cobimetinib. Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication when determining whether a certain medication strongly induces CYP3A4. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

In Cohorts II and III, the following additional medications are excluded while the patient is receiving study treatment:

- RANKL inhibitor (denosumab): patients who are receiving denosumab prior to randomization must be willing and eligible to receive a bisphosphonate instead while on study.
- Immunomodulatory agents, including but not limited to interferons or interleukin-2, during the entire study; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab.
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab.
- Any live, attenuated vaccine (e.g., FluMist®) within 28 days prior to randomization, treatment, or within 5 months following the last dose of atezolizumab.

Systemic corticosteroids and anti–TNF-α agents may also attenuate potential beneficial immunologic effects of treatment with atezolizumab, but may be administered at the discretion of the treating physician and for Cohort II patients receiving paclitaxel. If feasible, alternatives to these agents should be considered.

The concomitant use of herbal therapies is not recommended, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, their use for patients in the study is allowed at the discretion of the investigator.

For Cohort III, the use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance); in such patients, MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest must be performed.

In addition, patients should not receive other immunomodulatory agents for 10 weeks after atezolizumab discontinuation.

4.4.3 Concomitant Medications with Nab-Paclitaxel

The metabolism of nab-paclitaxel is catalyzed by cytochrome P450 (CYP) isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when nab-paclitaxel is concomitantly administered with known inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) and inducers (e.g., rifampin and carbamazepine) of CYP3A4.

Granulocyte-colony stimulating factor (G-CSF) treatment is permitted for patients receiving nab-paclitaxel. The primary prophylaxis should be administered per the American Society of Clinical Oncology, European Organization for Research and Treatment of Cancer (EORTC), and European Society for Molecular Oncology (ESMO) guidelines; namely, in patients who are $\geq$60 years of age and/or with comorbidities (Smith et al. 2006; Crawford et al. 2009; Aapro et al. 2011).

Evidence supporting the use of long-acting (pegylated) forms of G-CSF in patients receiving weekly chemotherapy is limited, and investigators should consider giving preference to conventional formulations of G-CSF.

Anti-emetics, anti-allergic measures, and other treatments for concomitant nab-paclitaxel toxicities may be used at the discretion of the investigator, taking into account precautions from the Package Insert.

Refer to the Package Insert for nab-paclitaxel for all boxed warnings and contraindications.

4.4.4 Prohibited Food and Supplements

Use of the following foods and supplements are prohibited during the study and for at least 7 days prior to initiation of study treatment, unless otherwise specified below:

- St. John's wort or hyperforin (potent CYP3A4 enzyme inducer)
- Grapefruit juice (potent CYP3A4 enzyme inhibitor)

Patients who require the use of any of these agents will be discontinued from study treatment and followed for safety outcomes for 4 weeks after the last dose of study treatment or until initiation of another subsequent anti-cancer therapy, whichever comes first. These patients will also continue to be followed for survival.

4.5 STUDY ASSESSMENTS

See Appendix 1 for the schedule of assessments performed during the study.

4.5.1 Description of Study Assessments

4.5.1.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the safety run-in or expansion stage of the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms (ICFs) 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 randomization. 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.

4.5.1.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, major surgeries, cancer history (including prior cancer therapies and procedures), and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the Cycle 1 Day 1 visit.

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

4.5.1.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

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.

Patients will be asked specifically about vision changes as part of each physical examination in addition to interval medical history. Note: If physical examinations are assessed within 7 days of the Cycle 1 Day 1 visit, they do not have to be repeated at Day 1.

4.5.1.4 Vital Signs

The following vital signs will be recorded for all patients on screening visit and Day 1, Day 8, and Day 15 of each cycle:

- Temperature (°C)
- Heart Rate (HR)
- Respiratory rate
- Systolic and diastolic blood pressure
  - Blood pressure and HR measurements will be recorded with the patient in the seated position after a 5-minute rest period.

If vital signs are assessed within 7 days of the Cycle 1 Day 1 visit, they do not have to be repeated at Day 1.

4.5.1.5 Tumor and Response Evaluations

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Baseline tumor assessments should be performed ≤28 days before Cycle 1, Day 1. Screening bone scans and head scans (CT or MRI) should be performed within 6 weeks before Cycle 1, Day 1. Response will be assessed by the investigator on the basis of physical examinations and CT or MRI scans, using RECIST v 1.1. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). To the extent that is it feasible, assessments should be performed by the same evaluator to ensure internal consistency across visits.

CT or MRI scans should include chest, abdomen, and pelvic scans; CT scans of the neck should be included if clinically indicated. At the investigator's discretion, CT scans may be repeated at any time if PD is suspected.

For Cohort III patients with a history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumor assessments performed using magnetic resonance imaging (MRI).

Evaluation of tumor response conforming to RECIST v1.1 [redacted] must be documented every 8 weeks ± 1 week (during the last week of every 2 treatment cycles) from the date of first

study drug administration (Cycle 1 Day 1) until documented investigator-determined PD or patient death. Tumor assessments must be performed independent of changes to the study treatment administration schedule (e.g., dose delay). If a tumor assessment has to be performed early or late, subsequent assessments should be conducted according to the original schedule based on the date of first study drug administration (Cycle 1 Day 1). Additional scans should be performed as clinically indicated. Confirmation of response (PR or CR) will be done no earlier than 28 days. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval not less than 6 weeks.

Patients who discontinue study treatment for any reason other than disease progression will continue to undergo tumor response evaluations (approximately every 8 weeks) until PD.

All tumor assessments should be provided to the Sponsor to allow independent review if deemed appropriate.

4.5.1.6 [redacted]

[redacted]

4.5.1.7 Ophthalmology Examination

All patients will undergo ophthalmologic examination at the following timepoints:

- Screening
- Cycle 2, Day 1 ±1 week
- On Day 1 of Cycles 5, 8 and 11 (every 3 treatment cycles) ±2 weeks
- On Day 1 of Cycles 15, 19, 23 (every 4 treatment cycles) ±2 weeks
- On Day 1 of Cycles 29, 35, 41, 47, etc. (every 6 treatment cycles) ±2 weeks
- End-of-study-treatment visit. If an ophthalmologic evaluation has been performed within the last 12 weeks of this visit, the ophthalmologic examination does not need to be performed during this visit.

All patients will need to undergo baseline ophthalmologic examination to evaluate for evidence of retinal pathology that is considered a risk factor for neurosensory retinal detachment, RVO or neovascular macular degeneration. Ophthalmologic examination must be performed by a qualified ophthalmologist. Risk factors for RVO include elevated serum cholesterol, hypertriglyceridemia, hyperglycemia, hypertension, and glaucoma. Patients with such conditions will be excluded from the study as detailed in the inclusion/exclusion criteria (Sections 4.1.1 and 4.1.2).

Baseline ophthalmologic examination will include visual acuity testing, slit lamp ophthalmoscopy, indirect ophthalmoscopy and spectral domain optical coherence tomography (OCT; spectral domain OCT, if not available, may be substituted with time-domain OCT).

Serial surveillance ophthalmologic examination will comprise visual acuity testing, slit lamp ophthalmoscopy, indirect ophthalmoscopy, and OCT (spectral or time domain). Ophthalmologic examination does not need to be performed at end-of-study-treatment visit if one has been performed within the last 12 weeks and there were no clinically significant findings and/or changes from prior exam.

4.5.1.8 Laboratory Assessments

All screening laboratory assessments should be obtained within 14 days prior to initiation of study drug on Cycle 1, Day 1.

Note: If screening laboratory specimens are collected within 7 days of the Cycle 1 Day 1 visit, they do not have to be repeated at Day 1.

Laboratory assessments required on the study are as follows:

- Hematology: Hemoglobin, WBC count, neutrophil count, lymphocyte count, and platelet count.
- Chemistry (including liver function tests): Fasting glucose (screening only), BUN, creatinine, albumin, CPK, potassium, magnesium, ALT, AST, total bilirubin, and alkaline phosphatase; thyroid stimulating hormone (TSH), free T3, free T4 (Cohorts II and III only),
- Pregnancy test and follicle-stimulating hormone (FSH): All women of childbearing potential (as defined in inclusion criteria) will have a serum pregnancy test at screening. Women who have had amenorrhea for > 12 months but < 2 years should have a screening of FSH.
- Urinalysis (screening only) Specific gravity, pH, glucose, protein, ketones, and blood.
- Serology (for Cohorts II and III only)

  HIV (tested prior to inclusion into the study)

  HIV-positive patients will be excluded from study participation.

  HBV serology (HBsAg, antibody to HBsAg [anti-HBs], anti-HBc)

  HBV DNA testing is required on or before Cycle 1 Day 1 if the patient has negative serology for HBsAg and positive serology for anti-HBc.

  HCV serology (anti-HCV)

These laboratory assessments will be analyzed at the study site's local laboratory.

Blood and tumor tissue samples for [redacted] pharmacogenomics sample, and PK samples will be sent to one or several Roche-designated central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

4.5.1.9 Pharmacokinetic Assessments

Plasma concentrations of paclitaxel and cobimetinib (Cohort I) and paclitaxel/nab-paclitaxel, cobimetinib, and serum concentrations of atezolizumab (Cohorts II and III) will be measured in a BioAnalytical Labs using validated assays. Venous blood samples will be collected according to the schedule of PK assessments (see Appendix 2).

On the days of PK sample procurement, patients are not required to fast. The time of the last dose prior to collection of the PK sample must be recorded in the eCRF.

The procedures for the collection, handling, and shipping of PK samples can be found in the laboratory manual.

Residual PK samples will be retained for any additional work such as further method development, validation and characterization if required. Samples will be stored for up to 5 years after the date of final clinical study report has been completed.

4.5.1.10 Cardiac Evaluation–ECGs and Evaluation of Left Ventricular Ejection Fraction

ECGs

ECG recordings will be obtained in triplicate at screening, as outlined in the schedule of assessments (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate (HR), including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

As the QT interval has an inverse relationship to HR, the measured QT intervals are generally corrected for HR in order to determine whether they are prolonged relative to baseline. Various correction formulae have been suggested, of which Bazett's and Fridericia's corrections are the most widely used. Bazett's correction overcorrects at elevated HRs and under corrects at HRs below 60 beats per minute and hence is not an ideal correction. Fridericia's correction is more accurate than Bazett's correction in patients with such altered HRs. Therefore, for QT interval evaluation in this protocol, the Fridericia's correction will be utilized:

$$\text{Fridericia's correction, } QTcF = QT / RR^{0.33}$$

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

If at a particular post-dose timepoint the mean QTcF is >500 ms and/or >60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 4.6.2. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

Evaluation of Left Ventricular Ejection Fraction

Although cobimetinib has not been shown to be associated with reduction in LVEF, there is a potential for MEKi to result in reductions in LVEF (Flaherty et al. 2012).

All patients will undergo evaluation of LVEF by ECHO or MUGA scan at the following timepoints:

- Screening
- Cycle 2, Day 1 ±1 week
- On Day 1 of every three treatment cycles there after starting with Cycle 5
- Treatment discontinuation visit
- All patients who restart treatment with a reduced dose of cobimetinib because of a decrease in LVEF should have LVEF measurements taken after approximately 2 weeks, 4 weeks, 10 weeks, and 16 weeks and then resume monitoring LVEF every 3 cycles (see Table 15).

Evaluation of LVEF does not need to be performed at end-of-study treatment visit if an evaluation has been performed within the last 12 weeks and there are no clinically significant findings and/or changes from baseline. Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment.

Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly encouraged that the same laboratory and operator perform ECHO/MUGA scans for each individual patient.

Investigators must be aware of local institution regulations regarding repeat MUGA scans. The repeat administration of radioisotopes is limited in some nuclear medicine laboratories and some patients in this study could require monitoring on 4 occasions or more.

All images for evaluation of left ventricular function may be collected for independent review.

[redacted]

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. All signed ICFs will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before the patient is randomized to study treatment. Screening assessments must be completed for all patients in both the safety run-in and expansion stages. Unless otherwise specified, screening and pretreatment tests and evaluations will be performed within 28 days of randomization. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to randomization may be used, and such tests do not need to be repeated for screening.

For a complete description of study assessments, refer to Section 4.5.1 and Appendix 1.

The following assessments will be performed at screening:

- Informed consent
- Medical history and demographics
- Concomitant medications
- Complete physical examination, ECOG Performance Status, height, weight, and vital signs.
- Hematology, serum chemistries, including fasting blood glucose and lipid panel, liver function tests (LFTs), and urinalysis
- Serum pregnancy test, FSH, if applicable 7 days prior to Cycle 1 Day 1
- ECG and evaluation of left ventricular function with either ECHO or MUGA
- Baseline complete ophthalmologic evaluation that includes visual acuity testing and indirect ophthalmoscopy
- CT or MRI of the head to be performed within 6 weeks prior to Cycle 1 Day 1
- Bone scan to be performed within 6 weeks prior to Cycle 1 Day 1
- Archival and/or baseline tumor biopsy (within 28 days of Cycle 1 Day 1). See Section 4.5.1.6.

The following assessments are required on Cycle 1, Day 1 (prior to administration of study treatment):

- Randomization with the IxRS (can be done up to 72 hours prior to Cycle 1 Day 1) – expansion stage patients only
- [redacted]
- Vital signs, weight, physical examination
  Note: If vital signs and physical examination are assessed within 7 days of the Cycle 1 Day 1 visit, they do not have to be repeated at Day 1.
- Hematology, serum chemistries, and LFTs
  Note: If screening laboratory specimens are collected within 7 days of the Cycle 1, Day 1 visit, they do not have to be repeated at Day 1.
- [redacted]
- Dispense diary for drug accountability

Please see Appendix 1 for the schedule of screening and pretreatment assessments.

4.5.2.2 Assessments during Study

Assessments scheduled on the day of study drug administration should be performed prior to study drug dosing, unless otherwise specified. Unless otherwise specified, assessments that are done weekly should be performed within a ±2 days window. Assessments that are performed monthly should be performed within a window of ±3 days.

[redacted]

For a complete description of study assessments, refer to Section 4.5.1 and Appendix 1.

The following assessments will be performed during the study as indicated in the schedule of assessments (Appendix 1):

- Interval medical history including documentation of new or worsening adverse events and concomitant medications
- Physical examination
- ECOG Performance Status
- Vital signs
- Hematology
- Serum chemistries and liver function tests
- Urine pregnancy test
- Evaluation of left ventricular function with either ECHO or MUGA
- Ophthalmologic evaluation. See Section 4.5.1.7.

- Tumor assessments: contrast-enhanced CT or MRI of the chest, abdomen, and pelvis
- PK assessments for cobimetinib, atezolizumab, paclitaxel, and nab-paclitaxel (only cobimetinib and atezolizumab PK samples are needed for the expansion stage)
- [redacted]
- On treatment biopsy (optional). See Section 4.5.1.6.
- [redacted]
- Drug accountability

Please see Appendix 1 for the Schedule of Assessments performed during the treatment period.

4.5.2.3 End-of-Study-Treatment Visit

Patients may remain on study treatment until disease progression as assessed by the investigator, unacceptable toxicity, or study termination by the Sponsor. The following are required as part of the end-of-study treatment visit:

- Interval medical history including documentation of new or worsening adverse events
- Concomitant medications
- Physical examination and vital signs
- Ophthalmologic evaluation, if one was not performed within the last 12 weeks
- ECG
- Evaluation of left ventricular function if one was not performed within the last 12 weeks.
- [redacted]
- [redacted]
- Drug accountability
- Tumor assessments*: contrast-enhanced CT or MRI of the chest, abdomen, and pelvis

* The visit at which the tumor assessment shows PD may be used as the treatment discontinuation visit.

4.5.2.4 Post-study Treatment and Survival Follow-Up Assessments

Please see Appendix 1 for the Schedule of Assessments performed during follow-up. Upon study treatment discontinuation or withdrawal from study treatment, patients are required to continue the following assessments as indicated in the Schedule of Assessments:

- Patients that have discontinued study treatment for reasons *other* than disease progression should continue to have tumor assessments until PD.
- Survival follow-up, including subsequent anti-cancer therapy information will be collected via telephone calls and/or clinic visits every 12 weeks until death.

All patients will be followed for survival information unless a patient requests to be withdrawn from follow up; this request must be documented in the patient's medical record and signed by the investigator. If the patient withdraws from study follow-up, the study staff may use a public information source (such as county records) to obtain information about survival status only.

4.5.2.5 Adverse Event Follow-Up

Ongoing adverse events thought to be related to cobimetinib, atezolizumab, and/or paclitaxel/nab-paclitaxel will be followed until the event has resolved to baseline grade, is assessed by the investigator as stable, new subsequent anti-tumor treatment is initiated, the patient is lost to follow up or withdraws consent, or when it has been determined that the study treatment or participation is not the cause of the adverse event.

After completion of study treatment, adverse events should be followed as outlined in Sections 5.5 and 5.6.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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 study treatment at any time. Reasons for withdrawal from study treatment may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance with the study and/or study procedures (e.g., dosing instructions, study visits)

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 are randomized and receive any study treatment will not be replaced.

4.6.2 Study Treatment Discontinuation

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

- Disease progression per investigator assessment using RECIST v1.1
- Intolerance of study treatment despite undergoing protocol defined dose reduction
- Pregnancy
- Withdrawal of consent
- Initiation of other anti-cancer therapy

Patients who discontinue study drug for any reason will be asked to return to the clinic for end-of-study-treatment visit and undergo follow-up assessments (see Section 4.5.2.3). The primary reason for study drug discontinuation should be documented on the appropriate eCRF. Patients discontinuing study treatment for reasons other than disease progression should continue to have tumor assessments until PD. Patients who discontinue study drug in the expansion stage will not be replaced.

4.6.3 Study and Site Discontinuation

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

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

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

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 Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP)
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

In the United States, atezolizumab is approved for the treatment of locally advanced or metastatic urothelial bladder cancer who have progressed during or following platinum-containing chemotherapy and for metastatic non–small cell lung cancer who have progressed during or following platinum-containing chemotherapy and if harboring an EGFR or ALK aberration have progressed on U.S. Food and Drug Administration-approved therapy for these aberrations. Atezolizumab is currently in clinical development for other indications, and the safety plan is based on results from nonclinical studies, completed and ongoing clinical studies, and published data on similar molecules. Please refer to the atezolizumab Investigator's Brochure for a complete summary of safety information.

Cobimetinib (for use with vemurafenib) is approved in the United States and European Union as well as other countries for the treatment of metastatic melanoma. The safety plan for patients in this study is based on clinical experience with cobimetinib in completed and ongoing studies. The anticipated important safety risks for cobimetinib are outlined below. Please refer to the cobimetinib Investigator's Brochure for a complete summary of safety information.

While a considerable amount of safety data for cobimetinib has already been generated, clinical development is ongoing and therefore, the entire safety profile continues to evolve. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

5.1.1 Risks Associated with Cobimetinib

Information related to risks attributed to cobimetinib is based on safety data from Phase III Study [redacted] (cobimetinib plus vemurafenib), Phase Ib Study NO25395 (cobimetinib plus vemurafenib), and Phase I Study MEK4592g (cobimetinib monotherapy). For further information regarding clinical safety, please refer to the current cobimetinib Investigator's Brochure.

5.1.1.1 Important Identified Risks Associated with Cobimetinib

Hemorrhage

Hemorrhage, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with cobimetinib. In clinical studies with cobimetinib, events of cerebral hemorrhage, gastrointestinal tract hemorrhage, reproductive tract hemorrhage, and hematuria, have been reported.

In the Phase III Study [redacted] Grade 1–4 hemorrhagic events were reported in [redacted] of patients treated with cobimetinib plus vemurafenib, and in [redacted] of patients treated with placebo plus vemurafenib. The majority of hemorrhagic events were Grade 1 or 2 and non-serious. Grade 3–4 hemorrhage events were reported in [redacted] of patients

receiving cobimetinib plus vemurafenib and 0.8% of patients receiving placebo plus vemurafenib.

Caution should be used in patients with additional risk factors for bleeding, such as brain metastases, and/or in patients that use concomitant medications that increase the risk of bleeding (including antiplatelet or anticoagulant therapy).

Instructions for dose modification for hemorrhage events are included in Table 11 in Section 5.1.6.6.

Serous Retinopathy

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK-inhibitors, including cobimetinib (Flaherty et al. 2012). Manifestations of serous retinopathy include visual disturbances, findings of retinal detachment, and retinopathy. Serous retinopathy events may also be asymptomatic.

Serous retinopathy has been characterized in the Phase III Study [redacted]. The study incorporated prospective serial ophthalmic examinations for all enrolled patients. Serous retinopathy was reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib [redacted], and approximately half the events were asymptomatic Grade 1 events. Few patients treated with cobimetinib plus vemurafenib experienced Grade ≥ 3 ocular events [redacted] the majority of these were managed with dose modification of both cobimetinib and vemurafenib.

To address serous retinopathy with cobimetinib treatment, all patients are required to undergo a baseline ophthalmologic examination to assess for history or evidence of retinal pathology that is considered to be a risk factor for or indicative of neurosensory retinal detachment, central serous chorioretinopathy, neovascular retinopathy, or retinopathy of prematurity. Patients will also undergo ophthalmologic examinations at specified time points throughout the study (see Appendix 1). Details regarding baseline and subsequent ophthalmologic examinations are provided in Appendix 1.

Guidelines for management of patients who develop Grade ≥ 2 visual disorders or retinopathy are provided in Section 5.1.6.7.

Left Ventricular Dysfunction

Decrease in left ventricular ejection fraction from baseline has been reported in patients receiving cobimetinib. Left ventricular dysfunction may occur with signs and symptoms of cardiac failure, or reduction in left ventricular ejection fraction events may be asymptomatic.

Left ventricular dysfunction has been characterized in the Phase III Study [redacted]. The study incorporated prospective serial left ventricular ejection fraction evaluation in all patients. With active surveillance, measured reductions in left ventricular ejection

fraction were observed more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib [redacted] respectively, of Grade 2 or 3 decrease). Of the patients treated with cobimetinib plus vemurafenib, [redacted] had symptomatic reduction in left ventricular ejection fraction and the remaining patients were asymptomatic. Most left ventricular ejection fraction reduction events in patients on cobimetinib plus vemurafenib [redacted] improved or resolved with management according to the dose-modification guidelines (see Section 5.1.6.8).

Rhabdomyolysis and CPK Elevations

Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as when administered with other agents. The majority of CPK elevation events were reported as asymptomatic, non-serious, and resolved with or without study drug interruption. [redacted] rhabdomyolysis was reported in the Phase III Study [redacted] (cobimetinib plus vemurafenib), and rhabdomyolysis has been reported in postmarketing experience.

In Study [redacted], elevated CPK was reported as an adverse event more frequently in patients treated with cobimetinib plus vemurafenib [redacted] than placebo plus vemurafenib [redacted]

CPK will be monitored at baseline and monthly during treatment or as clinically indicated. Instructions for Dose Modification for elevated CPK and rhabdomyolysis are included in Table 17 in Section 5.1.6.13.

Photosensitivity (when Administered with Vemurafenib)

No evidence of phototoxicity has been observed with cobimetinib as a single agent. However, photosensitivity was observed on the [redacted] trial with a higher frequency in the cobimetinib plus vemurafenib arm versus placebo plus vemurafenib arm [redacted]. The majority of events were Grades 1 or 2, with Grade ≥ 3 events occurring in [redacted] of patients in the cobimetinib plus vemurafenib arm versus [redacted] in the placebo plus vemurafenib arm. Grade ≥ 3 photosensitivity events in the cobimetinib plus vemurafenib arm were primary treated with topical medication in conjunction with interruption of study agents. Refer to Section 5.1.5.3 for photosensitivity management guidelines.

Pneumonitis

Events of pneumonitis have been reported in cobimetinib clinical studies. Most reported events were considered non-serious and low-severity grade. In the Phase III Study [redacted] pneumonitis events were reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib [redacted] There were no reported Grade ≥ 3 events in either study arm. Serious events were reported in [redacted] patients [redacted] treated with cobimetinib plus vemurafenib.

5.1.1.2 Potential Risks Associated with Cobimetinib

Liver Laboratory Abnormalities and Severe Hepatotoxicity

Liver laboratory test abnormalities, including increases in ALT, AST, and alkaline phosphatase have been reported as adverse events and serious adverse events in patients treated with cobimetinib plus vemurafenib.

In the Phase III Study [redacted], liver laboratory test abnormalities reported as Grade ≥ 3 adverse events occurred more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib [redacted]

Generally, elevations in liver laboratory tests were managed effectively with dose modification guidelines. In both study arms, the majority of Grade ≥ 3 liver laboratory test abnormalities resolved.

Impaired Female Fertility and Developmental Toxicity

There is a potential for effects on fertility and embryo-fetal toxicity based on results from nonclinical studies.

While no dedicated fertility studies have been conducted with cobimetinib in animals, degenerative changes observed in reproductive tissues included increased apoptosis/necrosis of corpora lutea and seminal vesicle, epididymal and vaginal epithelial cells in rats, and epididymal epithelial cells in dogs. These changes were reversible upon discontinuation of cobimetinib administration.

In a dedicated embryo-fetal toxicity study, cobimetinib produced fetal toxicity (resorptions and reductions in fetal weight), and teratogenicity (malformations of the great vessels and skull) at similar systemic exposures to those observed in patients administered the 60 mg dose.

5.1.1.3 Other Risks with Cobimetinib

Rash

In the Phase III Study [redacted], combined rash events of all types and grades were reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib [redacted] although Grade ≥ 3 events (approximately [redacted] of patients) and types of rash reported were similar between study arms. Specific events in patients treated with cobimetinib plus vemurafenib included rash [redacted] and rash maculo-papular [redacted]

Generally, Grade ≥ 3 rash events were effectively managed with dose modification guidelines. In Study [redacted], approximately [redacted] of Grade ≥ 3 rash events resolved in both arms.

Gastrointestinal Toxicity

A range of gastrointestinal adverse events, including nausea, vomiting, and diarrhea, have been reported in all cobimetinib studies in adult cancer patients.

In the Phase III Study [redacted], diarrhea was the most common adverse event reported. Diarrhea events of all severity grades were reported in [redacted] of patients and Grade 3 or 4 events were reported in [redacted] of patients treated with cobimetinib plus vemurafenib versus [redacted] (Grade 3) and [redacted] (Grade 4) in the patients treated with placebo plus vemurafenib. No Grade 5 events of diarrhea have been reported. Serious adverse events of diarrhea were reported in [redacted] of patients treated with cobimetinib plus vemurafenib.

Nausea and vomiting have been reported in association with cobimetinib. Most nausea and vomiting events were considered non-serious and low-severity grade. In the Phase III Study [redacted] nausea and vomiting events were reported more frequently in the active cobimetinib arm than the control arm [redacted] However, of patients treated with cobimetinib plus vemurafenib, few experienced Grade 3 events [redacted]

In the Phase I single-agent study (MEK4592g), all grades of nausea and vomiting were both reported as 33.9% with 0.9% reported for Grade ≥ 3 nausea and none reported for vomiting.

The combination of diarrhea, nausea, and vomiting has the potential to contribute to clinically significant volume depletion/dehydration from the combination of fluid losses with decreased oral intake. In the majority of cases, diarrhea has been effectively managed with antidiarrheal agents and supportive care. Routine antiemetic prophylaxis is not recommended.

Hypersensitivity

There have been few reports of hypersensitivity and/or anaphylaxis in clinical trials with patients who have been exposed to cobimetinib monotherapy or cobimetinib when used with other agents. These have appeared to be isolated reports, and in some cases, occurred in patients with histories of drug allergies. Thus, the relationship of cobimetinib to these events is unclear.

In the Phase III Study [redacted], Grade 3 hypersensitivity events were reported in [redacted] in the cobimetinib and vemurafenib arm compared with no such events in the placebo plus vemurafenib arm. All events required hospitalization and treatment with steroids.

Investigators should promptly evaluate and treat patients who are suspected of experiencing a hypersensitivity reaction.

5.1.2 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as infusion-related reactions and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, *and nephritis*. In addition, systemic immune activation is a potential risk associated with atezolizumab. Refer to the atezolizumab Investigator's Brochure *and Appendix 12* for a detailed description of anticipated safety risks for atezolizumab.

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is a potential risk when administered in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

5.1.3 Anticipated Overlapping Adverse Events for Cobimetinib and Atezolizumab

Special consideration is given to areas of potential overlapping toxicity based on data from previous clinical experience with each compound individually or with other molecules. Potential overlapping toxicities of cobimetinib and atezolizumab include dermatologic reactions, ocular toxicity, hepatic toxicity, liver laboratory abnormalities, pneumonitis, and gastrointestinal toxicity. Refer to the Atezolizumab Investigator's Brochure and the Cobimetinib Investigator's Brochure for details regarding these adverse events. Patients treated with cobimetinib and atezolizumab should be closely monitored for evidence of overlapping and/or potentiation of these and any other acute toxicities. If any evidence of overlapping and/or potentiation of the below toxicities is observed, patients should receive maximal supportive care as clinically indicated. Management guidelines for these potential overlapping toxicities are included in Section 5.1.6.

5.1.4 Risks Associated with Paclitaxel and Nab-Paclitaxel

In clinical studies and post-marketing experience, paclitaxel and nab-paclitaxel have been associated with alopecia, myelosuppression (primarily neutropenia, anemia, thrombocytopenia), peripheral neuropathy, cranial nerve palsies, hypersensitivity reactions, pneumonitis, gastrointestinal events (i.e., nausea, vomiting, diarrhea), myalgia, arthralgia, cardiotoxicity (myocardial disorders, cardiac failure, angina, tachycardia, ventricular arrhythmia), cystoid macular edema, Stevens-Johnson syndrome/toxic epidermal necrolysis, sepsis, infusion site reactions/extravasation, hepatic toxicity (drug–induced liver injury), acute renal failure, hemolytic-uremic syndrome, and drug–induced lupus erythematosus.

Patients will be monitored for paclitaxel and nab-paclitaxel–related adverse events, including hematologic, gastrointestinal, hepatic toxicities, and peripheral neuropathy.

For more details regarding the safety profile of paclitaxel and nab-paclitaxel and management of specific adverse events, refer to the respective prescribing information. Other specific instructions can be found in Sections 4.4.2 and 4.4.3 for paclitaxel and nab-paclitaxel, respectively.

5.1.5 General Safety Mitigation Plan

5.1.5.1 Eligibility Criteria

Eligibility criteria promulgated for this study will guard the safety of patients in this trial. The exclusion criteria for safety will include (but are not limited to) the following: major surgical procedure or significant traumatic injury within 28 days prior to first dose of study drug treatment; pregnancy or breastfeeding; clinically significant cardiovascular disease; inadequate bone marrow, hepatic, or renal function; and other clinically significant comorbid conditions.

Patients at risk for study–emergent autoimmune conditions or with a prior diagnosis of autoimmune disease, patients with evidence of acute infections, and patients who have received a live-attenuated viral vaccine within 4 weeks of randomization are excluded from Cohorts II and III only (see Section 4.1.2 for additional details).

5.1.5.2 Safety Monitoring

Safety will be evaluated in this study through the monitoring of all adverse events and targeted laboratory assessments according to NCI CTCAE v4.0. Patients will be monitored every 2 weeks during the first 2 cycles, then prior to each subsequent cycle, and as necessary throughout the study. All patients from the safety run-in stage will continue to be followed for safety even after they complete the first cycle of therapy.

All treatment-emergent adverse events and serious adverse events, whether or not deemed treatment related, will be followed until they resolve or become stabilized, the patient is lost to follow up or withdraws consent, or it has been determined that the study treatment or participation is not the cause of the adverse event or serious adverse event.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries, liver function tests, and blood counts.

During the study, all patients will be closely monitored for the development of any adverse events, including signs or symptoms of autoimmune conditions and infection.

All serious adverse events and protocol-defined adverse events of special interest will be reported in an expedited fashion.

5.1.5.3 Monitoring and Management of Specific Toxicities and Conditions That May Arise with Cobimetinib Treatment

Any toxicities associated with, or possibly associated with cobimetinib administration should be managed with symptomatic treatment, dose interruptions (maximum allowable length of treatment interruption is 28 days), and/or dose reductions. Toxicity due to paclitaxel/nab-paclitaxel administration will be managed by symptomatic treatment and/or dose interruptions/reductions. There will be no dose escalations during this study.

Ocular Toxicity

All patients will undergo ophthalmologic examination at the following timepoints:

- Screening
- Cycle 2 Day 1 ± 1 week
- On Day 1 of Cycles 5, 8, and 11 (every 3 treatment cycles) ± 2 weeks
- On Day 1 of Cycles 15, 19, and 23 (every 4 treatment cycles) ± 2 weeks
- On Day 1 of Cycles 29, 35, 41, 47, etc. (every 6 treatment cycles) ± 2 weeks
- End of study treatment visit. If an ophthalmologic evaluation has been performed within the last 12 weeks of the treatment discontinuation visit, the ophthalmologic examination does not need to be performed during this visit.

Baseline and serial surveillance ophthalmologic examination will include visual acuity testing, indirect ophthalmoscopy, and spectral-domain optical coherence tomography (not required at baseline). Spectral-domain optical coherence tomography, if not available, may be substituted with time-domain optical coherence tomography.

Evaluation of Left Ventricular Function

All patients will undergo evaluation of left ventricular ejection fraction, either by echocardiogram or multigated acquisition scan at the following timepoints:

- Screening
- Cycle 2, Day 1 ± 1 week
- On Day 1 of every 3 cycles thereafter starting with Cycle 5
- On Day 1 of Cycles 15, 19, and 23 (every 4 treatment cycles) ± 2 weeks
- On Day 1 of Cycles 29, 35, 41, 47, etc. (every 6 treatment cycles) ± 2 weeks

- End-of-study-treatment visit
- All patients who restart treatment with a reduced dose of cobimetinib because of a decrease in left ventricular ejection fraction should have left ventricular ejection fraction measurements taken after approximately 2 weeks, 4 weeks, 10 weeks, and 16 weeks and then resume monitoring left ventricular ejection fraction every 3 cycles.

5.1.6 Management of Specific Adverse Events

Criteria for treatment modifications and guidelines for the management of toxicities attributable to atezolizumab, cobimetinib, paclitaxel and/or nab-paclitaxel are summarized below. These guidelines are not intended to replace clinical judgment or dictate care of individual patients.

5.1.6.1 Dose Reductions

Recommended dose reductions for cobimetinib, paclitaxel and/or nab-paclitaxel are provided in Table 7. No dose reductions are permitted for atezolizumab.

Table 7 Dose Reductions for Cobimetinib, Paclitaxel, and Nab-Paclitaxel

Dose Level[a]	Cobimetinib/Placebo[b]	Paclitaxel	Nab-paclitaxel[c]
Starting dose	60 mg	80 mg/m^2	100mg/m^2
First dose reduction	40 mg	65 mg/m^2	75 mg/m^2
Second dose reduction	20 mg	40 mg/m^2	50 mg/m^2
Third dose reduction	Discontinue	Not applicable	Discontinue

[a] If the patient continues to experience specified drug-related adverse events after second reduction, the treatment should be discontinued.

[b] Placebo is only applicable in Cohort I expansion stage.

[c] For hematological drug–related adverse events, dose reduction and discontinuation advice is provided in Section 5.1.6.9.

Dose reduction of each drug is independent of other drugs.

Dose reduction of each study drug is independent of the other study drug. Dose re-escalation is not allowed.

5.1.6.2 Atezolizumab Treatment Interruption

Atezolizumab treatment may be interrupted 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 > 105 days, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 105 days to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being

withheld for > 105 days if the Medical Monitor agrees that the patient is likely to derive clinical benefit.

5.1.6.3 General Guidelines for Management of Adverse Events

Table 8 provides general guidelines for management of adverse events that can be followed for all cohorts when guidelines for specific events or drugs are not provided in subsequent sections of the protocol or in the prescribing information.

Table 8 General Guidelines for Management of Adverse Events in All Cohorts

Event	Action to Be Taken
Grade 1 toxicity [a]	• No action required.
Grade 2 toxicity [a]	• No action required.
Grade 3 or 4 toxicity [a]	• Interrupt dosing of cobimetinib/placebo or paclitaxel/nab-paclitaxel or atezolizumab depending on the attribution of the toxicity, at the discretion of the investigator. During this time, treatment may continue with the other non-attributable treatment agent (i.e., cobimetinib/placebo, paclitaxel/nab-paclitaxel, and/or atezolizumab). • If the event resolves to Grade ≤ 1 within 28 days, restart dosing of the attributable drug (with cobimetinib decreased by 1 dose level and/or paclitaxel/nab-paclitaxel decreased by 1 dose level at investigator's discretion). If the event does not resolve to Grade ≤ 1 within 28 days, permanently discontinue the attributable drug. • If event resolves to Grade ≤ 1 within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. • If one drug is discontinued, dosing of the other drugs may continue at the discretion of the investigator. • If a Grade 4 event recurs (a second time), the attributable drug should be discontinued. If one drug is discontinued, dosing of the other drugs may continue at the discretion of the investigator. • For Grade ≥ 3 toxicities associated primarily with laboratory abnormalities only, study treatment may continue without interruption and/or dose reduction at the discretion of the investigator per institutional practice.
IRRs and anaphylaxis and hypersentivity reactions	• Guidelines for management of infusion-related reactions associated with atezolizumab are provided in Appendix 12. For anaphylaxis precautions, see Appendix 10. • For severe hypersensivity reactions attributed to any study treatment, permanently discontinue study treatment.

AE = adverse event; IRR = infusion-related reaction.

[a] General guidelines can be followed when drug management guidelines are not provided in Sections 5.1.6.11–5.1.6.16 or in the prescribing information.

5.1.6.4 Gastrointestinal Toxicity in Cohort I

Diarrhea is a common adverse event with cobimetinib and should be managed promptly.

Patients should be educated to recognize the early signs and symptoms of diarrhea and instructed to promptly contact the investigators if they develop diarrhea. Patients should be asked to be cognizant of the onset, duration, severity, and frequency of symptoms and the medications administered.

Educational materials will be provided to patients outlining the necessary guidance and anti-diarrheal medication should be available prior to starting study treatment to ensure prompt intervention at onset.

For Cohort I patients, diarrhea should be managed according to the guidelines in Table 9. For patients in Cohorts II and III, diarrhea should be managed according to the guidelines in Section 5.1.6.16 and Table 21.

Prophylaxis for diarrhea may be used at the investigator's discretion if allowed by local guidance.

Table 9 Guidelines for Managing Cobimetinib-Associated Gastrointestinal Toxicity in Cohort I

Event	Management
Gastrointestinal events: general guidance	• Patients should receive maximum supportive care per institutional guidelines. • All events of diarrhea should be thoroughly evaluated for more common etiologies other than drug induced effects. • Administer anti-diarrheal agents and other maximal supportive care per institutional guidelines such as: at the first report of watery diarrhea or loose stool, initiate maximal anti-diarrheal treatment and supportive care (see below). • Maintenance loperamide dosing should be considered for any ongoing and intermittent Grade 1 diarrhea. • Suggested regimen: – Loperamide: Initiate dose with 4 mg, then 2 mg after each loose stool until diarrhea is controlled (no loose stools for 24 hours) after which the dosing of loperamide should be reduced to meet individual requirements. The maximum daily dose is 16 mg and clinical improvement is usually observed within 48 hours. – If Grade ≤ 2 diarrhea persists after 48 hr total treatment with loperamide, consider adding second-line agents (e.g., Lomotil® [diphenoxylate and atropine], octreotide, budesonide, tincture of opium or codeine). • Oral supplementation: – Initiate oral supplementation of potassium and/or magnesium if serum levels are < LLN. – Consider oral rehydration therapy (e.g., Pedialyte®) for Grade ≥ 1 diarrhea or vomiting. • Dietary modifications: – Stop all lactose-containing products and eat small meals. – The BRAT (banana, rice, apples, toast) diet, without fiber (other vegetables and fruits), may be helpful. – Encourage adequate hydration with salt-containing liquids, such as broth or Gatorade. • Prophylaxis for diarrhea: – Suggested regimen is loperamide (2 mg twice a day or 4 mg once a day) if allowed by local guidance and based on clinical judgement at any given time during the study.

Table 9 Guidelines for Managing Cobimetinib-Associated Gastrointestinal Toxicity in Cohort I (cont.)

Event	Management
Diarrhea, Grade 1	• Continue cobimetinib/placebo and paclitaxel. • Initiate anti-diarrheal therapy. • Initiate supportive care (encourage adequate oral hydration, oral supplementation, and dietary modification per general guidance above) and monitor patient closely.
Diarrhea, Grade 2	• Continue cobimetinib/placebo and paclitaxel. • Initiate anti-diarrheal therapy. **If event resolves to Grade 1 or better within 48 hours:** • The same cobimetinib/placebo dose is permitted with consideration of maintenance loperamide dosing at the investigator's discretion. Investigators may reduce cobimetinib by one dose level if deemed appropriate (see Table 7). • Initiate supportive care (encourage adequate oral hydration, oral supplementation, and dietary modification per general guidance above) and monitor patient closely. **If event does <u>not</u> resolve within 48 hours to ≤Grade 1:** • Withold cobimetinib/placebo and paclitaxel. • Consider introducing second-line anti-diarrheal agents (e.g., Lomotil (diphenoxylate and atropine), octreotide, budesonide, tincture of opium or codeine). • Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. • Two dose level reductions are allowed for diarrhea; if cobimetinib is still not tolerated then cobimetinib should be permanently discontinued. • Paclitaxel may be continued at the investigator's discretion and should be managed as per product label. If Grade 2 diarrhea recurs, see below.

Table 9 Guidelines for Managing Cobimetinib-Associated Gastrointestinal Toxicity in Cohort I (cont.)

Event	Management
Diarrhea, Grade 2 that recurs or Grade 3	• Withhold cobimetinib/placebo and paclitaxel. • Initiate anti-diarrheal therapy, maximum supportive care (encourage adequate oral hydration, oral supplementation, and dietary modification per general guidance above), and monitor patient closely. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib/placebo with dose reduced by one level. If not, permanently discontinue cobimetinib/placebo. • Two dose level reductions are allowed for diarrhea; if cobimetinib/placebo is still not tolerated then cobimetinib should be permanently discontinued. • Paclitaxel may be continued at the investigator's discretion and should be managed as per product label • Diarrhea prophylaxis such as loperamide is allowed at the investigators discretion. • Investigate etiology, referring patient to GI specialist for evaluation.
Diarrhea, Grade 4	• Permanently discontinue cobimetinib/placebo, interrupt paclitaxel and contact Medical Monitor. • Initiate maximum supportive care (encourage adequate oral hydration, oral supplementation, and dietary modification per general guidance above) and monitor patient closely. • Rule out bowel perforation. • Investigate etiology, referring patient to GI specialist for evaluation. • If event resolves to Grade 1 or better, paclitaxel may be continued at the investigator's discretion and should managed as per product label.

5.1.6.5 Grade ≥3 Hepatotoxicity, Rash, and CPK Elevations in Cohort I

General guidelines for the management of Grade ≥3 hepatotoxicity, rash, and CPK elevations in Cohort I (cobimetinib plus paclitaxel) are provided in Table 10.

Table 10 Guidelines for Management of Grade ≥ 3 Hepatotoxicity, Rash, and CPK Elevations in Cohort I

Event	Action to Be Taken
Liver laboratory test abnormalities Grade ≥3	• For Grade 3 ALT or AST elevation, cobimetinib/placebo may continue without interruption and/or dose reduction at the discretion of the investigator per institutional practice. • For Grade 4 ALT or AST elevation, hold cobimetinib/placebo dosing until Grade ≤ 1; Upon resolution of ALT or AST elevation to Grade ≤ 1, resume cobimetinib/placebo at 1 lower dose level. • If Hy's Law criteria (ALT or AST > 3 × ULN in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice, without initial findings of cholestasis (elevated serum alkaline phosphatase), and no other reason can be found to explain the combination of increased ALT/AST and total bilirubin, such as: liver metastasis; viral hepatitis A, B, or C; alcoholic and autoimmune hepatitis; other liver diseases; or exposure to other drugs known to cause liver injury) are met, or the ALT or AST elevation does not resolve to Grade ≤ 1 by 28 days, discontinue cobimetinib/placebo.[a]
Rash Grade ≥3	• Hold cobimetinib/placebo dosing until Grade ≤2. • Reduce cobimetinib/placebo by 1 dose level. If after restarting at reduced dose, the patient experiences skin toxicity Grade ≥3, hold cobimetinib until Grade ≤2 and then further reduce cobimetinib/placebo by another dose level. Permanently discontinue cobimetinib/placebo if restarting after second dose reduction, the patient experiences skin toxicity Grade ≥3. • Permanently discontinue cobimetinib/placebo if rash Grade ≥3 persists for >28 days despite adequate supportive care. [a]

AE = adverse event; CPK = creatine phosphokinase; GI = gastrointestinal; IV = intravenous; LLN = lower limit of normal; LFT= liver function test; NSAID = nonsteroidal anti-inflammatory drug; TNF = tumor necrosis factor; ULN = upper limit of normal.

[a] Patients who permanently discontinue study treatment must continue to have tumor assessments until disease progression (see Section 4.5.2.4).

Table 10 Guidelines for Management of Grade ≥ 3 Hepatotoxicty, Rash, and CPK Elevations in Cohort I (cont.)

Event	Action to Be Taken
Grade ≥ 3 CPK elevations	• Rule out cardiac cause (check ECG, serum cardiac troponin, and CPK-isoforms M and B fraction) and rule out rhabdomyolysis (clinical examination; serum creatinine, potassium, calcium, phosphorus, uric acid, and albumin; and urine myoglobin). Consider permanent discontinuation of cobimetinib if there is evidence of clinically significant cardiac injury or rhabdomyolysis. • Assess patient for any history of strenuous physical activity, blunt trauma, or recent intramuscular injections. • For Grade 3 CPK elevations that are asymptomatic and deemed not clinically significant, continue cobimetinib/placebo at current dose and schedule. Recheck CPK at least once a week. If CPK remains Grade 3 or decreases, continue cobimetinib/placebo at current dose and schedule. • For Grade 4 CPK elevations that are asymptomatic and deemed not clinically significant, hold cobimetinib/placebo and recheck CPK within 3 days. When CPK is Grade ≤3 within 4 weeks, cobimetinib/placebo (may be resumed with a dose reduction by 1 dose level on the same schedule (e.g., 60 mg to 40 mg). If CPK elevations do not improve to Grade ≤3 within 4 weeks following dose interruption, permanently discontinue cobimetinib treatment. • If Grade 4 CPK elevation recurs after 1 dose reduction, cobimetinib may be reduced by another dose level (e.g., 40 mg to 20 mg). Permanently discontinue cobimetinib/placebo if Grade 4 CPK elevation recurs after 2 dose reductions of cobimetinib/placebo.
Rhabdomyolysis or symptomatic CPK elevations	• Interrupt cobimetinib/placebo treatment. • If severity is improved by at least one grade and symptoms resolve within 4 weeks, restart cobimetinib/placebo at a dose reduced by 20 mg, if clinically indicated. • If rhabdomyoysis or symptomatic CPK elevations do not improve within 4 weeks, permanently discontinue cobimetinib/placebo treatment.

AE = adverse event; CPK = creatine phosphokinase; GI = gastrointestinal; IV = intravenous; LLN = lower limit of normal; LFT = liver function test; NSAID = nonsteroidal anti-inflammatory drug; TNF = tumor necrosis factor; ULN = upper limit of normal.

[a] Patients who permanently discontinue study treatment must continue to have tumor assessments until disease progression (see Section 4.5.2.4).

5.1.6.6 Hemorrhage (All Cohorts)

Hemorrhage has been reported with cobimetinib (see Section 5.1.1.1). See Table 11.

Table 11 Recommended Dose Modifications for Cobimetinib in Patients with Hemorrhage

Hemorrhage	
Grade 3 events	Interrupt cobimetinib treatment. There are no data on the effectiveness of cobimetinib dose modification for hemorrhage events. Clinical judgment should be applied when considering restarting cobimetinib treatment. Continue atezolizumab treatment.
Grade 4 hemorrhage or any grade cerebral hemorrhage	Interrupt cobimetinib treatment. Permanently discontinue cobimetinib for hemorrhage events attributed to cobimetinib. Continue atezolizumab treatment.

5.1.6.7 Visual Disorders (All Cohorts)

Any reported changes in vision or visual symptoms should be evaluated by an ophthalmologist. Guidelines for grading eye disorders per NCI CTCAE v4.0 are provided in Table 12.

Serous retinopathy is associated with cobimetinib. In clinical trials, most events were Grade 1 (asymptomatic) or 2 (symptomatic). Most events in clinical trials resolved or improved to asymptomatic Grade 1 following dose interruption or reduction. If serous retinopathy is diagnosed, cobimetinib should be withheld until visual symptoms improve to Grade $\leq$ 1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation.

Retinal vein occlusion has been reported in patients treated with MEK inhibitors other than cobimetinib.

Cobimetinib–associated ocular toxicity should be managed according to the guidelines in Table 13.

Uveitis or episcleritis and other immune–mediated ocular disease may be associated with atezolizumab and may be treated with topical corticosteroid eye drops. Atezolizumab should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

Atezolizumab–associated ocular toxicity should be managed according to the guidelines in Table 14 and Appendix 12.

Table 12 National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 Eye Disorders – Other, Specify

Grade	Description
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL
3	Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL
4	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye

ADL = activity of daily living.

For visual symptoms ≥ Grade 2:

- Interrupt cobimetinib.
- Consult ophthalmology and undergo complete ophthalmologic examination, which includes visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography
- If **neurosensory retinal detachment** is diagnosed, cobimetinib dosing should be interrupted until symptoms improve to Grade 1. Then cobimetinib should be dose reduced by 1 dose level when restarting. If visual symptoms of Grade ≥ 2 recur despite 2 dose level reductions, cobimetinib should be permanently discontinued. Paclitaxel dosing may continue.
- If retinal vein occlusion, neurosensory retinal detachment or uveitis/iritis are NOT identified:
  - and visual symptoms have **not resolved** to Grade 1 or less (with the continued use of local / non-invasive supportive care) within 28 days, then discontinue cobimetinib permanently
  - and visual symptoms have **resolved** to Grade 1 or less (with the continued use of local / non-invasive supportive care) within 28 days, resume use of cobimetinib at current doses
  - If visual symptoms of Grade ≥ 2 (despite the optimal use of local / non-invasive supportive care) recur, cobimetinib should be dose reduced by 1 level. If visual symptoms of Grade ≥ 2 recurs despite 2 dose level reductions of cobimetinib, and maximal supportive care, cobimetinib should be permanently discontinued

Table 13 Guidelines for Managing Cobimetinib-Associated Serous Retinopathy and Retinal Vein Occlusion for Cohorts I, II and III

Description	Management
Serous retinopathy Severity grade assessment based on NCI CTCAE v4 "Eye Disorders – Other" scale [a-d]	Serous retinopathy, Grade 1 [a] or 2 [b] (tolerable): • Continue cobimetinib and atezolizumab without dose change. • Continue ophthalmology follow-up as clinically indicated. Serous retinopathy, Grade 2 [b] (intolerable) or 3/4 [c,d]: • Interrupt cobimetinib until Grade ≤ 1. • Continue atezolizumab as clinically indicated. • Consult ophthalmology and undergo complete ophthalmologic examination, which includes visual acuity testing, intra-ocular pressure measurements, slit lamp ophthalmoscopy, indirect ophthalmoscopy, visual field, and OCT. Consider a fluorescein angiogram and/or indocyanine green angiogram, if clinically indicated. • Cobimetinib should be dose reduced by 1 dose level when restarting. • Consider permanent discontinuation of cobimetinib if serous retinopathy recurs despite 2 dose level reductions
Retinal vein occlusion Any grade	• If RVO (any grade) is diagnosed, cobimetinib dosing should be permanently discontinued and RVO treated per institutional guidelines. • Continue atezolizumab.

ADL = activities of daily living; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; RVO = retinal vein occlusion; OCT = optical coherence tomography.

[a] Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

[b] Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.

[c] Grade 3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL.

[d] Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye.

Table 14 Guidelines for Managing Atezolizumab–Associated Ocular Toxicity (Immune–Mediated Ocular Disease) for Cohorts II and III

Description	Management
Potential immune-related ocular toxicity (e.g., uveitis, iritis, episcleritis, or retinal events)	Follow guidelines provided in Appendix 12. Continue cobimetinib. Consult ophthalmologist.

5.1.6.8 Reduction in Left Ventricular Ejection Fraction (All Cohorts)

Decreased left ventricular ejection fraction has been seen with cobimetinib (see Section 5.1.1.1). Refer to Table 15 for guidelines for management of left ventricular ejection fraction. Permanent discontinuation of cobimetinib treatment should be considered if cardiac symptoms are attributed to cobimetinib and do not improve after temporary interruption.

Table 15 Recommended Dose Modifications for Cobimetinib and Atezolizumab in Patients with Left Ventricular Ejection Fraction Decrease from Baseline

Patient	LVEF value	Recommended action with cobimetinib/placebo and atezolizumab	LVEF value following treatment break	Recommended cobimetinib daily dose
Asymptomatic (see Appendix 7)	≥50% (or 40%–49% and <10% absolute decrease from BL)	Continue cobimetinib and atezolizumab at current dose	N/A	N/A
	<40% (or 40%–49% and ≥10% absolute decrease from BL)	Interrupt cobimetinib/placebo treatment for 2 wks. Continue atezolizumab as clinically indicated.	<10% absolute decrease from BL	First occurrence: 40 mg
				Second occurrence: 20 mg
				Third occurrence: permanent discontinuation
			<40% (or ≥10% absolute decrease from BL)	Permanent discontinuation
Symptomatic	N/A	Interrupt cobimetinib/placebo treatment for 4 wks. Consider withholding atezolizumab. Discuss with Medical Monitor regarding resumption of atezolizumab. Cardiology consultation is strongly recommended.	Asymptomatic and <10% absolute decrease from BL	First occurrence: 40 mg
				Second occurrence: 20 mg
				Third occurrence: permanent discontinuation
			Asymptomatic and <40% (or ≥10% absolute decrease from BL)	Permanent discontinuation
			Symptomatic regardless of LVEF	Permanent discontinuation

BL=baseline; LVEF=left ventricular ejection fraction; N/A=not applicable.

5.1.6.9 Neutropenia and/or Thrombocytopenia (All Cohorts)

Addition of hematopoietic growth factors is allowed. Patients should be counseled as to the risk of fever and infection and to the importance of contacting their treating physician immediately if these conditions occur, so that they can be promptly and appropriately managed.

If a dose delay is required as a result of neutropenia at any grade, patients should receive prophylactic granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor per institutional standards.

Patients who permanently discontinue study treatment must continue to have tumor assessments until disease progression (see Section 4.5.2.4).

Dosage modification guidelines for neutropenia and/or thrombocytopenia attributable to paclitaxel or nab-paclitaxel are outlined below.

Modification and Management of Hematologic Toxicity Related to Paclitaxel:

- Grade 2 neutropenia or thrombocytopenia: Paclitaxel may be administered at the previous dose when ANC has recovered to ≥ 1500/μL and when the platelet count has recovered to ≥ 100,000/μL. If the hematologic criteria do not recover within 14 days, the paclitaxel dose should be reduced (see Table 7).
- Grade ≥ 3 neutropenia or thrombocytopenia: Paclitaxel should be held, but the patient may continue the cobimetinib or placebo and atezolizumab. Dose for subsequent paclitaxel treatments should be reduced by one dose level (see Table 7). Following a treatment delay of 4 weeks, if recovery to ANC of ≥ 1500/μL or if recovery to platelet count of ≥ 100,000/μL does not occur before the next scheduled paclitaxel dose, the patient should permanently discontinue paclitaxel treatment but may continue the cobimetinib or placebo and atezolizumab*.
- Febrile neutropenia (ANC < 1000/μL and fever ≥ 38.5°C [101°F]): Paclitaxel should be held until adequate recovery and for up to 4 weeks. If Day 1 of paclitaxel is held, the patient can continue to receive the cobimetinib or placebo and atezolizumab. If the neutropenia recovers to ANC ≥ 1500/μL within 4 weeks, paclitaxel should be reduced by one level. Following a treatment delay of up to 4 weeks, if recovery to ANC of ≥ 1500/μL does not occur, the patient will permanently discontinue paclitaxel treatment and may continue the cobimetinib or placebo and atezolizumab*.

Modification and Management of Hematologic Toxicity Related to Nab-Paclitaxel:

- In general, ANC must be ≥ 1500/μL and platelet count must be ≥ 100,000/μL on Day 1 of each cycle. When nab-paclitaxel is administered on Day 1, it should not be administered on Days 8 or 15 of the cycle unless ANC ≥ 500 cells/μL and platelets ≥ 50,000 cells/μL. In certain situations, a cycle may begin with administration of atezolizumab/placebo plus cobimetinib but without the administration of nab-paclitaxel due to low platelet or ANC levels. Nab-paclitaxel should not be administered subsequently within that cycle until ANC ≥ 1500 cells/μL and platelet count ≥ 100,000 cells/μL. If the delay in restarting nab-paclitaxel is > 7 days

(i.e., counts do not recover until Day 15), dosing should be resumed with applicable reductions according to the criteria in Table 16.

- If the start of a treatment cycle is delayed for low counts, postpone Day 1 and resume dosing when counts recover with applicable reductions according to criteria in Table 16.
- If nab-paclitaxel cannot be administered on Day 8 of the cycle, it may be administered on Day 15 if counts have recovered to permissible levels with applicable dose reductions according to the criteria in Table 16.
- If nab-paclitaxel cannot be administered on Day 15 of the cycle, the next dose of nab-paclitaxel should be administered on Day 1 of the following cycle when ANC and platelets counts have recovered to permissible levels. When dosing resumes, the nab-paclitaxel doses should be permanently reduced as outlined in Table 16.

Table 16 Nab-Paclitaxel Permanent Dose Reductions for Hematologic Toxicity

Hematologic Toxicity	Occurrence	Weekly Nab-Paclitaxel Dose (mg/m^2)
Neutropenic fever (nadir ANC < 500/μL with fever > 38°C) or Delay of first administration of (nab)-paclitaxel in a cycle by > 7 days for nadir ANC < 1500/μL or Nadir ANC < 500/μL for > 7 days	First	75
	Second	50
	Third	Discontinue treatment
Nadir platelet count < 50,000/μL	First	75
	Second	Discontinue treatment

5.1.6.10 Neuropathy (All Cohorts)

If Grade ≥ 3 neuropathy (sensory or peripheral) attributable to paclitaxel/nab-paclitaxel develops in patients, paclitaxel/nab-paclitaxel should be held until the neuropathy recovers to Grade ≤ 1 (nab-paclitaxel) or to ≤ 2 (for paclitaxel). During this time, the patient may continue the cobimetinib or placebo at the discretion of the investigator. If the peripheral neuropathy recovers to Grade ≤ 2 (paclitaxel) or to Grade ≤ 1 (nab-paclitaxel) within 4 weeks or resolution, dosing of paclitaxel/nab-paclitaxel may resume reduced by one dose level. If recovery of the peripheral neuropathy to Grade ≤ 2 (paclitaxel) or to Grade ≤ 1 (nab-paclitaxel) does not occur within a maximum

of 4 weeks, the patient will permanently discontinue paclitaxel/nab-paclitaxel but may continue the study treatment, cobimetinib or placebo and atezolizumab, at the discretion of the investigator. Patients who permanently discontinue study treatment must continue to have tumor assessments until disease progression (see Section 4.5.2.4).

5.1.6.11 Guidelines for Adverse Events in Cohorts II and III

Appendix 12 provides guidelines for the following atezolizumab-associated adverse events: endocrine events, ocular events, immune-related myocarditis, infusion-related reactions, pancreatic events, neurologic disorders, and immune-related meningoencephalitis, *dermatologic events, and renal events*. Guidelines for management of elevated CPK and rhabomyolosis, hepatoxicity, pulmonary toxicity, dermatologic toxicity, and gastrointestinal toxicity in Cohorts II and III are provided in Sections 5.1.6.12–5.1.6.16. Table 8 (see Section 5.1.6.3) provides general guidelines for management of toxicities that can be followed when guidelines for specific events or drugs are not provided in subsequent sections or in the prescribing information.

5.1.6.12 Elevated CPK and Rhabdomyolysis in Cohorts II and III

Elevated CPK has been reported with cobimetinib (see Section 5.1.1.1). See Table 17 for guidelines for management of elevated CPK and rhabdomyolysis.

Table 17 Recommended Dose Modifications for Cobimetinib and Atezolizumab in Patients with CPK Elevations and Rhabdomyolysis in Cohorts II and III

Description	Management
General guidance	• Rule out cardiac cause (check ECG, serum cardiac troponin, and CPK-isoforms M and B fraction) and rule out rhabdomyolysis (clinical examination; serum creatinine, potassium, calcium, phosphorus, uric acid, and albumin; and urine myoglobin). • Assess patient for any history of strenuous physical activity, blunt trauma, or recent IM injections.
For Grade ≤ 3 CPK elevations that are asymptomatic and deemed not clinically significant	• Cobimetinib dosing and atezolizumab do not need to be modified or interrupted to manage asymptomatic Grade ≤ 3 CPK elevations. • Recheck CPK at least once a week.
For Grade 4 CPK elevations that are asymptomatic and deemed not clinically significant	• Interrupt cobimetinib and atezolizumab treatment. • If improved to Grade ≤ 3 within 28 days, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. • If CPK elevations do not improve to Grade ≤3 within 28 days following dose interruption, permanently discontinue cobimetinib treatment. • Resumption of atezolizumab may be considered in patients who are deriving benefit.[a,b,c]
Rhabdomyolysis or symptomatic CPK elevations	• Interrupt cobimetinib and atezolizumab treatment. • If severity is improved by at least one grade and symptoms resolve within 28 days, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. • If rhabdomyoysis or symptomatic CPK elevations do not improve within 28 days, permanently discontinue cobimetinib treatment • Resumption of atezolizumab may be considered in patients who are deriving benefit after discussion with the Medical Monitor.[a,b,c]

IM = intramuscular.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

5.1.6.13 Hepatotoxicity in Cohorts II and III

Hepatoxicity has been associated with the administration of atezolizumab and cobimetinib. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminase, and liver function will be monitored throughout study treatment.

While in this study, patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests performed immediately and reviewed before administration of the next dose of study drug.

If liver function tests increase, neoplastic, concurrent medications, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes for the increased liver function tests. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal antibodies, and anti-smooth muscle antibody tests should be considered.

Cohort II and III patients with liver function test abnormalities should be managed according to the guidelines in Table 18.

Table 18 Guidelines for Managing Atezolizumab and Cobimetinib–Associated Hepatotoxicity in Cohorts II and III

LFT Abnormalities	Management
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin ≤ 2 × ULN	• Continue atezolizumab and cobimetinib.
AST/ALT > 3 × ULN to 5 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue atezolizumab and cobimetinib. • Monitor LFTs at least weekly. • Consider patient referral to a hepatologist and liver biopsy. **Suspected immune-related events of > 5 days' duration:** • Consider withholding atezolizumab [c] • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If atezolizumab is withheld and event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks after event onset, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [a, b, c]
AST/ALT > 5 × ULN to < 10 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue atezolizumab and cobimetinib. • Monitor LFTs at least weekly. • Consider patient referral to a hepatologist and liver biopsy. **Suspected immune-related events:** • Withhold atezolizumab. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks after event onset, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [a, b, c]

IV = intravenous; LFT = liver function test; q4w = every 4 weeks; TNF = tumor necrosis factor; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 18 Guidelines for Managing Atezolizumab and Cobimetinib–Associated Hepatotoxicity in Cohorts II and III (cont.)

LFT Abnormalities	Management
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin > 2 × ULN	• Investigate causes for elevated bilirubin and initiate treatment as indicated per institutional guidelines. • Use best medical judgment when determining whether to continue study treatment.
AST/ALT > 3 × ULN with total bilirubin > 2 × ULN	• Withhold atezolizumab and cobimetinib. • Monitor LFTs every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist and consider liver biopsy. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent followed. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks after event onset, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c] • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. • Permanently discontinue atezolizumab and cobimetinib for life-threatening hepatic events, and contact the Medical Monitor.

IV = intravenous; LFT = liver function test; q4w = every 4 weeks; TNF = tumor necrosis factor; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 18 Guidelines for Managing Atezolizumab and Cobimetinib–Associated Hepatotoxicity in Cohorts II and III (cont.)

LFT Abnormalities	Management
AST/ALT > 10 × ULN	• Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor.[c] • Monitor LFTs every 48–72 hours until decreasing and then follow weekly. • Refer patient to hepatologist and consider liver biopsy. • Consider administering 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent or dose escalating the corticosteroid. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN, taper corticosteroids over ≥ 1 month.

IV = intravenous; LFT = liver function test; q4w = every 4 weeks; TNF = tumor necrosis factor; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

5.1.6.14 Pulmonary Toxicity in Cohorts II and III

Mild-to-moderate events of pneumonitis have been reported with atezolizumab and cobimetinib. Dyspnea, cough, fatigue, hypoxia, and pulmonary infiltrates have been associated with the administration of atezolizumab.

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

For events concerning for pneumonitis, consider comprehensive infectious evaluation, including viral etiologies.

Patients will be assessed for pulmonary signs and symptoms throughout the study. Patients will also have computed tomography scans of the chest at every tumor assessment.

Pulmonary toxicity should be managed according to the guidelines in Table 19.

Table 19 Guidelines for Managing Atezolizumab– and Cobimetinib–Associated Pulmonary Toxicity in Cohort II and III

Pulmonary Toxicity	Management
Pulmonary event, Grade 1	Continue atezolizumab and cobimetinib. Re-evaluate on serial imaging. Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	Withhold atezolizumab (for up to 12 weeks after event onset) and cobimetinib. Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. Resume atezolizumab and cobimetinib if event resolves to Grade 1.[a,b] Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks.[a,b,c] For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	Permanently discontinue atezolizumab and cobimetinib.[c] Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If pulmonary event does not improve within 48 hours or worsens, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage; IVIg = intravenous immunoglobulin.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after the event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

5.1.6.15 Dermatologic Toxicity in Cohorts II and III

Treatment-emergent rash has been associated with atezolizumab and cobimetinib. 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.

Dermatologic toxicity and rash should be managed according to the guidelines in Table 20.

Table 20 Guidelines for Managing Atezolizumab and Cobimetinib Rash in Cohorts II and III

Dermatologic Toxicity/Rash (e.g., maculo-papular or purpura)	Management
Dermatologic event, Grade 1 or 2	• Continue atezolizumab and cobimetinib. • Initiate supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids. • For Grade 2 rash, consider referral to dermatologist. **Acneiform rash:** • Consider topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.
Dermatologic event, Grade 3	• Withhold atezolizumab (for up to 12 weeks after event onset) and cobimetinib. [b] • Refer patient to dermatologist. A biopsy should be performed if appropriate. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [a] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • If event resolves to Grade 2 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. **Acneiform rash:** • Consider continuation of topical corticosteroids (e.g., 2.5% alclometasone) and oral antibiotics (e.g., minocycline, doxycycline or antibiotics covering skin flora) when restarting cobimetinib.
Dermatologic event, Grade 4	• Permanently discontinue all study treatment and contact Medical Monitor.

BID = twice daily; BSA = body surface area; PRN = as needed.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

5.1.6.16 Gastrointestinal Toxicity in Cohorts II and III

Diarrhea and immune-related colitis have been associated with the administration of cobimetinib and atezolizumab, respectively.

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

Diarrhea is a common adverse event with cobimetinib and should be managed promptly.

Patients should be educated to recognize the early signs and symptoms of diarrhea and instructed to promptly contact the investigators if they develop diarrhea. Patients should be asked to be cognizant of the onset, duration, severity, and frequency of symptoms and the medications administered.

Educational materials will be provided to patients outlining the necessary guidance and anti-diarrheal medication should be available prior to starting study treatment to ensure prompt intervention at onset.

Prophylaxis for diarrhea may be used at the investigator's discretion if allowed by local guidance.

See Table 21 for guidelines on how to manage gastrointestinal toxicity in patients treated with cobimetinib plus atezolizumab.

Table 21 Guidelines for Managing Atezolizumab- and Cobimetinib-Associated Gastrointestinal Toxicity in Cohorts II and III

Event	Management
Gastrointestinal events: general guidance	• Patients should receive maximum supportive care per institutional guidelines. • All events of diarrhea or colitis should be thoroughly evaluated for more common etiologies other than drug induced effects. • For events of significant duration or severity or associated with signs of systemic inflammation or acute phase reactants, check for immune-related colitis. • Administer anti-diarrheal agents and other maximal supportive care per institutional guidelines such as: at the first report of watery diarrhea or loose stool, initiate maximal anti-diarrheal supportive care (see below). • Maintenance loperamide dosing should be considered for any ongoing and intermittent Grade 1 diarrhea. • Suggested regimen: – Loperamide: Initiate dose with 4 mg, then 2 mg after each loose stool until diarrhea is controlled (no loose stools for 24 hours) after which the dosing of loperamide should be reduced to meet individual requirements. The maximum daily dose is 16 mg and clinical improvement is usually observed within 48 hours. – If Grade ≤ 2 diarrhea persists after 48 hr total treatment with loperamide, consider second-line agents (e.g., Lomotil® [diphenoxylate and atropine], octreotide, budesonide, tincture of opium or codeine). • Oral supplementation: – Initiate oral supplementation of potassium and/or magnesium if serum levels are < LLN. – Consider oral rehydration therapy (e.g., Pedialyte®) for Grade ≥ 1 diarrhea or vomiting. • Dietary modifications: – Stop all lactose-containing products and eat small meals. – The BRAT (banana, rice, apples, toast) diet, without fiber (other vegetables and fruits), may be helpful. – Encourage adequate hydration with salt-containing liquids, such as broth or Gatorade. • Prophylaxis for diarrhea: – Suggested regimen is loperamide (2 mg twice a day or 4 mg once a day) if allowed by local guidance and based on clinical judgement at any given time during the study.

Table 21 Guidelines for Managing Atezolizumab- and Cobimetinib-Associated Gastrointestinal Toxicity in Cohorts II and III (cont.)

Event	Management
Diarrhea, Grade 1	• Continue atezolizumab and cobimetinib. • Initiate anti-diarrheal therapy. • Initiate supportive care (encourage adequate oral hydration, oral supplementation, and dietary modification per general guidance above) and monitor patient closely. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis if appropriate.
Diarrhea, Grade 2	• Continue atezolizumab, cobimetinib, and paclitaxel/nab-paclitaxel. • Initiate anti-diarrheal therapy. If event resolves to Grade 1 or better within 48 hours: • The same cobimetinib dose is permitted with consideration of maintenance loperamide dosing at the investigator's discretion. Investigators may reduce cobimetinib by one dose level if deemed appropriate (see Table 7). • Initiate supportive care (encourage adequate oral hydration, oral supplementation, and dietary modification per general guidance above) and monitor patient closely. If event does not resolve within 48 hours to ≤Grade 1: • Withhold atezolizumab, cobimetinib, and paclitaxel/nab-paclitaxel. • Consider introducing second-line anti-diarrheal agents (e.g., Lomotil (diphenoxylate and atropine), octreotide, budesonide, tincture of opium or codeine). • Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy, if appropriate. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. [a,b,c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. • Two dose level reductions are allowed for diarrhea; if cobimetinib is still not tolerated then cobimetinib should be permanently discontinued. • Paclitaxel/nab-paclitaxel may be continued at the investigator's discretion and should be managed as per product label. If Grade 2 diarrhea recurs, see below.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 21 Guidelines for Managing Atezolizumab- and Cobimetinib-Associated Gastrointestinal Toxicity in Cohorts II and III (cont.)

Event	Management
Diarrhea, Grade 2 that recurs or Grade 3	• Withhold atezolizumab, cobimetinib, and paclitaxel/nab-paclitaxel. • Initiate anti-diarrheal therapy, maximum supportive care (encourage adequate oral hydration, oral supplementation, and dietary modification per general guidance above), and monitor patient closely. If ongoing for longer than 5 days, inform Medical Monitor. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. [a,b,c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. • Two dose level reductions are allowed for diarrhea; if cobimetinib is still not tolerated then cobimetinib should be permanently discontinued. • Paclitaxel/nab-paclitaxel may be continued at the investigator's discretion and should be managed as per product label.
Diarrhea, Grade 4	• Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [c] • Initiate maximum supportive care (encourage adequate oral hydration, oral supplementation, and dietary modification per general guidance above) and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. • Rule out bowel perforation. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 21 Guidelines for Managing Atezolizumab- and Cobimetinib-Associated Gastrointestinal Toxicity in Cohorts II and III (cont.)

Event	Management
Colitis, Grade 1	• Continue atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS). • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy if symptoms persist for > 7 days.
Colitis, Grade 2	• Withhold atezolizumab (for up to 12 weeks after event onset) and cobimetinib. [b] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS). • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab at fixed dose. [a,b,c] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 21 Guidelines for Managing Atezolizumab- and Cobimetinib-Associated Gastrointestinal Toxicity in Cohorts II and III (cont.)

Event	Management
Colitis, Grade 3	• Withhold atezolizumab (for up to 12 weeks after event onset) and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS). • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [a,b,c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.
Colitis, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor. [c] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS). • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal; IV = intravenous; NSAID = non-steroidal anti-inflammatory drug.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and 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 GCP, 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), except as described in Section 5.3.5.10
- 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:

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

  Note: 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)

- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, or thyroid disease
- Systemic lupus erythematosus
- Neurologic: Guillain-Barré syndrome, myasthenia gravis, meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response system, or infusion-reaction syndromes
- Ocular toxicities (e.g., uveitis, retinitis)
- Retinal vein occlusion
- Serous retinopathy, including events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment, and central serous chorioretinopathy
- Myositis
- Rhabdomyolysis or Grade ≥ 3 CPK elevation
- Grade ≥ 3 hemorrhage or any grade cerebral hemorrhage

- Grade ≥ 3 rash
- Grade ≥ 3 diarrhea
- Significant liver toxicity
- Hepatitis, including AST and/or ALT > 10 × ULN
  - Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
    - Treatment emergent ALT or AST > 3 × ULN in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice, without initial findings of cholestasis (elevated serum alkaline phosphatase)
    - No other reason can be found to explain the combination of increased ALT/AST and total bilirubin, such as: liver metastasis; viral hepatitis A, B, or C; alcoholic and autoimmune hepatitis; other liver diseases; or exposure to other drugs known to cause liver injury
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Symptomatic heart failure or Grade ≥ 2 left ventricular ejection fraction reduction
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

Adverse events suggestive of an autoimmune disorder (for patients exposed to atezolizumab (Cohorts II and III):

- Pneumonitis
- Grade ≥ 3 hypoxia or dyspnea
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, or adrenal insufficiency
- Vasculitis
- Hepatitis
- Systemic lupus erythematosus
- Guillain-Barre syndrome
- Skin reactions: vitiligo, pemphigoid

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 to 5.6. For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study 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, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug for patients in Cohort I and 30 days after the last dose of study drug for patients in Cohorts II and III. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any post study serious adverse events or adverse events of special interest (see 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 22 will be used for assessing severity of adverse events that are not specifically listed in the NCI CTCAE.

Table 22 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 AE [d]

AE = adverse event; 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 or not 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:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

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 paclitaxel or nab-paclitaxel or atezolizumab administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

5.3.5.5 Abnormal Laboratory Values

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

- 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
- Clinically significant in the investigator's judgment

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

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

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

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:

- 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
- 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.7 Liver Laboratory Test Abnormalities

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2)

and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of metastatic triple–negative breast cancer should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, 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).

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").*

During survival follow-up, deaths attributed to progression of metastatic triple–negative breast cancer should be recorded only on the Survival eCRF.

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 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse events 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
- 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

5.3.5.11 Adverse Events Associated with an Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic case report form (eCRF). All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious 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).

5.3.5.12 [redacted]

[redacted]

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

- Serious adverse events
- Adverse events of special interest
- Pregnancies

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 Institutional Review Board/Ethics Committee (IRB/EC).

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the last dose of study drug *for patients in*

Cohort I and 30 days after the last dose of study drug for patients in Cohorts II and III. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

Instructions for reporting serious adverse events that occur >28 days after the last dose of study treatment *for patients in Cohort I and >30 days after the last dose of study treatment for patients in Cohorts II and III* 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, within 6 months after the last dose of paclitaxel/nab-paclitaxel, within 5 months after the last dose of atezolizumab, and within 3 months after the last dose of cobimetinib. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug 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 (i.e., no more than 24 hours after learning of the pregnancy) if their partner becomes pregnant during the study or within 6 months after the last dose of paclitaxel/nab-paclitaxel or 3 months after the last dose of cobimetinib. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email

address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. *When permitted by the site, t*he pregnant partner *would* need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. *If* the authorization has been signed, the investigator *should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.* An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

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

5.5.2 Sponsor Follow-Up

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

5.6 POST STUDY ADVERSE EVENTS

After the end of the adverse event reporting period (defined as 28 days after the last dose of study drug for patients in Cohort I and 30 days after the last dose of study drug for patients in Cohorts II and III), 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 study drug treatment, the event should be reported through use of the Adverse Event eCRF.

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:

- Cobimetinib Investigator's Brochure
- Atezolizumab Investigator's Brochure
- Package Inserts for paclitaxel and nab-paclitaxel

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This Phase II study is designed to evaluate the safety and efficacy of cobimetinib plus paclitaxel, of cobimetinib plus atezolizumab plus paclitaxel, and of cobimetinib plus atezolizumab plus nab-paclitaxel.

The analysis populations are defined as follows:

- The intent-to-treat (ITT) population is defined as all enrolled patients, whether or not the assigned study treatment was received.
- The safety-evaluable population is defined as patients who received any amount of any study drug.

Cohort I

Safety run-in stage

Patients enrolled in the Cohort I open-label safety run-in stage will be analyzed separately from patients in the expansion stage (blinded). Safety analysis will be performed on safety-evaluable population.

Expansion stage

In the expansion stage of Cohort I, efficacy analyses will be performed on the ITT population and will be analyzed according to the treatment arm to which they were randomized.

Safety analyses for the expansion stage of Cohort I will be performed on the safety evaluable population according to the treatment regimen they actually received.

Cohorts II and III

Efficacy analyses will be performed on the ITT population in each cohort. Patients will be analyzed according to the treatment arm (i.e., Cohort II or Cohort III) to which they were randomized. Each cohort will be analyzed separately.

Safety analyses will be performed on the safety evaluable population according to the treatment regimen they actually received.

Additional details on the efficacy and safety analyses are provided in Section 6.4 and Section 6.5, respectively.

6.1 DETERMINATION OF SAMPLE SIZE

This study is designed to evaluate the safety and to provide preliminary evidence of activity for:

- Cohort I: cobimetinib plus paclitaxel versus placebo plus paclitaxel
- Cohort II: cobimetinib plus atezolizumab plus paclitaxel
- Cohort III: cobimetinib plus atezolizumab plus nab-paclitaxel

6.1.1 Cohort I: Safety Run-In Stage

The number of patients enrolled during the safety run-in stage in Cohort I (n = 12) allows for a reasonable likelihood of observing a given adverse event in at least 1 patient even when the incidence of the specific adverse event is low.

Table 23 shows the probability of observing an adverse event in at least 1 patient and at least 2 patients of 12 for different underlying incidences.

Table 23 Probabilities of Observing Adverse Events with Different Underlying Incidences: Cohort I Safety Run-In Stage

Underlying AE incidence	Probability of observing the AE in ≥ 1 patient of 12	Probability of observing the AE in ≥ 2 patients of 12
0.01	0.11	0.006
0.025	0.26	0.03
0.05	0.46	0.12
0.075	0.61	0.23
0.10	0.72	0.34

AE = adverse event.

6.1.2 Cohort I: Expansion Stage

The study will randomize approximately 90 patients in the Cohort I randomized stage. For the evaluation of the primary efficacy endpoint of PFS in this cohort, patients will be followed until approximately 60 investigator–assessed PFS events have occurred among the 90 randomized patients.

One of the purposes of this study is to estimate the effect of the addition of cobimetinib on duration of PFS relative to the current standard of care in patients with metastatic or locally advanced, triple-negative adenocarcinoma of the breast who have not received prior systemic therapy for MBC. Point and interval estimates of the true underlying hazard ratio will be obtained. It is assumed that the median duration of PFS in the control arm is 6 months. Operating characteristics (power and 95% CI) for true underlying hazard ratio values of 0.50, 0.60, and 0.67 are provided in Table 24.

Table 24 Operating Characteristics for Proposed Study Design for Several Possible True Underlying Hazard Ratio Values

	True Underlying Hazard Ratio			
	0.48	0.50	0.60	0.75
Expected number of events	60	60	60	60
Power of log-rank test [a]	81%	77%	51%	20%
95% CI for true hazard ratio [b]	(0.29, 0.80)	(0.30, 0.83)	(0.36, 1.00)	(0.45, 1.24)

Note: Operating characteristics are based on the following assumptions: event times are exponentially distributed, median progression-free survival in the control arm is 6 months, and patients are enrolled over 12 months and followed for an additional 9 months.

[a] Two-sided $\alpha = 0.05$.

[b] Confidence intervals are based on the assumption that the point estimate is equal to the true underlying value of the hazard ratio in each column.

This study is able to detect only a large benefit of combination therapy with cobimetinib and paclitaxel, and will not have adequate power to detect minimum clinically meaningful differences between treatment arms at a statistically significant α (type 1) error level of 5%. For example, with 60 events in the two comparator arms, there is an 80% power to detect a hazard ratio of 0.48 at a two-sided significance level of 0.05. However, there is only a 51% power to detect a hazard ratio of 0.60. Thus, a statistically negative outcome on the primary PFS does not necessarily rule out a clinically meaningful outcome.

6.1.3 Cohorts II and III: Safety Run-In Stage

The number of patients enrolled into Cohort II and III during the safety run-in stage (n = 15 per cohort) allows for a reasonable likelihood of observing a given adverse event in at least 1 patient even when the incidence of the specific adverse event is low.

Table 25 shows the probability of observing an adverse event in at least 1 patient and at least 2 patients of 15 for different underlying incidences.

Table 25 Probabilities of Observing Adverse Events with Different Underlying Incidences: Cohorts II and III Safety Run-In Stage

Underlying AE incidence	Probability of observing the AE in ≥ 1 patient of 15	Probability of observing the AE in ≥ 2 patients of 15
0.01	0.14	0.01
0.025	0.32	0.05
0.05	0.54	0.17
0.075	0.69	0.31
0.10	0.79	0.45

AE = adverse event.

6.1.4 Cohorts: II and III: Expansion Stage

The study is also designed to estimate the effect of cobimetinib plus atezolizumab plus paclitaxel and cobimetinib plus atezolizumab plus nab-paclitaxel (relative to cobimetinib plus paclitaxel in mTNBC).

To evaluate the primary endpoint of overall response rate, the analyses will be performed after the last recruited patient in each Cohort (combining both safety run-in and expansion stages) has completed two post-baseline tumor assessments.

No formal statistical hypothesis testing is planned in this Phase II study. Instead, the analysis here is for hypothesis generation and the emphasis is on estimations. Table 26 shows estimated ORR and its 95% CI based on Clopper-Pearson method given various observed numbers of responders among the 30 patients in cohort II and III, respectively. Thirty patients provide reasonably reliable estimates for hypothesis generation.

Table 26 Estimated Overall Response Rate and its 95%CI for 30 Patients in Cohorts II and III, Respectively

Number of Responders	ORR (%)	95% CI
6	20	7.7 - 38.6
9	30	14.7 - 49.4
12	40	22.7 – 59.4
15	50	31.3 – 68.7
18	60	40.6 – 77.3
21	70	50.6 – 85.3
24	80	61.4 – 92.3
27	90	73.5 – 97.9

ORR = overall response rate.

6.2 SUMMARIES OF CONDUCT OF STUDY

For the Cohort I safety run-in stage, listings will be used in place of tables due to the small sample size. Data to be displayed in the listings include enrollment, major protocol violations, discontinuations from treatment and/or study, reasons for discontinuation, demographic and baseline characteristics (e.g. age, sex, race, weight, and baseline ECOG performance status).

For the Cohort I expansion stage, enrollment, study treatment administration, eligibility exceptions, major protocol violations, and discontinuation from the study will be summarized overall and by treatment arm for all randomized patients. The reasons for study treatment discontinuation will be tabulated. All patients randomized in Cohorts II and III will be presented similarly.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Summaries of treatment group comparability will be performed for the Cohort I expansion stage, Cohort II, and Cohort III. Demographic variables such as age, sex, race/ethnicity, and baseline characteristics (e.g., weight, primary tumor histologic subtype, duration of malignancy) will be summarized by treatment arm for all randomized patients. Continuous variables will be summarized using means, standard deviations, medians, and ranges. Categorical variables will be summarized by proportions.

The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

6.4 EFFICACY ANALYSES

The efficacy analyses will be performed on all ITT population for the Cohort I expansion stage, Cohort II, and Cohort III. Patients will be grouped according to the treatment assigned at randomization.

6.4.1 Primary Efficacy Endpoint for Cohort I Expansion Stage

The primary efficacy endpoint for Cohort I is PFS, defined as the time from randomization to the first occurrence of disease progression as determined by investigator per RECIST v1.1 (see Appendix 3), or death from any cause, whichever occurs first.

Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm and Kaplan-Meier curves will be produced. Stratified log-rank tests will be used to compare cobimetinib plus paclitaxel with placebo plus paclitaxel. The hazard ratio estimates and their 95% CI will be determined by the stratified Cox proportional hazards model. The stratification factors include prior neoadjuvant/adjuvant taxane therapy (yes or no) and disease-free interval from last dose of chemotherapy ($\leq$ 12 months vs. $>$ 12 months/no prior chemotherapy) and will be determined by the eCRF data, unless the eCRF data are missing, in which case data collected by the IxRS at the time of randomization will be used. Data for randomized patients without disease progression or death will be censored at the last tumor assessment date. If no tumor assessment was performed after randomization, data will be censored at the randomization date. Results from an unstratified log-rank test will also be prepared.

6.4.2 Primary Efficacy Endpoint for Cohorts II and III

The primary efficacy endpoint for Cohorts II and III is ORR, defined as the proportion of a PR or CR occurring after randomization and confirmed $\geq$ 28 days later as determined by the investigator using RECIST v1.1 (see Appendix 3). An estimate of the ORR and its 95% CIs will be calculated for each treatment arm (Clopper and Pearson 1934). CIs for the difference in ORR will be calculated as well.

6.4.3 Secondary Efficacy Endpoints for Cohort I Expansion Stage

The secondary efficacy endpoints are as follows:

- OS, defined as the time from randomization to death from any cause, regardless of whether the death occurs during the study or following treatment discontinuation. For patients who have not died, OS will be analyzed similarly to the primary endpoint. In addition, 1-year survival rate will be estimated from a Kaplan-Meier curve.
- ORR, as described in Section 6.4.2.
- Duration of objective response, defined as the time from the first occurrence of a documented objective response to the time of disease progression, as determined by the investigator using RECIST v1.1 (see Appendix 3), or death from any cause during the study, whichever occurs first. Duration of objective response will be analyzed only on the basis of patients with objective response. Methods for handling censoring and for analysis are the same as those described for PFS. No adjustments will be made to account for the non-random nature of this comparison.
- ORR_uc (ORR confirmation not required), defined as the rate of a PR or CR occurring after randomization as determined by the investigator using RECIST v1.1, confirmation not required

6.4.4 Secondary Efficacy Endpoints for Cohort II and III

The secondary efficacy endpoints are as follows:

- OS, as previously described in Section 6.4.3
- DOR, as described in Section 6.4.3
- PFS, as described in Section 6.4.1
- ORR_uc, as described in Section 6.4.3

6.5 SAFETY ANALYSES

Safety analyses will include all patients who received at least one dose of study treatment (paclitaxel, nab-paclitaxel, cobimetinib/placebo, or atezolizumab). For Cohort I, the safety analyses will be performed separately for the safety run-in stage and the expansion stage. For Cohorts II and III, the safety analyses will be performed at the time of the interim analysis after the safety run-in stage, and at the primary analysis for these cohorts when all safety data obtained in the expansion stage and in the safety run-in stage are combined to generate a cumulative safety data for each cohort (Cohorts II and III).

For the Cohort I, II, and III safety run-in stages, data on study treatment exposure and adverse events will be listed respectively for each cohort.

For the Cohort I expansion stage, safety will be assessed through summaries of all treatment-emergent adverse events, including serious adverse events, deaths, adverse events of special interest (see Section 5.2.3), and adverse events leading to

discontinuation of study treatment, changes in laboratory test results, and changes in vital signs will be presented by treatment arms, with patients grouped according to the treatment actually received.

For Cohorts II and III, at the time of primary analysis for these cohorts, the combined/aggregated safety data obtained in the expansion stage and in the safety run-in stage will be summarized similarly as described above for patients in the Cohort I expansion stage.

A treatment-emergent event is defined as an event occurring on or after the first dose of any study treatment. All adverse events will be summarized by MedDRA term, appropriate MedDRA levels, and NCI CTCAE v4.0 grade. For each patient, if multiple incidences of the same adverse events occur, the maximum severity reported will be used in the summaries. Verbatim descriptions of adverse events will be mapped to MedDRA terms.

Selected laboratory values will be summarized by time and toxicity grade (NCI CTCAE v4.0), with NCI CTCAE Grade 3 and Grade 4 values identified, where appropriate. Changes in NCI CTCAE grade will be tabulated by treatment arm.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population for each drug will include patients who received at least one dose of study drug and provide evaluable PK data. PK analyses will be conducted for patients with sufficient data to enable estimation of key parameters (see Section 2), with patients grouped according to the cohort, stage (safety run-in or expansion), and treatment within the expansion stage.

Individual and median plasma cobimetinib, paclitaxel, nab-paclitaxel, and serum atezolizumab concentration versus time data will be tabulated and plotted by drug, cohort, study phase, study visit, and dose level. The plasma or serum pharmacokinetics of cobimetinib, paclitaxel, nab-paclitaxel, and serum pharmacokinetics of atezolizumab will be summarized (such as mean, standard deviation, coefficient of variation [CV%], median, minimum, maximum, geometric mean and geometric mean coefficient of variation [CVb%] as appropriate). See Section 2 for the safety run-in stage (as appropriate for data collected).

PK parameters from both phases will be tabulated and summarized (geometric mean and geometric mean CV (CVb%) median, minimum, maximum as appropriate). Sparse PK sampling will be implemented for cobimetinib in the expansion stage and concentrations may be summarized and reported if data warrants. The sparse samples will be analyzed using mixed effect modeling (popPK) to determine individual patient pharmacokinetics; however, this will not be reported in the clinical study report.

6.7 [redacted]

6.8 [redacted]

6.9 [redacted]

6.10 INTERIM ANALYSES

Given the hypothesis-generating nature of this study, the Sponsor may conduct up to two interim analyses of efficacy. The decision to conduct such an interim analysis and its timing will be documented in the Sponsor's study master file prior to the conduct of the interim analysis. The clinical study report will also document that such an interim analysis occurred. The interim analysis, should it occur, will be performed and interpreted by members of the Sponsor study team and management who would then be unblinded at the treatment-group level.

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

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

[redacted]

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. Electronic case report forms should be reviewed and electronically signed and dated by the investigator or a designee.

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

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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 [redacted], evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be

entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP 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 U.S. or under a U.S. Investigational New Drug (IND) application will comply with FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (EU) or European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample ICFs for the safety run-in and expansion stages for all cohorts 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 ICFs 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.

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 U.S., 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 of 1996 (HIPAA). 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 ICFs, 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 9.5).

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 ICF (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.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other 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 final OS analysis.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

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, ICFs, 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.

9.1 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.*

9.2 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.

9.3 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in the Roche Standard Operational Procedures.

This study will be sponsored by Genentech Inc., a member of the Roche Group, and managed with the support of a CRO, which will provide clinical monitoring, sample management, and project management support. Approximately 75 centers globally may participate in the study and will randomize approximately 100 patients.

Randomization for the expansion stage will occur through an IxRS. Central facilities will be used for certain study assessments [redacted] Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

Data for this study will be recorded via an EDC system using eCRFs. Data will be transcribed by site personnel from the paper source documents onto the eCRF. In no case is the eCRF to be considered as source data for this trial.

Since the majority of the study is open-label (except for the Cohort I expansion stage), an independent data safety monitoring board is not planned. However, safety data will be reviewed at regular intervals by the study Steering Committee as described in Section 3.1.1.2.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. 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.

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

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

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

9.5 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).

10. REFERENCES

Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer 2011;47:8–32.

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365 – 76.

Adams S, Diamond J, Hamliton E, et al. Abstract P2-11-06: Safety and clinical activity of atezolizumab (anti-PDL1) in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer. SABCS. 2015 (abstr 850477). Cancer Res 2016;76; P2-11-06.

Adams S, Gray R, Demaria S, et al. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. J Clin Oncol 2014;32:2959–66.

Anderson WF, Chatterjee N, Ershler WB, et al. Estrogen receptor breast cancer phenotypes in the surveillance, epidemiology, and end results database. Breast Cancer Res Treat 2002;76:27 – 36.

Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012;51:119–35.

Balko JM, Cook RS, Vaught DB, et al. Profiling of residual breast cancers after neoadjuvant chemotherapy identifies DUSP4 deficiency as a mechanism of drug resistance. Nat Med 2012;18:1052–9.

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to exhaustion: an update on implications for chronic infection and tumour evasion. Cancer Immunol Immunother 2007;56:739–45.

Blum JL, Savin MA, Edelman G, et al. Phase II study of weekly albumin-bound paclitaxel for patients with metastatic breast cancer heavily pretreated with taxanes. Clin Breast Cancer 2007;7:850–6.

Bonni A, Brunet A, West AE, et al. Cell survival promoted by the RAS-MAPK signaling pathway by transcription-dependent and –independent mechanisms. Science 1999;286:1358 – 62.

Brufsky A, Kim S-B, Velu TJ, et al. Cobimetinib (C) + paclitaxel (P) as first-line treatment in patients (pts) with advanced triple-negative breast cancer (TNBC): Updated results and biomarker data from the phase 2 COLET study. 2016 ASCO Annual Meeting: Abstract 1075. [Resource on the Internet; accessed 6 June 2016] Available from: http://abstracts.asco.org/176/AbstView_176_165251.html.

Butte MJ, Keir ME, Phamduy TB. Programmed death□ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Cardoso F, Harbeck N, Fallowfield L, et al. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii11-9.

Cargnello M, Roux PP. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiol Mol Biol Rev 2011;75:50–83.

Carrick S, Parker S, Wilcken N, et al. Single agent versus combination chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev 2005.

Carson WE 3rd, Shapiro CL, Crespin TR, et al. Cellular immunity in breast cancer patients completing taxane treatment. Clin Cancer Res 2004;10:3401–9.

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi AE et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. Journal of Clinical Oncology 1993; 11(3 Suppl.2):570-9.

Cella DF, Wang M, Wagner L, Miller K. Survival-adjusted health-related quality of life (HRQoL) among patients with metastatic breast cancer receiving paclitaxel plus bevacizumab versus paclitaxel alone: results from Eastern Cooperative Oncology Group Study 2100 (E2100). Breast Cancer Res Treat 2011; 130(3):855-861.

Cella D. Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System. Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare and Northwestern University, Evanston IL, Version 4. 1997.

Choritz H, Busche G, and Kreipe H. Quality assessment of HER2 testing by monitoring of positivity rates. Virchows Arch 2011;459:283–9.

Cimino-Mathews A, Ye X, Meeker A, et al. Metastatic triple-negative breast cancers at first relapse have fewer tumor-infiltrating lymphocytes than their matched primary breast tumors: a pilot study. Hum Pathol 2013;44:2055–63.

Clopper C, Pearson ES. "The use of confidence or fiducial limits illustrated in the case of the binomial". Biometrika 1934;26:404–413.

Cragg MS, Harris C, Strasser A, et al. Unleashing the power of inhibitors of oncogenic kinases through BH3 mimetics. Nature Rev Cancer 2009;9:321–326.

Crawford J, Caserta C, Roila F, et al., on behalf of the ESMO Guidelines Working Group. Hematopoietic growth factors: ESMO recommendations for the applications. Ann Oncol 2009;20:162–5.

Davies BR, Logie A, McKay JS, et al. AZD6244 (ARRY-142886), a potent inhibitor of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase 1/2 kinases: mechanism of action in vivo, pharmacokinetic/pharmacodynamics relationship, and potential for combination in preclinical models. Mol Cancer Ther 2007;6:2209–19.

Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007;13:4429–34.

Di Giacomo AM, Biagioli M, Maio M. The emerging toxicity profiles of anti–CTLA-4 antibodies across clinical indications. Semin Oncol 2010;37:499–507.

Downward J. Targeting RAS signalling pathways in cancer therapy. Nat Rev Cancer 2003;3:11–22.

Ebert PJ, Cheng J, Yang Y, et al. MAP kinase inhibition promostes T cell and anti-tumor activity in combination with PD-L1 checkpoint blockade. Immunity 2016;44:609–21.

Fayers P, Aaronson N, Bjordal K, et al. EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: EORTC Publications, 2001.

Flaherty KT, Robert C, Hersey P, et al. Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma. N Engl J Med 2012;367:107–14.

Fossella FV, DeVore R, Kerr RN, et al. Randomized Phase III trial of docetaxel versus vinorelbine or isosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. J Clin Oncol 2000;18:2354 – 62.

Gandara DR, Hiret S, Blumenschein GR, et al. Oral MEK1/MEK2 inhibitor trametinib (GSK1120212) in combination with docetaxel in KRAS-mutant and wild-type (WT) advanced non-small-cell lung cancer (NSCLC): a phase 1/1b trial. J Clin Oncol 2013;31(Suppl; abstr 8028).

Gennari A, Stockler M, Puntoni M, et al. Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. J Clin Oncol 2011;29:2144-9.

Gradishar WJ, Krasnojon D, Cheporov M, et al. Significantly Longer Progression-Free Survival With nab-Paclitaxel Compared With Docetaxel As First-LineTherapy for Metastatic Breast Cancer. J Clin Oncol 2009;27:3611-3619.

Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil–based paclitaxel in women with breast cancer. J Clin Oncol 2005;23:7794–803.

Haass NK, Sproesser K, Nguyen TK, et al. The mitogen-activated protein/extracellular signal-regulated kinase kinase inhibitor AZD6244 (ARRY-142886) induces growth arrest in melanoma cells and tumor regression when combined with docetaxel. Clin Cancer Res 2008;14(1):230 – 9.

Hammond MEH, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Oncol Pract 2010;6(4):195–7.

Hanahan D, Weinberg RA. The Hallmarks of Cancer. Cell 2000;100:57–70.

Harris LN, Broadwater G, Lin NU, et al., Molecular subtypes of breast cancer in relation to paclitaxel response and outcomes in women with metastatic disease: results from CALGB 9342. Breast Canc Res 2006;8:R66.

Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563-567.

Hoeflich KP, O'Brien C, Boyd Z, et al. In vivo antitumor activity of MEK and phosphatidylinositol 3-kinase inhibitors in basal-like breast cancer models. Clin Cancer Res 2009;15:4649 – 64.

Holt SV, Logie A, Odedra R, et al. The MEK1/2 inhibitor, selumetinib (AZD6244; ARRY-142886), enhances anti-tumor efficacy when combined with conventional chemotherapeutic agents in human tumour xenograft models. Br J Cancer 2012; 106:858–66.

Janne PA, Shaw AT, Pereira JR, et al. Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomized, multicenter, placebo-controlled, phase-2 study. Lancet Oncol 2013;14:38–47.

Jing J, Greshock J, Holbrook JD, et al. Comprehensive predictive biomarker analysis for MEK inhibitor GSK1120212. Mol Cancer Ther 2012;11:720–9.

Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.

Kim SB, Miles D, Velu T, et al. Cobimetinib (COBI) + Paclitaxel (PTX) as first-line treatment in patients (pts) with advanced triple-negative breast cancer (TNBC): Interim safety review of the ongoing phase 2 COLET study. 2016:EBCC 2015 (abstract 358).

Koren E, Smith HW, Shores E, et al. Recommendations on risk-based strategies for detection and characterization of antibodies against biotechnology products. J Immuno Methods 2008;333:1–9.

Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest 2011;121:2750–67.

Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Annals of Internal Medicine 2006;145: 247–54.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Annals of Internal Medicine 2009;150:604–12.

Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008;26:1275 – 81.

Loi S. Host antitumor immunity plays a role in the survival of patients with newly diagnosed triple-negative breast cancer. J Clin Oncol 2014;32:2935–7.

Loi S, Dushyanthen S, Beavis PA, et al RAS/MAPK activation is associated with reduced tumor-infiltrating lymphocytes in triple-negative breast cancer: therapeutic cooperation between MEK and PD-1/PD-L1 immune checkpoint inhibitors. Clin Cancer Res 2016;22:1499–509.

MacKeigan JP, Collins TS, and Ting JP. MEK inhibition enhances paclitaxel-induced tumor apoptosis. J Biol Chem 2000;275(50):38953–6.

Maheswaran S, Sequist LV, Nagrath S, et al. Detection of mutations in EGFR in circulating lung-cancer cells. N Engl J Med 2008;359(4):366–77.

Martin M, Romero A, Cheang MC, et al. Genomic predictors of response to doxorubicin versus docetaxel in primary breast cancer. Breast Cancer Res Treat 2011;128(1):127–136.

McDaid HM and Horwitz SB. Selective potentiation of paclitaxel (taxol)-induced cell death by mitogen-activated protein kinase kinase inhibition in human cancer cell lines. Mol Pharmacol 2001;60(2):290-301.

Meng J, Fang B, Liao Y, et al. Apoptosis induction by MEK inhibition in human lung cancer cells is mediated by Bim. PloS One 2010; 5(9):e13026.

Menon SS, Whitfield LR, Sadis S, et al. Pharmacokinetics (PK) and pharmacodynamics (PD) of PD 0325901, a second generation MEK inhibitor after multiple oral doses of PD 0325901 to advanced cancer patients. Proceedings of the 41st ASCO Annual Meeting: 2005 Jun; Orlando.
Available from http://meeting.ascopubs.org/cgi/content/short/23/16_suppl/3066.

Miles DW, Diéras V, Cortés J, et al. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. Ann Oncol 2013;24:2773-80.

Nabholtz JM, Gelmon K, Bontenbal M, et al. Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. J Clin Oncol 1996;14:1858–67.

National Comprehensive Cancer Network. Breast Cancer (Version 3.2014). http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 16 June 2014.

Okano J, Rustgi AK. Paclitaxel induces prolonged activation of the RAS/MEK/ERK pathway independently of activating the programmed cell death machinery. J Biol Chem 2001;276:19555–64.

Perez EA, Vogel CL, Irwin DH, et al. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol 2001;19(22):4216 – 23.

Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature 2000;406:747 – 52.

Piccart-Gebhart MJ, Burzykowski T, Buyse M, et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. J Clin Oncol 2008;26(12):1980–6.

Rakha EA, El-Sayed ME, Green AR, et al. Prognostic markers in triple-negative breast cancer. Cancer 2007;109:25–32.

Rosenberg AS, Worobec AS. A risk-based approach to immunogenicity concerns of therapeutic protein products. BioPharm Intl 2004;17:34–42.

Rugo Hs, Barry WT, Moreno-Aspitia A, et al Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab As First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance). J Clin Oncol 2015;33:3261–2369.

Sasieni PD, Shelton J, Ormiston-Smith N, et al. What is the lifetime risk of developing cancer: the effect of adjusting for multiple primaries. Br J Cancer 2011;105(3):460–5.

Schiff PB, Fant J, Horwitz SB. Promotion of microtubule assembly in vitro by taxol. Nature 1979;277:665–7.

Schwarzenbach H, Hoon DS, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. Nat Rev Cancer 2011;11(6):426–37.

[SEER] Surveillance, Epidemiology, and End Results Program 2013 Database [resource on internet]. Available from: http://seer.cancer.gov/statfacts/html/breast.html.

Seidman AD, Berry D, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with assignment to trastuzumab or not in HER-2 nonoverexpressors: final results for cancer and leukemia group B protocol 9840. J Clin Oncol 2008;26:1642 – 9.

Seidman AD, Tiersten A, Hudis C, et al. Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. J Clin Oncol 1995;13:2575–81.

Shepard FA, Dancey J, Rambau , et al. Prospective Randomized Trial of Docetaxel Versus Best Supportive Care in Patients with Non-Small-Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy. J Clin Oncol 2000;18:2095-2103.

Shinozaki M, O'Day SJ, Kitago M, et al. Utility of circulating B RAF DNA mutation in serum for monitoring melanoma patients receiving biochemotherapy. Clin Cancer Res 2007;13:2068–74.

Siegel R, DeSantis C, Virgo K et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012;62:220–41.

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006:3187–205.

Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 2001;98(19):10869 – 74.

Tan T, Degenhardt K, Nelson DA, et al. Key roles of BIM-driven apoptosis in epithelial tumors and rational chemotherapy. Cancer Cell 2005;7:227–38.

Thompson RH, Kuntz SM, Leibovich BC, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Res 2006;66:3381–5.

van't Veer LJ, Dai H, Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002;415:530 – 6.

Wang X, Li M, Wang J, et al. The BH3-only protein, PUMA, is involved in oxaliplatin-induced apoptosis in colon cancer cells. Biochem Pharmacol 2006;71(11):1540 – 50.

Webster, K., Odom, L., Peterman, A., Lent, L., Cella, D. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: Validation of version 4 of the core questionnaire. Quality of Life Research 1999, 8(7):604

Wilson WH, Berg SL, Bryant G, et al. Paclitaxel in doxorubicin-refractory or mitoxantrone-refractory breast cancer: a phase I/II trial of 96-hour infusion. J Clin Oncol 1994;12:1621–9.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immunetherapy activity in solid tumors: immune-related response criteria Clin Can Res 2009;15:7412–20.

Wolff AC, Hammond ME, Hicks DG, et al.; American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 2013;31:3997–4013.

Yang J, Riella LV, Chock S. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 2011;187:1113–9.

Zitvogel L, Apetoh L, Ghiringhelli F et al. The anticancer immune response: indispensable for therapeutic success? J Clin Invest 2008;118:1991–2001.

Appendix 1
Schedule of Assessments

	Screening[a] (Day −28 to Day −1)	Cycle 1			Cycle 2			Cycles 3 and 4			Beyond Cycle 4			End of Study Tx Visit[b]	Tumor Follow Up	Survival Follow Up[c]
		D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15			
Signed informed consent[d]	x															
Demographics, medical history, prior cancer treatment	x															
Physical examination[e]	x	x		x			x	x		x	x		x	x		
Weight and height	x															
Vital signs[f]	x	x	x	x	x	x	x	x	x	x	x	X	x	x		
ECOG performance status	x	x			x			x			x			x		
Hematology[g]	x	x	x	x	x	x	x	x	x	x	x	X	x	x		
Chemistry[h]	x	x		x	x		x	x		x	x		x	x		
Urinalysis	x															
Serum pregnancy test[i]	x	x[i]			x[i]			x[i]			x[i]			x[i]		
Screening HIV, HBV, HCV serology[j] (Cohorts II and III only)	x															
PK samples[k]		See Appendix 2														
[redacted]																
ECHO or MUGA scan[m]	x				x						x			x		
12-lead ECG	x													x		
Ophthalmologic exam[n]	x				x						x					
Tumor assessments[o]	x							x			x			x[b]	x	

Appendix 1
Schedule of Assessments (cont.)

	Screening[a] (Day -28 to Day -1)	Cycle 1			Cycle 2			Cycles 3 and 4			Beyond Cycle 4			End of Study Tx Visit[b]	Tumor Follow Up	Survival Follow Up[c]
		D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15			
[redacted]																
Head scan (CT or MRI scan)[p]	x															
Bone scan[q]	x															
Cobimetinib /placebo dispension/ accountability		x			x			x			x					
Paclitaxel administration (Cohorts I and II only)		x	x	x	x	x	x	x	x	x	x	X	x			
Nab-paclitaxel administration (Cohort III only)		x	x	x	x	x	x	x	x	x	x	X	x			
Atezolizumab administration (Cohorts II and III only)		x		x	x		x	x		x	x		x			
Adverse events and concomitant medications[r]	x	x	x	x	x	x	x	x	x	x	x	X	x	x		
[redacted]																
Survival and anti-cancer therapy follow up[t]																x
[redacted]																
Tumor biopsy[w]	x													x		

Appendix 1
Schedule of Assessments (cont.)

	Screening[a] (Day –28 to Day –1)	Cycle 1			Cycle 2			Cycles 3 and 4			Beyond Cycle 4			End of Study Tx Visit[b]	Tumor Follow Up	Survival Follow Up[c]
		D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15			
Optional on treatment tumor biopsy w				x												

[redacted]

AE = adverse event; [redacted] CT = computed tomography; D = day; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; [redacted] MUGA = multiple-gated acquisition; MRI = magnetic resonance imaging; OS = overall survival; PD = progressive disease; PK = pharmacokinetic; [redacted] RECIST = Response Evaluation Criteria in Solid Tumors; Tx = Treatment

Notes: Unless otherwise specified, assessments that are done weekly should be performed within a window of ± 2 days. Assessments that are performed monthly should be performed within a window of ± 3 days. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. On treatment days, pre-infusion laboratory samples should be drawn 0–4 hours before the start of infusion, and post-infusion laboratory samples should be drawn 0–30 minutes after the end of infusion, unless otherwise specified.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit 28 (±7) days after the last dose of study drug. The visit at which response assessment shows PD may be used as the treatment discontinuation visit. (Patients in Cohorts II and III will be assessed using immune-modified RECIST.)

[c] Required follow-up information will be collected via telephone calls and/or clinic visits every 3 months until death, loss to follow-up, or study termination by the Sponsor.

[d] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment. There will be separate ICFs for the safety run-in stage and the expansion stage (Cohort I) and a single ICF for Cohort II and III patients. All consents will also include optional consent for on-treatment biopsy.

Appendix 1
Schedule of Assessments (cont.)

[e] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[f] Includes pulse rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

[g] Includes hemoglobin, WBC count, neutrophil count, lymphocyte count, and platelet count.

[h] Includes fasting glucose (screening only), magnesium and alkaline phosphatase (screening and as clinically indicated only), BUN, creatinine, albumin, CPK, potassium, total and direct bilirubin, ALT, and AST. Thyroid stimulating hormone (TSH), free T3, free T4 is required at screening and Day 1 of every cycle thereafter for patients in Cohorts II and III.

[i] All women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening within 7 days prior to Cycle 1 Day 1 and at the treatment discontinuation visit. A urine pregnancy test is required on Day 1 of every cycle for patients in Cohort II and III. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[j] All patients will be tested for HIV locally prior to the inclusion into the study; HIV-positive patients will be excluded from the clinical trial. Hepatitis B surface antigen, anti-HBc, and anti-HBs should be collected during screening and tested locally. HBV DNA must be collected prior to randomization in patients who have negative serology for hepatitis B surface antigen and positive serology for anti-HBc.

[k] See Appendix 2 for detailed schedule of PK assessments.

[l] [redacted]

[m] All patients will undergo evaluation of LVEF, either by ECHO or MUGA at the following timepoints:

- Screening
- Cycle 2, Day 1 ± 1 week
- On Day 1 of every 3 treatment cycles thereafter, starting with Cycle 5
- End-of-study-treatment visit
- All patients who restart treatment with a reduced dose of cobimetinib because of a decrease in LVEF should have LVEF measurements taken after approximately 2 weeks, 4 weeks, 10 weeks, and 16 weeks and then resume monitoring LVEF every 3 cycles. Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment. For patients (asymptomatic and symptomatic) who discontinue cobimetinib, LVEF assessments should continue post-treatment 6 weeks or as clinically indicated until the LVEF recovers to LLN or 50% and/or symptoms resolve.

Evaluation of left ventricular function does not need to be performed at end-of-study-treatment visit if it has been performed within the last 12 weeks. Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment. Evaluation of left ventricular function must be performed by the same method for each patient.

[n] All patients will undergo ophthalmologic examination at the following timepoints:

- Screening
- Cycle 2, Day 1 ± 1 week
- On Day 1 of Cycles 5, 8 and 11 (every 3 treatment cycles) ± 2 weeks
- On Day 1 of Cycles 15, 19, 23 (every 4 treatment cycles) ± 2 weeks
- On Day 1 of Cycles 29, 35, 41, 47 etc. (every 6 treatment cycles) ± 2 weeks
- End-of-study-treatment visit. If an ophthalmologic evaluation has been performed within the last 12 weeks of this visit, the ophthalmologic examination does not need to be performed during this visit.

Baseline ophthalmologic examination will evaluate for evidence of retinal pathology that is considered a risk factor for neurosensory retinal detachment, RVO, or neovascular macular degeneration. Risk factors for RVO include elevated serum cholesterol, hypertriglyceridemia, hyperglycemia, hypertension and glaucoma. Ophthalmologic examination will include visual acuity testing, slit lamp ophthalmoscopy, indirect ophthalmoscopy, and OCT (spectral or time domain).

[o] Tumor assessments will include contrast-enhanced CT or MRI of the chest, abdomen, and pelvis as well as the site of the primary tumor (if applicable). Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. Evaluation of tumor response conforming to RECIST v1.1 [redacted] must be documented every 8 weeks ± 1 week (after every 2 treatment cycles) from the date of first study drug administration (Cycle 1 Day 1) until documented investigator-determined PD or the patient dies. Tumor assessments must be performed independent of changes to the study treatment administration schedule (e.g., dose delay). If a tumor assessment has to be performed early or late, subsequent assessments should be conducted according to the original schedule based on the date of first study drug administration (Cycle 1 Day 1). Tumor assessments should continue regardless of whether patients start new anticancer therapy in the absence of disease progression unless they withdraw consent.

[p] Performed within 6 weeks prior to Day 1, Cycle 1.

[q] An initial bone scan should be performed within 6 weeks prior to Day 1, Cycle 1. For patients with known or suspected bone metastasis, follow-up bone scans should be performed during Days 16–28 of every fourth cycle (every 16 weeks) and at the study termination visit.

Appendix 1
Schedule of Assessments (cont.)

[r] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study drug. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any poststudy serious adverse events or adverse events of special interest (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[redacted]

[t] Survival assessment will be used to collect OS during long-term follow-up; patient should be followed up every 12 weeks until death, withdrawal of consent, or loss to follow-up. Subsequent anti-cancer therapy information will be collected at the same time as survival assessment.

[u] A mandatory blood sample for genotyping of drug transporters in case of abnormal drug exposures are observed and germline control for calling tumor specific mutations analysis will be collected on Cycle 1 Day 1.

[redacted]

[w] Biopsies of accessible lesions are at baseline and time of progression are mandatory upon patient's consent to participate in the trial. FFPE tumor biopsy sample is required and a fresh-frozen tumor biopsy sample is requested for these timepoints. For patients consenting to provide optional on-treatment (Cycle 1, Day 15) samples, an FFPE tumor biopsy sample is preferred and a fresh-frozen tumor biopsy sample is requested.

- Baseline sample: during screening within 28 days of Cycle 1 Day 1
- Optional - On treatment cycle: on Cycle 1, Day 15 (±1 week)
- Disease progression sample: at time of PD

Appendix 1
Schedule of Assessments (cont.)

Baseline sample biopsies should be completed at least 48 hours before the initiation of study drug therapy on Cycle 1 Day 1. Archival tissue may be submitted in place of newly obtained tumor tissue for the baseline sample biopsy. It is highly recommended that the biopsy at disease progression be collected within 14 days after last study treatment. Excisional biopsies, punch biopsies, 14-18 gauge core needle biopsies are acceptable. Fine needle aspiration biopsies are not acceptable. Biopsy is required if patient has accessible lesion at disease progression.

[redacted]

Appendix 2 Schedu[redacted]rmacokinetic [redacted] Assessments

COHORT I

Table 1 Schedule of Pharmacokinetic Assessments for Cohort I (Cobimetinib plus Paclitaxel) Safety Run-In Stage

Visit	Timepoint	Sample Type	Drug
Cycle 1 Day 8	Predose	Plasma PK	Cobimetinib Paclitaxel
Cycle 1 Day 15	Predose and 0.5, 1, 2, 4, and 6 hrs postdose	Plasma PK	Cobimetinib Paclitaxel

hr=hour; PK=pharmacokinetic.

Table 2 Schedule of Pharmacokinetic Assessments for Cohort I (Cobimetinib plus Paclitaxel) Expansion Stage

Visit	Timepoint	Sample Type	Drug
Cycle 1 Day 15	Predose Anytime between 1 and 4 hrs postdose	Plasma PK	Cobimetinib
Cycle 2 Day 15	Predose	Plasma PK	Cobimetinib

hr=hour; PK=pharmacokinetic.

Appendix 2 Sch [redacted] etic [redacted] (cont.)

COHORT II

Table 3 Schedule of Pharmacokinetic Assessments for Cohort II (Cobimetinib plus Atezolizumab plus Paclitaxel) Safety Run-In Stage

Visit	Timepoint	Sample Type	Drug
Cycle 1 Day 1	Predose 30 min (+/- 10 min) post-atezolizumab dose	Serum PK	Atezolizumab
		[redacted]	Atezolizumab
Cycle 1 Day 8	Predose	Plasma PK	Cobimetinib Paclitaxel
Cycle 1 Day 15	Predose and 2 and 4 hrs postdose	Plasma PK	Cobimetinib Paclitaxel
Cycle 3 Day 1	Predose 30 min (±10 min) post-atezolizumab dose	Serum PK	Atezolizumab
		[redacted]	Atezolizumab
Cycle 2, 4, 8 and every 8 Cycles thereafter	Predose	Serum PK	Atezolizumab
		[redacted]	Atezolizumab
Treatment discontinuation visit	At visit	Serum PK	Atezolizumab
		[redacted]	Atezolizumab
120 (±30) days after last dose of atezolizumab	At visit	Serum PK	Atezolizumab
		[redacted]	Atezolizumab

[redacted] hr=hour; PK=pharmacokinetic.

Appendix 2 Sch [redacted]

Table 4 Schedule of Pharmacokinetic Assessments for Cohort II (Cobimetinib plus Atezolizumab plus Paclitaxel) Expansion Stage

Visit	Timepoint	Sample Type	Drug
Cycle 1 Day 1	Predose	Serum PK	Atezolizumab
	30 min (±10 min) post-atezolizumab dose	[redacted]	Atezolizumab
Cycle 1 Day 15	Predose Anytime between 1 and 4 hrs postdose	Plasma PK	Cobimetinib
Cycle 2 Day 15	Predose	Plasma PK	Cobimetinib
Cycle 3 Day 1	Predose	Serum PK	Atezolizumab
	30 min (±10 min) post-atezolizumab dose	[redacted]	Atezolizumab
Cycle 2, 4, 8 and every 8 Cycles thereafter	Predose	Serum PK	Atezolizumab
		[redacted]	Atezolizumab
Treatment discontinuation visit	At visit	Serum PK	Atezolizumab
		[redacted]	Atezolizumab
120 (±30) days after last dose of atezolizumab	At visit	Serum PK	Atezolizumab
		[redacted]	Atezolizumab

hr=hour; PK=pharmacokinetic; [redacted].

Appendix 2 Sch [redacted] etic [redacted] (cont.)

COHORT III

Table 5 Schedule of Pharmacokinetic Assessments for Cohort III (Cobimetinib plus Atezolizumab plus Nab-paclitaxel) Safety Run-In Stage

Visit	Timepoint	Sample Type	Drug
Cycle 1 Day 1	Predose 30 min (+/- 10 min) post-atezolizumab dose	Serum PK [redacted]	Atezolizumab Atezolizumab
Cycle 1 Day 8	Predose	Plasma PK	Cobimetinib nab-Paclitaxel
Cycle 1 Day 15	Predose and 2 and 4 hrs postdose	Plasma PK	Cobimetinib nab-Paclitaxel
Cycle 3 Day 1	Predose 30 min (+/- 10 min) post-atezolizumab dose	Serum PK [redacted]	Atezolizumab Atezolizumab
Cycle 2, 4, 8 and every 8 Cycles thereafter	Predose	Serum PK [redacted]	Atezolizumab Atezolizumab
Treatment discontinuation visit	At visit	Serum PK [redacted]	Atezolizumab Atezolizumab
120 (±30) days after last dose of atezolizumab	At visit	Serum PK [redacted]	Atezolizumab Atezolizumab

hr = hour; PK = pharmacokinetic; [redacted]

Appendix 2 Sch [redacted] tic [redacted] cont.)

Table 6 Schedule of Pharmacokinetic Assessments for Cohort III (Cobimetinib plus Atezolizumab plus Nab-paclitaxel) Expansion Stage

Visit	Timepoint	Sample Type	Drug
Cycle 1 Day 1	Predose	Serum PK	Atezolizumab
	30 min (+/- 10 min) post-atezolizumab dose	[redacted]	Atezolizumab
Cycle 1 Day 15	Predose Anytime between 1 and 4 hrs postdose	Plasma PK	Cobimetinib
Cycle 2 Day 15	Predose	Plasma PK	Cobimetinib
Cycle 3 Day 1	Predose	Serum PK	Atezolizumab
	30 min (+/- 10 min) post-atezolizumab dose	[redacted]	Atezolizumab
Cycle 2, 4, 8 and every 8 Cycles thereafter [a]	Predose	Serum PK	Atezolizumab
		[redacted]	Atezolizumab
Treatment discontinuation visit	At visit	Serum PK	Atezolizumab
		[redacted]	Atezolizumab
120 (±30) days after last dose of atezolizumab	At visit	Serum PK	Atezolizumab
		[redacted]	Atezolizumab

[redacted] hr=hour; PK=pharmacokinetic.

[a] *To be done on Day 1 of the visit cycle.*

Appendix 3 Response Evaluation Criteria in Solid Tumors Version 1.1 – Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 [1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor 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 of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Nontarget Lesions" for information on lymph node measurement.

---

[1] 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.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), 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 masses/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:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure 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 noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of 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.

Method of Assessment

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

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

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

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast due to allergy or renal insufficiency, the decision as to whether a noncontrast 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 noncontrast CT or MRI (enhanced or nonenhanced) 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.

Ultrasound. Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NONTARGET 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 in instances where 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 recorded as non-measurable lesions (even if the size is > 10 mm by CT scan).

Appendix 3 Response Evaluation Criteria in Solid Tumors Version 1.1 – Modified Excerpt from Original Publication (cont.)

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

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

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

<u>All other lesions (or sites of disease), including pathological lymph nodes, should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."</u>

In addition, it is possible to record multiple nontarget 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").

Appendix 3 Response Evaluation Criteria in Solid Tumors Version 1.1 – Modified Excerpt from Original Publication (cont.)

RESPONSE CRITERIA

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- **Complete response (CR)**: disappearance of all target lesions

  Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.

- **Partial response (PR)**: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- **Progressive disease (PD)**: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- **Stable disease (SD)**: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Special Notes on the Assessment of Target Lesions

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 nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While in the study, all lesions (nodal and non-nodal) that are recorded at baseline should be recorded as actual measurements 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 the CT scan that the radiologist may not feel comfortable assigning an exact measure 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 below measurable limit (BML) 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 BML should also be ticked.)

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

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. 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 maximal longest diameter for the coalesced lesion.

Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. While some nontarget lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- **CR**: disappearance of all nontarget 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 nontarget lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- **PD**: unequivocal progression of existing nontarget lesions

  The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Nontarget Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

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 partial or complete response. 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, then progression should be declared using the date of the initial scan.

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore nontarget) disease only, Table 2 is to be used.

Table 1 Timepoint Response: Patients with Target Lesions (with or without Nontarget Lesions)

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not 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 3 Response Evaluation Criteria in Solid Tumors Version 1.1 – Modified Excerpt from Original Publication (cont.)

Table 2 Timepoint Response: Patients with Nontarget Lesions Only

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

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

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

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, 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 lesion(s) 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.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more nontarget lesions are not assessed, the response for nontarget lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the nontarget response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Appendix 3 Response Evaluation Criteria in Solid Tumors Version 1.1 – Modified Excerpt from Original Publication (cont.)

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

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

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

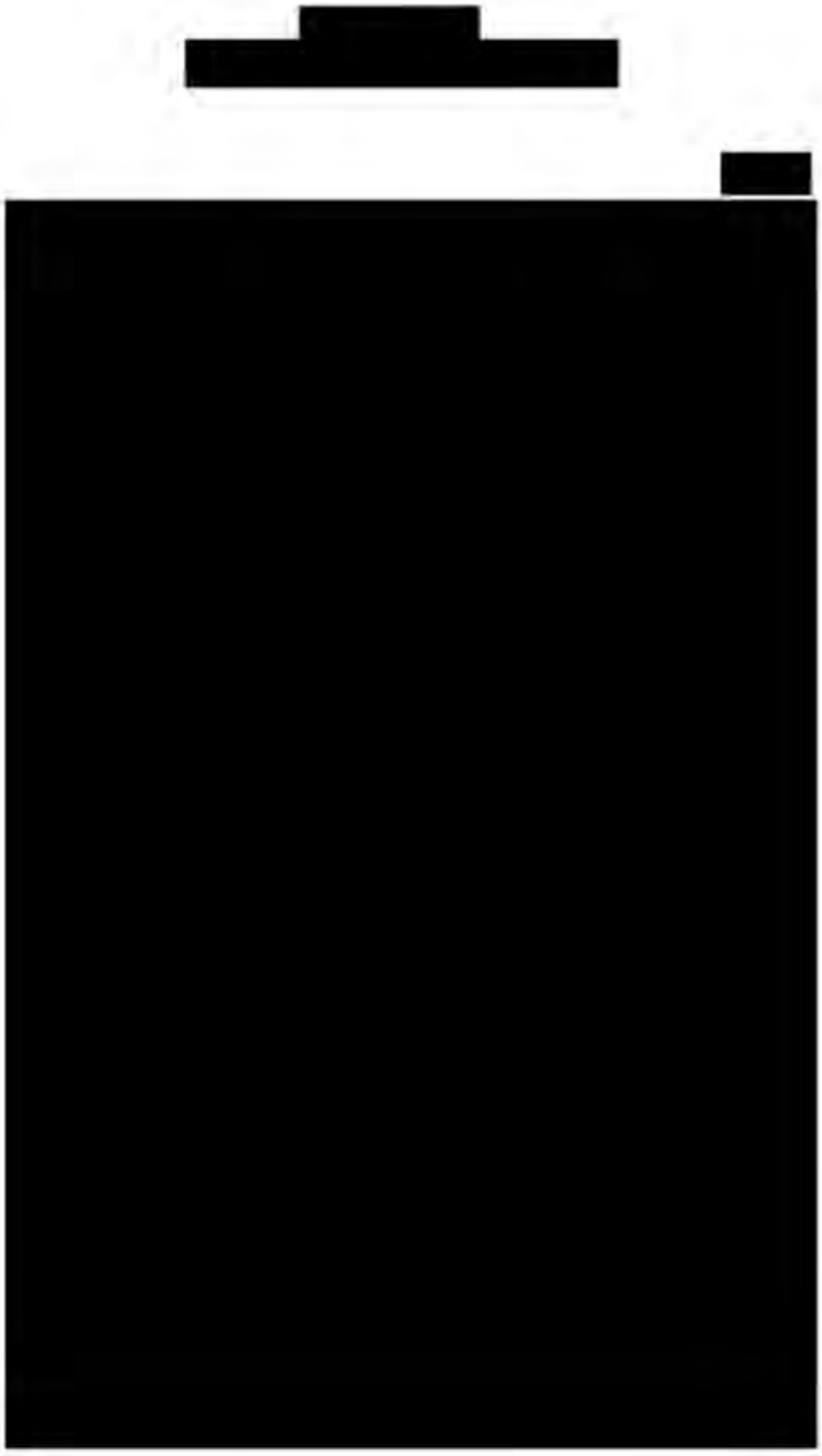
When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

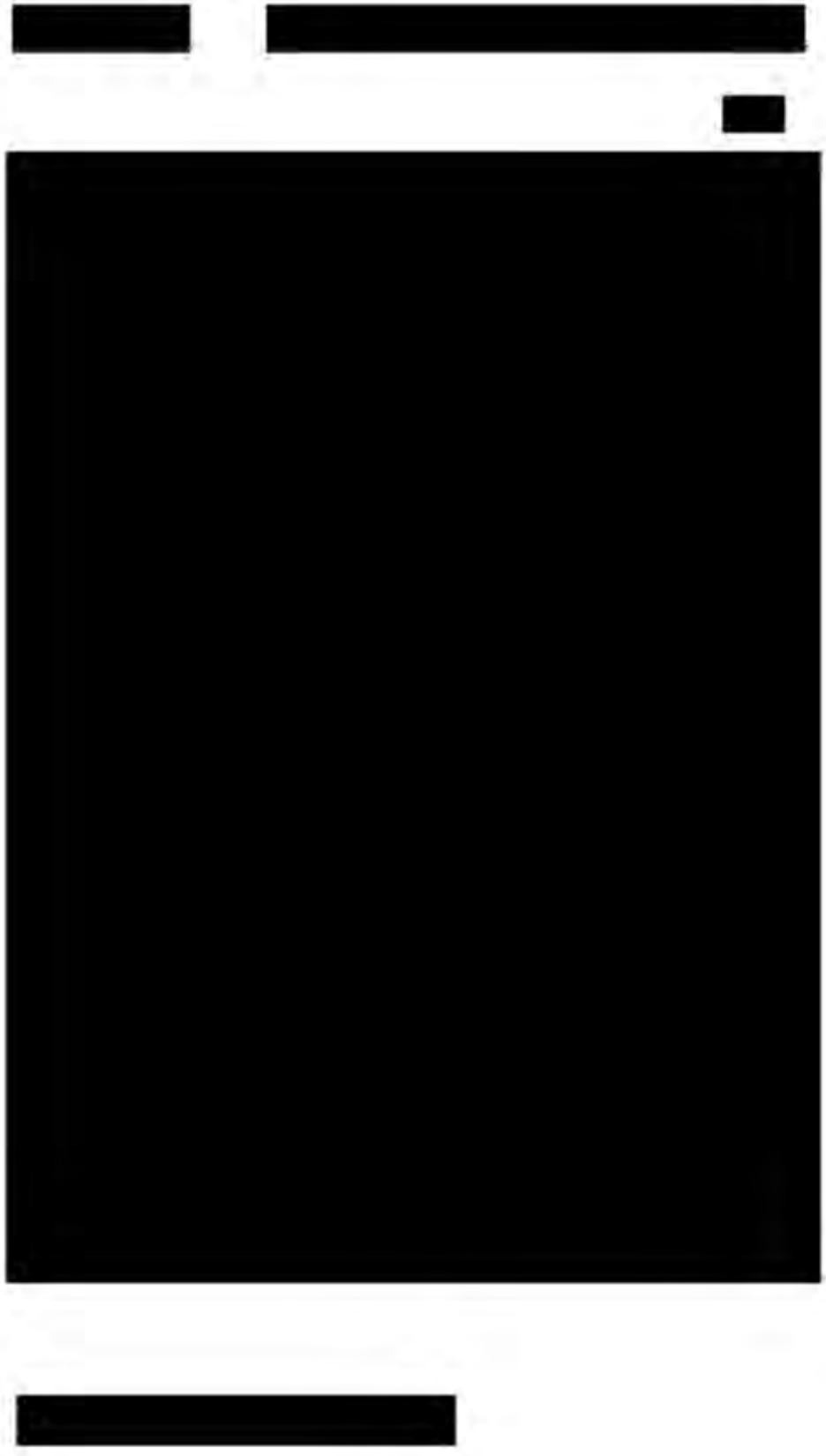
Appendix 3 Response Evaluation Criteria in Solid Tumors Version 1.1 – Modified Excerpt from Original Publication (cont.)

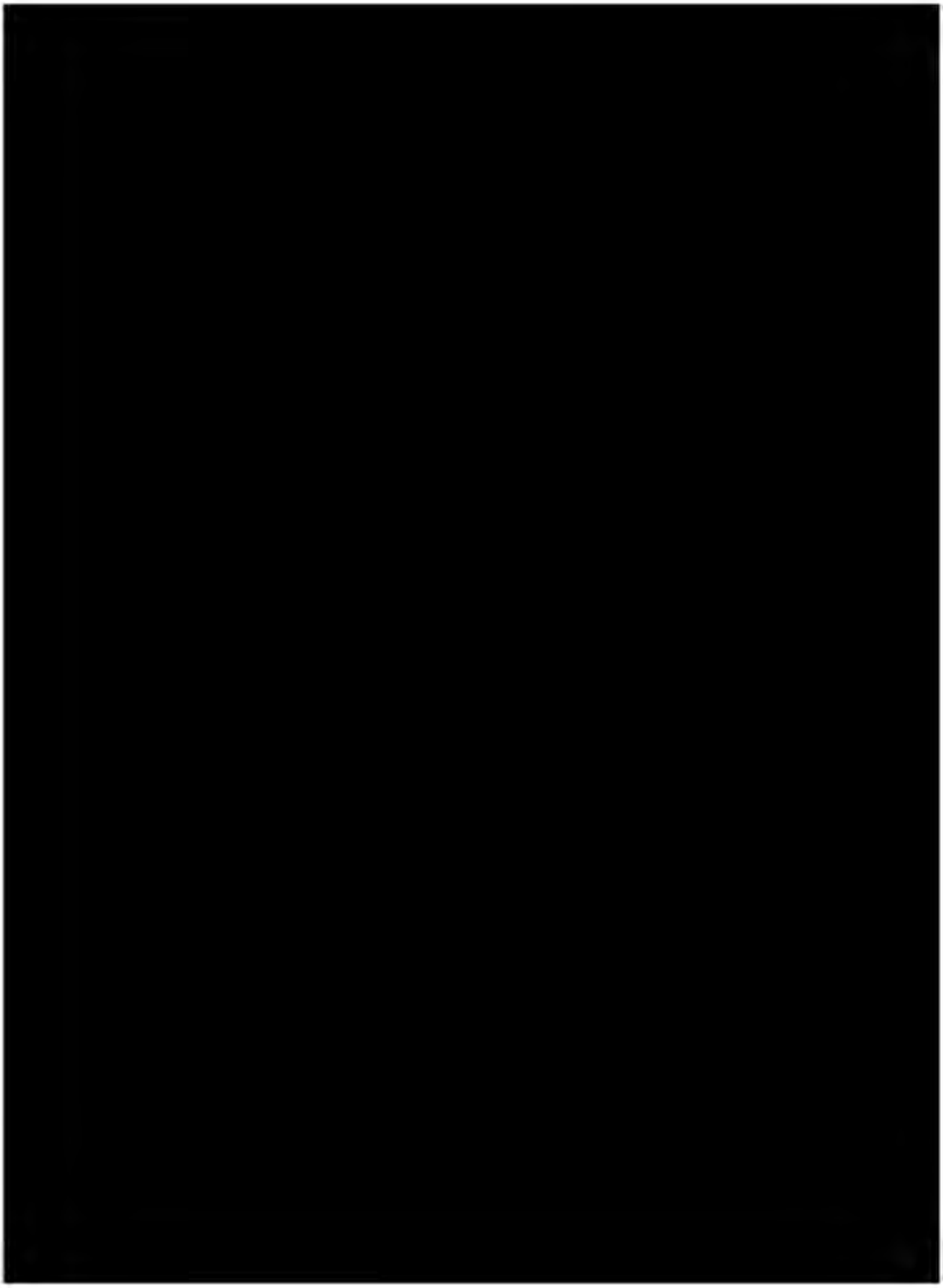
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. 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 nontarget disease as shown in Table 1, Table 2, and Table 3.

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.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or nontarget lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or nontarget lesion.







[redacted]

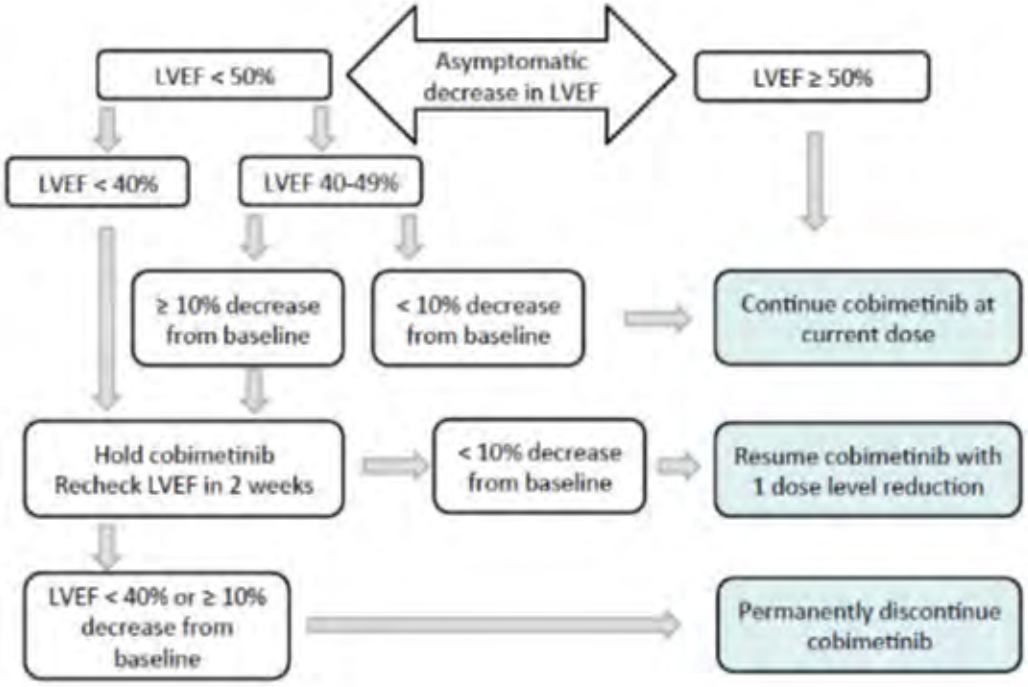
Appendix 6 Eastern Cooperative Oncology Group Performance Status

Patients will be graded according to the ECOG Performance Status scale and criteria as described below:

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

Reference: Oken, MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649 – 55.

Appendix 7 Guidelines for Management of Asymptomatic Reduction in Ejection Fraction

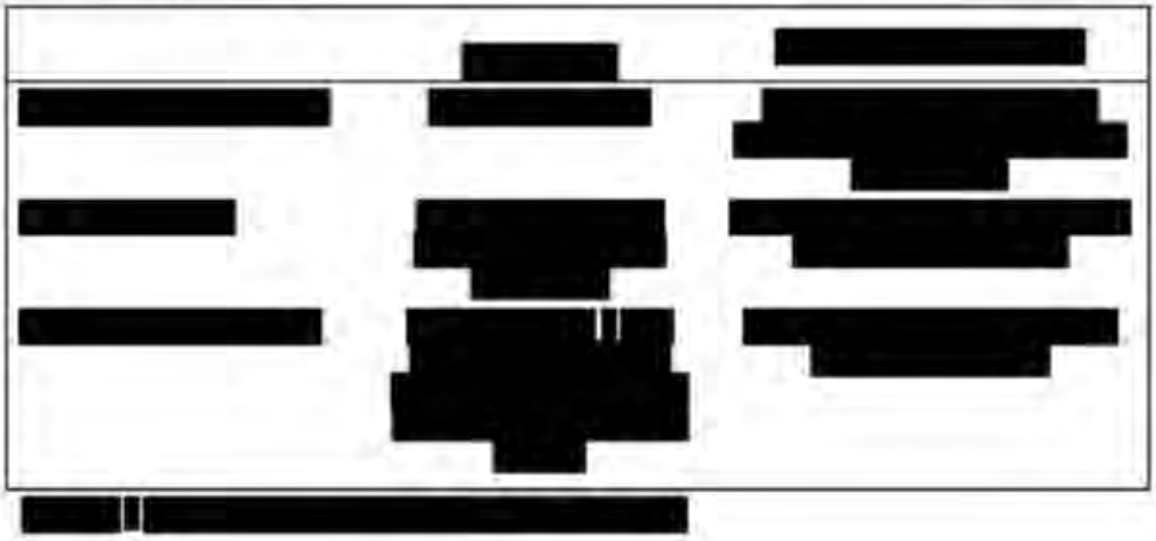


Appendix 8 New York Heart Association Classification of Functional Cardiac Capacity

Class	
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

Reference: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964:114.

[redacted]



[redacted]

[redacted]

[redacted]

Appendix 10 Anaphylaxis Precautions

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 drug. 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 11
Preexisting Autoimmune Diseases

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Please contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Acute disseminated encephalomyelitis	Dysautonomia	Ord's thyroiditis
Addison's disease	Epidermolysis bullosa acquista	Pemphigus
Ankylosing spondylitis	Gestational pemphigoid	Pernicious anemia
Antiphospholipid antibody syndrome	Giant cell arteritis	Polyarteritis nodusa
Aplastic anemia	Goodpasture's syndrome	Polyarthritis
Autoimmune hemolytic anemia	Graves' disease	Polyglandular autoimmune syndrome
Autoimmune hepatitis	Guillain-Barré syndrome	Primary biliary cirrhosis
Autoimmune hypoparathyroidism	Hashimoto's disease	Psoriasis
Autoimmune hypophysitis	IgA nephropathy	Reiter's syndrome
Autoimmune myocarditis	Inflammatory bowel disease	Rheumatoid arthritis
Autoimmune oophoritis	Interstitial cystitis	Sarcoidosis
Autoimmune orchitis	Kawasaki's disease	Scleroderma
Autoimmune thrombocytopenic purpura	Lambert-Eaton myasthenia syndrome	Sjögren's syndrome
Behcet's disease	Lupus erythematosus	Stiff-Person syndrome
Bullous pemphigoid	Lyme disease - chronic	Takayasu's arteritis
Chronic fatigue syndrome	Meniere's syndrome	Ulcerative colitis
Chronic inflammatory demyelinating polyneuropathy	Mooren's ulcer	Vitiligo
Chung-Strauss syndrome	Morphea	Vogt-Kovanagi-Harada disease
Crohn's disease	Multiple sclerosis	Wegener's granulomatosis
Dermatomyositis	Myasthenia gravis	
	Neuromyotonia	
	Opsoclonus myoclonus syndrome	
	Optic neuritis	

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

PULMONARY EVENTS

Management guidelines for pulmonary events are provided in Section 5.1.6.14.

HEPATIC EVENTS

Management guidelines for hepatic events are provided in Section 5.1.6.13.

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Section 5.1.6.16.

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 1.

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.

Table 1 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-related hyperthyroidism.[c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 1 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 1 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 2.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 2 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-RELATED MYOCARDITIS

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 3.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 3 Management Guidelines for Immune-Related Myocarditis

Event	Management
Immune-related myocarditis, Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
Immune-related myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.[a] • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.[c]
Immune-related myocarditis, Grade 3-4	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.[a,b] • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

INFUSION-RELATED REACTIONS

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

Guidelines for medical management of IRRs during Cycle 1 are provided in Table 4. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 4 Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	• Interrupt atezolizumab infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs.
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue atezolizumab and contact Medical Monitor.[a]

IRR=infusion-related reaction.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 5.

Table 5 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI=gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 5 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

DERMATOLOGIC EVENTS

Management guidelines for dermatologic events are provided in Section 5.1.6.15.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 6.

Table 6 Management Guidelines for Neurologic Disorders

Event	Management
Immune-related neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-related neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-related neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-RELATED MENINGOENCEPHALITIS

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 7.

Table 7 Management Guidelines for Immune-Related Meningoencephalitis

Event	Management
Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor.[a] • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

RENAL EVENTS

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common

etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 8.

Table 8 Management Guidelines for Renal Events

Event	*Management*
Renal event, Grade 1	• *Continue atezolizumab.* • *Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.*
Renal event, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to renal specialist.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Renal event, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* • *Refer patient to renal specialist and consider renal biopsy.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*