PROTOCOL TITLE:

BRE 17107: A Phase Ib/II Trial of Atezolizumab (an anti-PD-L1 monoclonal antibody) with Cobimetinib (a MEK1/2 inhibitor) or Idasanutlin (an MDM2 antagonist) in Metastatic ER+ Breast Cancer

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- Protocol Revision Record -

Original Protocol:	12/15/2017
Amendment #1:	[3/29/2018] *Sections changed:* [Immuno-PET removed; information on Idasanutlin updated]
Amendment #2:	6/6/2018 Updated CTCAE version from 4.03 to 5.0
Amendment #3:	7/16/2018 Corrected inconsistencies within protocol
Amendment #4:	3/14/2019 Updated (1) Atezolizumab safety language per IB version 14 (October 2018), (2) Idasanutlin safety language per IB version 11 (November 2018), (3) Vanderbilt and other sites contacts, and (4) primary endpoint and statistical considerations

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1.1. PROTOCOL SYNOPSIS

Sponsor	Vanderbilt-Ingram Cancer Center
Protocol Title	BRE 17107: A Phase Ib/II Trial of Atezolizumab (an anti-PD-L1 monoclonal antibody) with Cobimetinib (a MEK1/2 inhibitor) or Idasanutlin (an MDM2 antagonist) in Metastatic ER+ Breast Cancer
Protocol Number	BRE 17107
Phase of Development	Phase Ib/II
Investigational Product and Mechanism	• Cobimetinib - MEK inhibitor • Idasanutlin - MDM2 antagonist • Atezolizumab - PD-L1 inhibitor
Treatment Schedule Dose/Route	• Cobimetinib 60 mg PO Days 1 – 21, every 28 days • Idasanutlin (final dose to be determined by the phase Ib portion of the study) PO Days 1 – 5, every 28 days • Atezolizumab 840 mg IV on Days 1 and 15, every 28 days
Objectives	• Phase Ib portion: determine the safety and tolerability of ATEZO and IDASA in patients with ER+ mBC • Phase II portion: determine the anti-tumor effect and adverse effects profile of ATEZ with COBI or IDASA in patients with ER+ mBC
Endpoints	**Primary Endpoint:** • Phase Ib: Dose Limiting Toxicity (DLT), Maximum Tolerated Dose (MTD) and Recommended Phase II Dose (RP2D) determination for the ATEZO and IDASA combination • Phase II: Progression Free Survival (PFS) for each treatment arm **Secondary Endpoints:** • Clinical Benefit Rate (CBR; percentage of patients without disease progression at 6 months) for each treatment arm • Immune-related Response Criteria (irRC), • Duration of Response (DOR) • Overall Response Rate (ORR; by RECIST 1.1 – for patients with measurable disease), • Percentage of patients alive at 12 months (% OS) • Adverse Event profile for each treatment arm **Other:** Exploratory Endpoints
Trial Design	This is an open-label, multicenter, two-arm phase Ib/II clinical trial that will evaluate the anti-tumor effect of atezolizumab (ATEZ; an anti- PD-L1 mAb) in combination with cobimetinib (COBI; a MEK inhibitor) in patients with *TP53*-mutated ER+ mBC, or idasanutlin (IDASA; an MDM2 antagonist) in patients with *TP53*-wt ER+ mBC.

Number of Patients	• Phase Ib: minimum of 9, maximum of 18 patients • Phase II: minimum of 33, maximum of 66 patients
Duration of Therapy	In the absence of treatment delays due to adverse events, treatment will continue until: • Disease progression • Inter-current illness that prevents further administration of treatment • Unacceptable adverse event(s) • Patients decides to withdraw from the study • Significant patient non-compliance with protocol
Duration of Follow-up	• Patients will be followed until 28 days (+/- 7 days) following study treatment discontinuation due to disease progression • Patients removed from study treatment for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 1 or lower • Patients who have discontinued atezolizumab, cobimetinib or idasanutlin for any reason other than disease progression will be followed until disease progression
Patient Selection	<u>Inclusion Criteria</u> *1.* Signed and dated written informed consent. *2.* Subjects ≥ 18 years of age. *3.* Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. *4.* Clinical stage IV invasive mammary carcinoma or unresectable locoregional recurrence of invasive mammary carcinoma that is: • ER/PR-positive (> 1% cells) by IHC and HER2 negative (by IHC or FISH) • Previously exposed to an aromatase inhibitor (AI) or a selective estrogen-receptor modulator/ downregulator (SERM; SERD) + a CDK4/6 inhibitor • Appropriate candidates for chemotherapy • Amenable to biopsy at the time of study entry *5.* Adequate organ function including: • Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L • Platelets ≥ 100 × 10^9/L • Hemoglobin ≥ 9/g/dL (may have been transfused) • Total serum bilirubin ≤ 1.5 times upper limit of normal (ULN) • Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤ 2.5 × ULN (or ≤ 5 × ULN if liver metastases are present) • Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance ≥ 50 mL/min as calculated using the Cockcroft-Gault (CG) equation • Thyroid Stimulating Hormone (TSH) ≤ 1 x ULN • Amylase ≤ 1 x ULN • Lipase ≤ 1 x ULN • CPK ≤ 1.5 x ULN

- LVEF (echo) ≥ LLN (Cobi arm only)

6. Female patients of childbearing potential must agree to use at least two methods of acceptable contraception from 15 days prior to first trial treatment administration until at least 5 months after study participant's final dose of study drugs. See appendix C for details.
   Note: Females of childbearing potential are defined as those who are not surgically sterile or post-menopausal (i.e. patient has not had a bilateral tubal ligation, a bilateral oophorectomy, or a complete hysterectomy; or has not been amenorrheic for 12 months without an alternative medical cause). Post-menopausal status in females under 55 years of age should be confirmed with a serum follicle-stimulating hormone (FSH) level within laboratory reference range for postmenopausal women.
7. Patients unable to read/write in English are eligible to participate in the overall study but will not participate in the Patient-Reported Outcome questionnaires throughout the trial
8. Re-enrollment of a subject that has discontinued the study as a pre-treatment screen failure (i.e. a consented patient who did not receive study drugs) is permitted. If re-enrolled, the subject must be re-consented. Only the screening procedures performed outside of protocol-specified timing must be repeated.

Exclusion Criteria

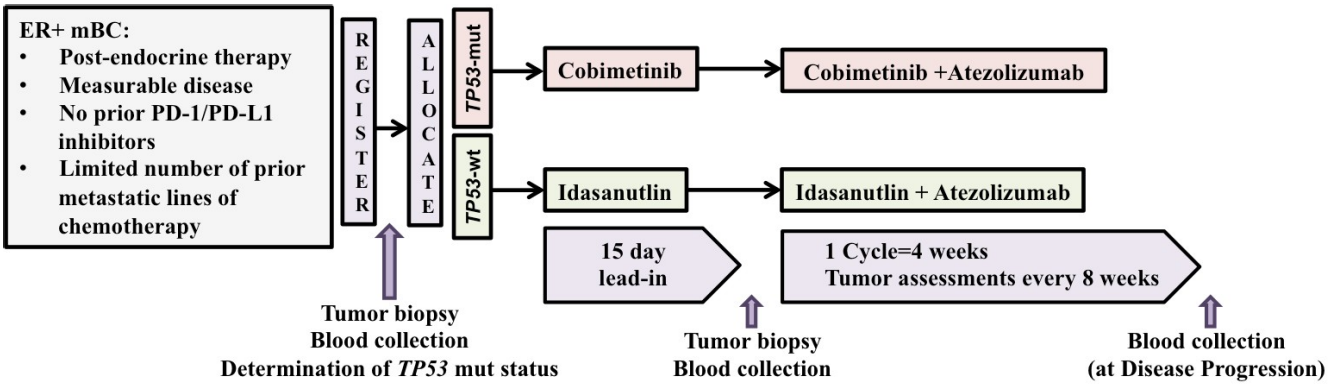
1. Prior therapy with anti-PD-L1 and anti-PD1 antibodies, MEK inhibitors or MDM2 antagonists.
2. No more than 3 lines of chemotherapy in the metastatic setting
3. No concurrent anticancer therapy. Required washout from prior therapy:
   - Endocrine therapy: no required wash-out
   - Chemotherapy: 14 days
   - Major surgery: 14 days (provided wound healing is adequate)
   - Radiation: 7 days
   - Investigational/Biologic Therapy (half –life ≤ 40 hours): 14 days
   - Investigational/Biologic Therapy (half –life > 40 hours): 28 days
   - Use of corticosteroids or immunosuppressive medication is exclusionary, except the following in the absence of active autoimmune disease:
     - Subjects are permitted the use of corticosteroids with minimal systemic absorption (e.g. topical, ocular, intra-articular, intranasal, and inhaled);
     - Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent are permitted;
     - Adrenal replacement steroid doses including doses > 10 mg daily prednisone are permitted;
     - A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g. CT scan premedication against contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
4. Previous malignant disease other than breast cancer within the last 5 years, with the exception of basal or squamous cell carcinoma of the skin,

	cervical carcinoma in situ, or low-risk cancers considered curatively treated (i.e. complete remission achieved at least 2 years prior to first dose of study drugs AND additional therapy not required while receiving study treatment). 5. All subjects with brain metastases, except those meeting the following criteria: • Brain metastases that have been treated locally and are clinically stable for at least 2 weeks prior to enrollment • No history of intracranial or spinal cord hemorrhage • No evidence of interim CNS disease progression • Metastasis to the midbrain, pons, and medulla • No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable. • Subjects must be either off steroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) 6. Receipt of any organ transplantation including allogeneic stem-cell transplantation. 7. Significant acute or chronic infections including, among others: • Known history of testing positive for human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS). • Active tuberculosis • Positive test for hepatitis B virus (HBV) surface antigen (and/or core antibody) and/or confirmatory hepatitis C virus (HCV) RNA (if anti-HCV antibody tested positive). 8. Interstitial lung disease that is symptomatic or which may interfere with the detection or management of suspected drug-related pulmonary toxicity. 9. Active autoimmune disease with reasonable possibility of clinically significant deterioration when receiving an immunostimulatory agent: • Subjects with Type 1 diabetes mellitus, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunossupressive treatment are eligible • Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or 10 mg equivalent prednisone per day • Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intra-ocular, or inhalation) are acceptable. 10. Uncontrolled asthma [defined as having 3 or more of the following features of partially controlled asthma within 28 days prior to starting study treatment: Daytime symptoms more than twice per week, any limitation of activities, any nocturnal symptoms/awaking, need for reliever/rescue inhaler more than twice per week, or known lung function (PEF or FEV1) without administration of a bronchodilator that is < 80% predicted or personal best (if known)]. 11. Current symptomatic congestive heart failure (New York Heart

	Association > class II), unstable cardiac arrhythmia requiring therapy (e.g. medication or pacemaker), unstable angina (e.g. new, worsening or persistent chest discomfort), or uncontrolled hypertension (systolic > 160 mmHg or diastolic > 100mmHg). Or any of the following occurring within 6 months (180 days) prior to first dose of study drugs: Myocardial infarction, coronary/peripheral artery bypass graft, cerebrovascular accident or transient ischemic attack. (Use of antihypertensive medication to control blood pressure is allowed.) 12. Concurrent treatment with a non-permitted drug as well as foods or supplements that are strong or moderate CYP3A4 enzyme inducers or inhibitors. Any of the above has to be discontinued at least 7 days prior to Cycle 1/ Day 1 of study treatment. See supplemental packet for guidance. 13. Requirement of anticoagulant therapy with oral vitamin K antagonists such as Coumadin (warfarin). Low-dose anticoagulants for the maintenance of patency in a central venous access device or the prevention of deep vein thrombosis or pulmonary embolism is allowed. Therapeutic use of low molecular weight heparin is allowed provided patients are safely able to interrupt it prior to biopsy procedures. 14. Persisting non-hematological toxicity related to prior therapy that has not reduced to Grade 1 [National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 5.0]; however, alopecia and sensory neuropathy Grade ≤ 2 are acceptable and Grade ≤ 2 non-hematological toxicities well controlled with medical management are allowed (for example: hypomagnesemia well controlled on magnesium replacement). 15. Known severe (Grade ≥ 3 NCI-CTCAE) hypersensitivity reactions to monoclonal antibodies, or history of anaphylaxis. 16. Vaccination within 28 days of the first dose of study drugs and while on trial is prohibited, except for administration of inactivated vaccines (for example, inactivated influenza vaccine). 17. Pregnant or breastfeeding females. 18. Known current alcohol or drug abuse 19. Prisoners or subjects who are involuntarily incarcerated. 20. Known psychiatric condition, social circumstance, or other medical condition reasonably judged by the patient's study physician to unacceptably increase the risk of study participation; or to prohibit the understanding or rendering of informed consent or anticipated compliance with scheduled visits, treatment schedule, laboratory tests and other study requirements. 21. Known risk factors for ocular toxicity (cobi arm only), consisting of any of the following: • presence of serous retinopathy within 6 months of protocol enrollment • presence of retinal vein occlusion (RVO) within 6 months of protocol enrollment
Study Assessments	<u>Safety Assessment:</u>

	• History, physical exam, and routine blood work such as blood counts and comprehensive metabolic panel will be performed on day 1 of each treatment cycle. Echocardiograms and ophthalmologic examinations will be performed periodically for those on the cobi arm. • Analyses will be performed for all patients having received at least one dose of study drugs. The study will use the NCI CTCAE v5.0. <u>Anti-tumor Assessments:</u> • CT scans of the chest, abdomen, and pelvis and bone scan (when applicable) are to be performed approximately every 8 weeks

SCHEMA



1. STUDY DESIGN/ SUMMARY

The experience with immune checkpoint inihibitors (ICI) in other cancer types demonstrate responses tend to be more durable and more likely to lead to improved overall survival than other therapies, highlighting their importance. Therefore, strategically combining molecularly-targeted agents that may support an ICI response will be especially advantageous to clinical outcomes. Improving response rates to ICI in ER+ metastatic breast cancer (ER+ mBC) may be a challenge because these tumors typically demonstrate a 'cold' immune microenvironment - that is to say they often have few T cells in the tumor microenvironment - which is indicative of an overall failure of the immune system to recognize the tumor, rather than a reliance on peripheral tolerance (i.e. engagement of PD-1-PD-L1). One strategy to engage the immune system, thereby promoting response to immunotherapies, is to administer therapies that increase recognition of tumor cells through enhanced antigen presentation and/or increase T cell homing. This clinical trial will incorporate each of these different strategies in a genotype-specific (mutually exclusive and exhaustive across all ER+ breast cancers) manner that is supported by scientific preclinical data. The approaches have been shown to either 1) enhance Major Histocompatibility Complex (MHC)-mediated antigen presentation and PD-L1 expression or 2) increasing T cell homing to the tumor through upregulation of T cell homing chemokines, setting the stage for clinical response to checkpoint inhibitors.

The clinical trial associated with this proposal is a multicenter, open-label, 2-arm phase Ib/II trial that will evaluate the anti-tumor effect of Atezolizumab (an anti- PD-L1 mAb) in combination with Cobimetinib (a MEK inhibitor) in patients with *TP53*-mutated ER+ mBC, or Idasanutlin (an MDM2 antagonist) in patients with *TP53*-wt ER+ mBC. All participants will have targeted Next Generation Sequencing (NGS) performed prior to treatment arm allocation for *TP53* mutation status determination and assess tumor mutation burden. We would expect about – 40% of all patients with ER+ mBC to have a *TP53* mutation (*TP53*-mut) in their tumor[3]. Briefly, patient's eligibility criteria will include: ER+ mBC refractory to endocrine therapies with biopsy-accessible tumor, no prior use of MEK, MDM2, PD-1 or PD-L1 inhibitors/ antagonists, no more than 3 lines of chemotherapy in the metastatic setting, ECOG performance status ::1, normal baseline blood counts and chemistry laboratory profile, no concurrent use of immunosuppressive medications,

and no concurrent uncontrolled illness, including autoimmune diseases with reasonable possibility of clinically significant complications. In the phase Ib portion of the trial we will determine the safety and tolerability [Dose Limiting Toxicity (DLT), Maximum Tolerated Dose (MTD) and Recommended Phase II Dose (RP2D) determination] of Atezolizumab and Idasanutlin in patients with ER+ mBC. With three possible dosing cohorts, a minimum of 9 and a maximum of 18 subjects may be recruited for the dose escalation portion of the study. In the phase II portion of the trial we will determine the anti-tumor effect and adverse event profile of Atezolizumab with Cobimetinib or Idasanutlin in patients with ER+ mBC [Progression Free Survival (PFS) and/or Clinical Benefit Rate (CBR; percentage of patients without disease progression at 6 months); immune-related Response Criteria (irRC), Overall Response Rate (ORR; by RECIST 1.1 – for patients with measurable disease), Percentage of patients alive at 12 months (% OS), and Adverse Event profile]. A minimum of 33 and a maximum of 66 patients (total in both arms) will be allocated to receive:

- Arm 1 (*TP53*-mut) – Atezolizumab 840 mg IV, on Days 1 and 15, and Cobimetinib 60 mg PO daily, on Days 1 - 21, every 28 days (on Cycle 1 only Atezolizumab will start on Day 15); or
- Arm 2 (*TP53*-wt) – Atezolizumab 840 mg IV, on Days 1 and 15, and Idasanutlin (final dose to be determined by the phase Ib portion of the trial) PO daily, on Days 1 - 5, every 28 days (on Cycle 1 only Atezolizumab will start on Day 15),

until disease progression, unacceptable adverse event(s), concurrent illness that prevents further administration of treatment, patient withdrawal from study, or significant non-compliance with protocol. To assess the anti-tumor effect of therapy, we will estimate the overall tumor burden at baseline to which subsequent measurements (performed every 8 weeks using the Solid Tumor Response Criteria [RECIST] v1.1) will be compared.

Tumor biopsies (fixed for IHC analysis and snap-frozen for RNA extraction) and peripheral blood will be collected prior to initiating Cobimetinib (COBI)/Idasanutlin (IDASA) (PRE-Bx), after 15 days of COBI/IDASA and prior to adding Atezolizumab (ATEZ) (POST-Bx). The following parameters will be assessed from these samples:

Parameter	Arm	Sample type	Comparison	Expectation	Endpoint
CD8+ T cells, IHC/multiplexed IF	BOTH	FFPE tumor	PRE:POST	Increase	Primary
Other cell markers: CD4, PD-L1, Foxp3, IHC/multiplexed IF	BOTH	FFPE tumor	PRE:POST	Increase	Secondary
TILs, H&E	BOTH	FFPE tumor	PRE:POST	Increase	Secondary
HLA-DR, HLA-A/B/C IHC/IF	COBI	FFPE tumor	PRE:POST	Increase	Secondary
***CCL5, CXCL9, CXCL10, CXCL1* mRNA, RNAseq**	IDASA	Frozen tumor	PRE:POST	Increase	Secondary
Immune signatures, RNAseq	BOTH	Frozen tumor	PRE:POST	Increase/decrease	Exploratory
CyTOF/T cell compartments	BOTH	PBMCs	PRE:POST	Increase/decrease	Exploratory

2. OBJECTIVES

	Objective	Endpoint
Phase I		
Primary	To determine the safety and tolerability of Atezolizumab and Idasanutlin in patients with ER+ mBC	• Dose Limiting Toxicity (DLT) • Maximum Tolerated Dose (MTD) • Recommended Phase II Dose (RP2D)
Phase II		
Primary	To determine the anti-tumor effect of Atezolizumab and Cobimetinib or Idasanutlin in patients with ER+ mBC	• Progression Free Survival (PFS)
Secondary	To determine the anti-tumor duration of effect of Atezolizumab and Cobimetinib or Idasanutlin in patients with ER+ mBC	• Clinical Benefit Rate (CBR; percentage of patients without disease progression at 6 months) – for all patients • Immune related response criteria (irRC) • Duration of Response (DOR) • Overall Response Rate (ORR; by RECIST 1.1 – for patients with measurable disease) • Percentage of patients alive at 12 months (% OS)
	To determine the safety and tolerability of Atezolizumab and Cobimetinib or Idasanutlin in patients with ER+ mBC	Adverse event profile
Exploratory	To evaluate if CD8+ T cells are enhanced in the tumor with either MEK or MDM2 inhibition.	• Multiplexed IHC for CD8 (also CD4, FoxP3, PD-L1, MHC-I, MHC-II)
	To evaluate if MHC-I/II and/or PD-L1 expression is enhanced with MEK inhibition	• PD-L1 expression in the tumor and on TILs • Expression of MHC I and II in the tumor
	To evaluate if T cell chemotractants (CCL5, CXCL9,10,11,13) are upregulated upon MDM2 antagonism	• RNAseq gene expression data
	To determine if baseline or changes in PD-L1 expression, MHC expression, presence of tumor infiltrating lymphocytes, neoantigen expression/ mutation burden (using RNA-and whole exome sequencing), *CCL5, CXCL9, CXCL10, CXCL11, and CXCL13* correlate with clinical outcome.	• Multiplexed IHC • Presence of tumor infiltrate lymphocytes (TIL) • Tumor RNA-sequencing (RNA-Seq) Tumor whole exome sequencing

3. BACKGROUND

3.1. Breast Cancer

Despite advances in early detection and therapeutic options, unresectable or metastatic breast cancer remains incurable and is one of the leading causes of cancer-related mortality[4]. Breast cancer is a molecularly heterogeneous disease with three distinct molecular subtypes[5]. The first group is characterized by estrogen receptor (ER) expression positivity and/or progesterone receptor (PgR) positivity with the absence of over-expression or amplification of HER2 (ER+ BC). The second group is characterized by over-expression or amplification of HER2 (HER2+ BC), with more than half of these tumors being positive (+) for expression of ER/PgR. The third group lacks detectable ER and PgR, and overexpression of HER2, and is thus referred to as triple-negative breast cancer (TNBC). Approximately 65% of newly diagnosed breast cancers are ER/PgR+ and HER2-negative (also referred to as luminal tumors), while an additional 20% of newly diagnosed cases are HER2+.

3.1.1 Estrogen receptor-positive (ER+) Breast Cancer

ER-targeted drugs, specifically drugs that antagonize estrogen binding to the ER (tamoxifen), drugs that block estrogen biosynthesis (non-steroidal and steroidal aromatase inhibitors [AI] - only effective in postmenopausal patients), and drugs that antagonize and downregulate the ER (fulvestrant), have been the mainstay of systemic treatment for patients with both localized and metastatic ER/PgR+ breast cancers[6]. However, acquired resistance (and occasionally primary resistance) to anti-estrogen therapy universally develops in patients with ER+ MBC[7].

Although ER+ disease is generally less aggressive and can be treated with endocrine agents, there is still a high mortality rate for ER+ MBC. Multiple targeted agents (i.e. endocrine agents, cyclin-dependent kinase 4/6 [CDK4/6] inhibitors, and mammalian target of rapamycin [mTOR] inhibitors) and chemotherapy are usually effective in ER+ MBC, but complete clinical cures are rare, and acquired resistance is commonplace. Due to the high prevalence of mBC patients with ER+ disease, new strategies with curative potential are sought. Contrary to TNBC, in ER+BC, the tumor's total mutation burden (TMB) is generally low, but in a subset of tumors following extensive prior endocrine therapy, TMB increases[8], suggesting that in these cancers immunotherapeutic strategies could be further explored.

3.2. Immune checkpoint inhibition in cancer therapy

PD-L1 is a 40kD type I transmembrane protein that functions as a ligand for its primary receptor, PD-1. PD-L1 is broadly expressed on professional antigen-presenting cells (APC) among other hematopoietic and non-hematopoietic cells, while PD-1 is expressed on activated lymphocytes and myeloid cells[9]. PD-L1 can also be potently up-regulated on many cell types, including epithelial cells upon interferon-gamma (IFNγ) stimulation. Upon ligation of PD-L1 to PD-1, an activated lymphocyte (most notably T-cells) is modulated toward regulatory (suppressive; Treg) phenotype, or induced to anergy/apoptosis (**Fig. 1**)[9,10].

These molecules exist as a putative mechanism to protect against immune self-recognition, and this pathway is thought to be hijacked by cancer cells in a variety of malignancies[10-15]. In some tumors, interruption of this ligation with blocking antibodies for PD-1 or PD-L1 can induce profound and durable anti-tumor immune responses[9-11,17,18]. However, only a subset of patients benefit from these targeted agents thus emphasizing the need for surrogate biomarkers of response.

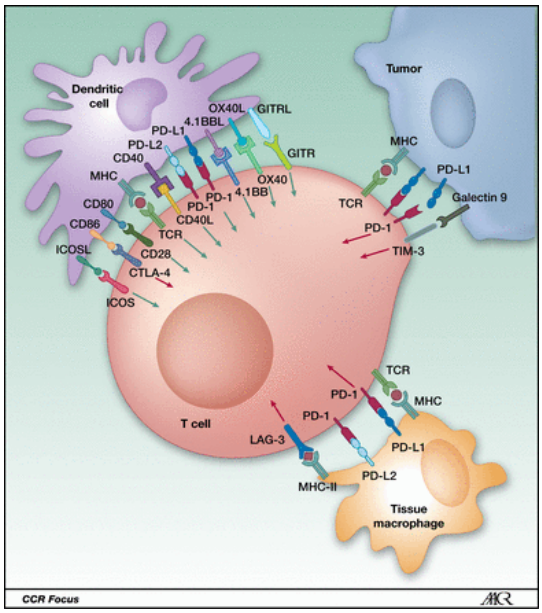


Figure 1: Immune checkpoint receptor/ligand signaling axis in cancer. Image reproduced from ref [2].

Immune checkpoint inhibitors (ICIs) have transformed the treatment of many cancers including melanoma, NSCLC, RCC, head and neck SCC, and urothelial cancer[16]. Single agent monoclonal antibody (mAb)-mediated blocking of immune checkpoint ligand/receptor interactions (e.g. CTLA-4, PD-1, and PD-L1) has resulted in unprecedented anti-tumor responses in lung and renal cancer, as well as melanoma and Hodgkins disease[13,15]. In particular, targeting the PD-1/PD-L1 axis has produced substantial responses with significantly more manageable toxicity profiles compared to CTLA-4 mAb (ipilimumab). Phase I and II results for PD-1/PD-L1 mAbs in other solid tumors are also promising[14]. In light of these single agent results, synergistic combinations of PD-1/PD-L1 targeted agents with other active therapeutics are being investigated[17].

Despite some success of PD-1/PD-L1 targeted therapy in triple-negative breast cancers (response rates of ~20%)[18,19], data in ER+ breast cancer are more limited and results thus far have not been encouraging (response rates of ~12%, median progression free survival of 2 months)[18,20,21,22]. The experience with ICI in other cancer types demonstrate responses tend to be more durable and more likely to lead to improved overall survival than other therapies, highlighting their importance. Therefore, strategically combining molecularly-targeted agents that may support an ICI response will be especially advantageous to clinical outcomes. Improving response rates to ICI in ER+ mBC may be a challenge because these tumors typically demonstrate a 'cold' immune microenvironment - that is to say they often have few T cells in the tumor microenvironment - which is indicative of an overall failure of the immune system to recognize the tumor, rather than a reliance on peripheral tolerance (i.e. engagement of PD-1-PD-L1). One strategy to engage the immune system, thereby promoting response to IT, is to administer therapies that increase recognition of tumor cells through enhanced antigen presentation and/or increase T cell homing. This proposal will incorporate each of these different strategies in a genotype-specific (mutually exclusive and exhaustive across all ER+ breast cancers) manner that is supported by scientific preclinical data. The approaches have been shown to either 1) enhance Major Histocompatibility Complex (MHC)-mediated antigen presentation and PD-L1 expression or 2) increasing T cell homing to the tumor through upregulation of T cell homing chemokines, setting the stage for clinical response to checkpoint inhibitors.

3.3. The RAS/Raf/MEK pathway in breast cancer

The Ras/Raf/MEK pathway conveys growth factor receptor signals from cell surface receptors to the nucleus to activate transcriptional programs of proliferation and survival. The commonly activated oncogenes K-Ras and B-Raf are mutated in a variety of malignancies, but are rarely observed in breast cancer[23-26]. Nonetheless, this pathway appears to be highly transcriptionally activated in TNBC as opposed to ER+ and HER2+ primary breast cancers, which frequently redirect growth factor signals to the PI3K pathway[27-30]. We have previously shown that at least one mechanism of Ras/Raf/MEK pathway activation in TNBC and some ER+ breast cancers can result from frequent genomic or epigenetic loss of DUSP4, a negative regulator of ERK[31-33]. Of those ER+ breast cancers that demonstrate DUSP4 loss, the majority lie in the Luminal B subtype[31,33], which are often resistant to endocrine therapy and are more likely to metastasize, both of which lead to increased patient mortality[34]. The Ras/Raf/MEK pathway has frequently been implicated in the acquisition of endocrine resistance in ER+ breast cancers and ovarian cancer[35-38].

Molecularly, ER+ breast cancer can be divided into “luminal A” and “luminal B” phenotypes[34,39]. While being more intrinsically resistant to endocrine therapy, luminal B tumors may be more reliant of growth factor pathways, such as RAS/MEK. Indeed, genetic activation of the Ras/MEK pathway in preclinical ER+ mouse models generates metastatic phenotypes which replicate luminal B disease[40]. One marker of luminal A/B status is the presence of highly clonal *TP53* mutations, which exist in only 5-15% of the luminal A subtype, and ~30-40% of luminal B tumors[41,42]. *TP53* mutations also mark ER+ tumors that may be more likely to be of the Her2-enriched (despite lack of HER2 amplification) or basal-like subgroups, both of which have a high degree of intrinsic MEK activity[31]. *TP53*-mutated ER+ tumors are more likely to demonstrate luminal B like behavior, which is partially characterized by loss of Ras/MAPK negative regulators[33,43]. In these tumors, inability to present antigen, rather than T cell recruitment, appears to be the limiting factor. MEK activation suppresses antigen presentation, while MEK inhibition (i.e. Cobimetinib) can derepress it, leading to enhanced responses to PD-L1 targeted therapy[1]. This principle was recently demonstrated in patient samples by Genentech[44]. Thus, MEK inhibition may have the greatest value in *TP53*-mutant ER+ breast tumors.

We have published multiple preclinical models and mechanistic data demonstrating that MEK inhibition is synergistic with PD-1/PD-L1 inhibition[45]. In this work, we found that treatment with a MEK inhibitor upregulates antigen-presenting MHC-I and II molecules, both innate, and in response to interferon γ (IFNγ). Enhanced antigen presentation is likely to improve anti-tumor immunity through increase in T-cell recognition. Likewise, MEK inhibition sensitizes tumors to PD-L1 inhibition by unmasking the tumor from the immune system, leaving the PD-1/PD-L1 interaction as the ‘gatekeeper’ of a full anti-tumor response (**Fig. 2**).

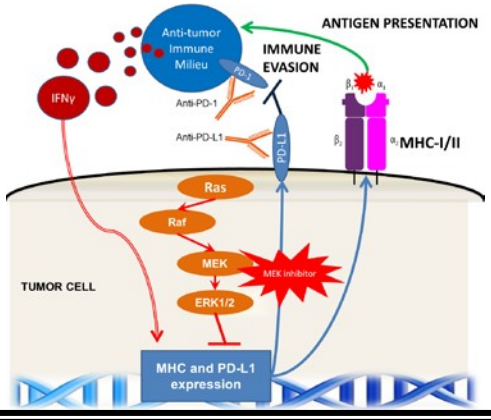
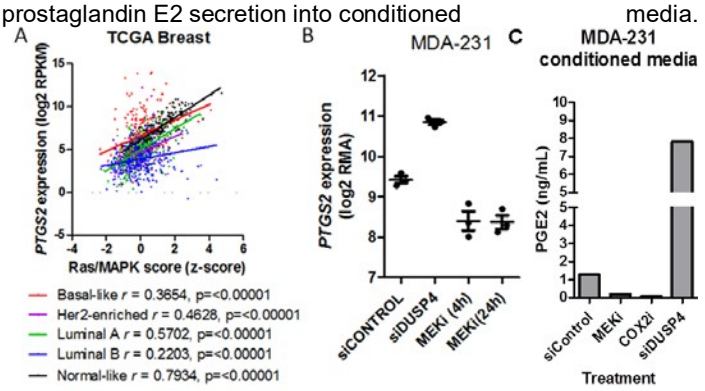


Figure 2: Proposed mechanism of MEK inhibition in sensitizing TNBC to PD-L1 inhibition. IFNγ secreted from activated immune cells in the tumor microenvironment stimulates expression of MHC-I and MHC-II via activation of STAT1, which increases antigen presentation thereby perpetuating immune activation. However, PD-L1 expression is also stimulated by the same pathway, promoting immune tolerance. The Ras/Raf/MEK pathway suppresses both of these signals, while MEK inhibition upregulates them. Co-treatment with a PD-L1 inhibitor counteracts the immune evasion arm of this response.

Additional beneficial immune-mediate mechanisms of action of MEK inhibitors include downregulation of *COX2* (*PTGS2*), which is an immediate early gene that is robustly modulated by the Ras/MAPK pathway. In the TCGA breast cancer data, *COX2* expression is tightly linked to Ras/MAPK transcriptional activity. Furthermore, inhibition of MEK in MDA-231 TNBC cell lines potently downregulates *PTGS2* gene expression while loss of the Ras/MAPK suppressor DUSP4 upregulated *PTGS2* **(Fig 3).** This finding is important because a recent study demonstrated that prostaglandin synthesis by COX-2 from tumor cells can induce immune-evasion, and inhibition of prostaglandin synthesis augmented response to PD-1/PD-L1 therapy[46]. Thus, although exploratory, these data suggest a possible additional immune-mechanistic effect of MEK inhibition in breast cancer. This effect can be explored in the context of molecular biomarker studies in the proposed trial herein.

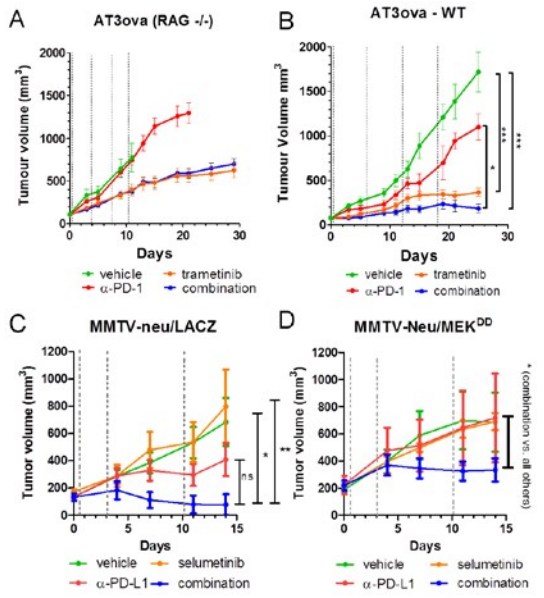
Figure 3: Role of MAPK pathway on *COX2/PTGS2* expression. Prostaglandin synthesis is rate-limited by *PTGS2* expression which is tightly controlled in breast cancer by MEK activation (A). In B, we show that loss of *DUSP4*, a frequent event in TNBC and some ER+ tumors which activates MEK, upregulates *PTGS2* gene expression, while MEK inhibition reduces it. C) Mass-spec analysis demonstrates loss of DUSP4 enhances, while MEK (or COX2) inhibition decreases prostaglandin E2 secretion into conditioned media.



Collectively, these data suggest that MEK inhibition may upregulate the expression of antigen presenting molecules, aiding in CTL recognition of tumor cells. Additional beneficial effects on anti-tumor immunity likely include suppression of prostaglandin synthesis, and immune-independent effects of suppression of tumor cell proliferation.

We already know from recently presented data that PD-1/PD-L1 axis inhibition is effective in a fraction of TNBC[18,19] and ER+ tumors[21]. Although not confined to TNBC, PD-L1 expression is higher in basal-like and claudin-low breast cancers, which are often clinically triple-negative[47-52], making this subtype an attractive target. In metastatic luminal-like ER+ disease, the potential for a breakthrough in therapy lies in our preclinical data demonstrating activity of the combination of MEK and PD-L1 inhibition in two independent luminal-like breast cancer models (**Fig. 4**) with separate MEK inhibitors (trametinib and selumetinib) and separate mAbs targeting PD-1 and PD-L1,

Figure 4: Preclinical activity. A) MEKi and PD-1 therapy do NOT synergize in a T-cell deficient host (RAG -/-), but DO synergize in an immunocompetent host. C) In the luminal MMTV-neu model, MEK inhibition synergizes with PD-L1 targeted therapy, and **is required** for anti-PD-L1 activity in the presence of genetic MEK activation (MEK^{DD}). Details of these studies can be found in ref[1].



respectively. Thus, this activity is a class-effect since different agents were used with similar results[1]. These data have been independently reproduced in a variety of other solid tumor models[53]. Furthermore, preliminary clinical data presented at ASCO 2016 showed that patients with microsatellite-stable colorectal cancer achieved a 20% response rate[44] with dual MEK and PD-L1 inhibition, compared to a near 0% response rate in previous studies with single agents targeting the PD-1/PD-L1 interaction[15,54]. The significance of the activity of this combination has prompted Genentech to proceed directly to a Phase III (NCT02788279) trial, without a Phase II, in patients with metastatic colorectal cancer. Thus, the breadth of existing preclinical data and the timing are highly supportive for this trial.

3.4. Senescence in cancer therapy

CD8+ T-cell marker expression correlates with expression of CXCL9 and CCL5 chemokines, and high CXCL9 and CCL5 expression correlates with enhanced survival based on TCGA analysis of 1105 invasive breast cancers[41,42]. Therapies that induce senescence would activate NF-κB and recruit CD45+ immune cells, which is accompanied by enhanced production of T-cell recruiting chemokines CCL5, CXCL9, and CXCL11 (**Fig. 5**).

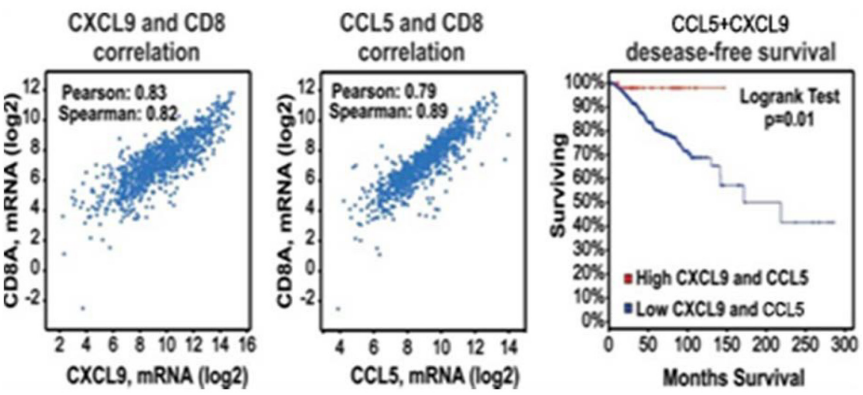


Figure 5: Senescence and T cell recruitment. (Left) Senescence-associated T cell recruiting cytokines CXCL9 and CCL5 are strongly correlated with the expression of CD8A in the tumor microenvironment across >1000 breast cancers (TCGA,[41,42]). (Right) Patients with high expression of these cytokines have improved outcomes.

TP53 is the most highly mutated gene in breast cancer as a whole. Functionally, *TP53* mutations uncouple p53 protein from its natural negative regulator MDM2, but also inhibit or alter its ability to induce apoptosis or senescence[55]. MDM2 antagonists (such as nutlin or Idasanutlin) de-repress wild-type (wt)-p53, but not mutant p53, and prevent the ubiquitination and proteosomal degradation of wt-p53. This effect allows wt-p53-mediated senescence programs (**Fig. 6**). While senescence is not a preferred therapeutic outcome, as it does not eliminate cancer cells, the innate senescence program (termed Senescence-Associated Secretory Program [SASP]) recruits immune cells through secretion of T cell homing chemokines (i.e. CCL5, CXCL-9,11, and 13 et al)[56]. Thus, we hypothesize that the TME of wt-p53 tumors can be enhanced by MDM2 antagonists.

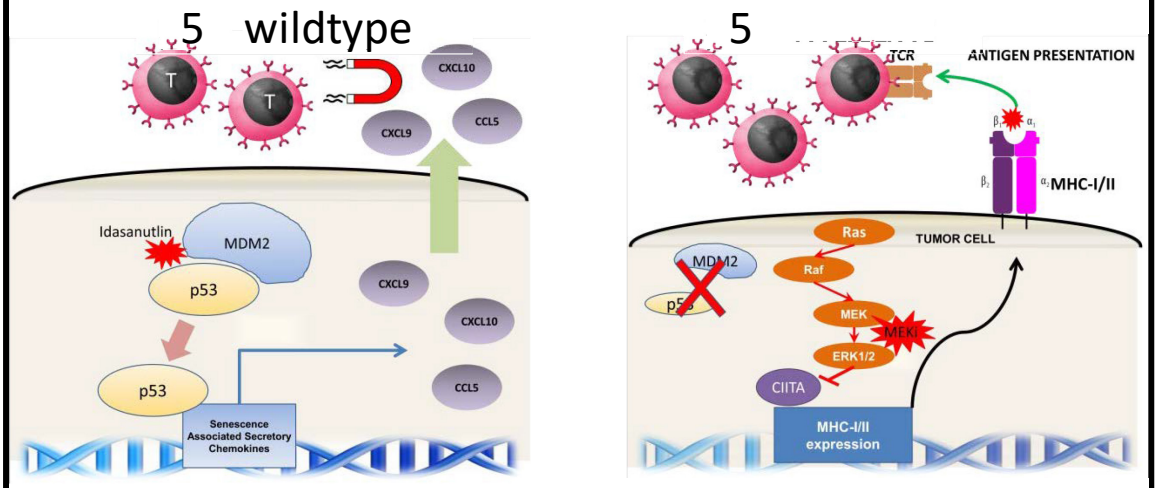


Figure 6: p53 mediated senescence programs. (Left) In *p53*-wt tumors, ldasanutlin treatment will disengage and activate p53-mediated senescence transcriptional programs leading to upregulation of T-cell chemokines, and the recruitment of T cells to the tumor microenvironment. (Right) In *p53*-mutant tumors, MDM2 antagonism will be largely ineffective, as mutated p53 will not engage MDM2. However, *p53*-mutated ER+ tumors are more likely to demonstrate luminal B like behavior, which is partially characterized by loss of Ras/MAPK negative regulators[33,43]. In these tumors, inability to present antigen, rather than T cell recruitment, appears to be the limiting factor. MEK activation suppresses antigen presentation, while MEK inhibition (i.e. Cobimetinib) can de-repress it, leading to enhanced responses to PD-L1 targeted therapy[1]. This principle was recently demonstrated in patient samples by Genentech[44].

3.5. Clinical Trial Rationale

Immune checkpoint inhibitors therapy in ER+ breast cancer has not been encouraging thus far. However, strategically combining molecularly-targeted agents that may increase immune recognition of tumor cells through enhanced antigen presentation and/or increase T cell homing may increase ICI response. This clinical trial will examine these different strategies in a genotype-specific (mutually exclusive and across all ER+ breast cancers) manner:

- MEK inhibition (MEKi) in ***TP53*-mutant ER+ breast cancer**: ER+ tumors with MAPK pathway activation exhibit metastatic phenotypes of luminal B (more often *TP53*-mutated) disease. In luminal-like breast cancer models, a combination of MEKi and PD-1/PD-L1 ICI induces profound anti-tumor effects, in part by blocking na"ve CD8+ T cell priming, increasing neoantigen-specific CD8+ T effector cells in the tumor microenvironment (TME), and by protecting CD8+TIL cytotoxicity through inhibition of apoptosis driven by chronic TCR stimulation.
- MDM2 antagonism in ***TP53*-wt ER+ breast cancer**: MDM2 antagonists both de-repress wt-p53, not mutant p53 and prevent proteosomal degradation of *TP53*-wt allowing wt-p53 to activate its transcriptional program of senescence (termed Senescence-Associated Secretory Program [SASP]) The SASP recruits immune cells through secretion of T cell homing chemokines.

We hypothesize that approaches which enhance antigen presentation (MHC-I/II) or PD-L1 through MEK inhibition, or enhance expression of T-cell recruiting chemokines via MDM2 inhibition, will increase activated tumor-specific CD8+ T cells in the TME and augment the efficacy of the anti-PD-L1 mAb Atezolizumab in ER+ mBC.

Correlative studies using tumor tissue and blood will determine whether the respective molecularly-targeted agent enhances CD8+ T cells in the tumor microenvironment, enhances antigen presentation, and/or increases T cell homing chemokines. These molecular endpoints will be tested for their association with patient-specific clinical outcome. If these strategies indeed modify the tumor microenvironment as predicted, we may turn immune-unresponsive tumors like ER+BC into immune-responsive to anti-PD-L1 therapies. This would have major implications on the use of anti-PD-L1 in other "cold" solid tumors as well, by defining one or more approaches to turn "non-inflamed into inflamed tumors". Thus, the breadth of existing preclinical data and the timing are highly supportive for this trial.

3.6. Correlative Science Background

A number of correlatives for response to immunotherapies have been proposed using retrospective data analyses, but almost none of them have been conclusively shown to associate with PD-1/PD-L1 targeted therapy response in well-controlled clinical trials to date, including PD-L1. Other proposed biomarkers have been tumor infiltrating lymphocytes (TILs)[57,58], CD8+ T cells[59], mutation burden[60], neoantigen burden[61-63]. It will be important to collect these data to determine their utility in breast cancer patients, and how combinations of molecularly-targeted therapies affect these correlatives.

MEK signaling pathway. Our previous preclinical studies have clearly demonstrated a connection between enhanced MHC-I/MHC-II and PD-L1 expression following MEK inhibition and improved response to anti-PD-L1 immunotherapy[1]. Furthermore, in melanoma, we have demonstrated an association between MHC-II expression and clinical outcome including objective response, progression-free survival, and overall survival[64]. This finding has now been confirmed in over 100 clinical specimens. MEK inhibition sensitizes tumors to PD-L1 inhibition by upregulating MHC-I and MHC-II antigen presentation while leaving the PD-1/PD-L1 interaction as the 'gatekeeper' of a full anti-tumor response. Upregulation of CD8, MHC-I, and PD-L1 was observed with cobimetinib in Phase I-treated colorectal cancer patients[44]. Thus, we have reason to hypothesize that MEK inhibition will alter the expression of MHC-I and II, and that this will be correlated to clinical response in patients.

Senescence-associated transcriptional programs. The work of our colleagues[65-67] have demonstrated that senescence-associated cytokines can recruit T cells to the tumor microenvironment and facilitate T cell responses. This program can in part be activated by senesence-inducing therapies that stabilize p53. Nutlin, or idasanutlin (MDM2 antagonsts) are an effective way to activate senescence-associated transcriptional programs. Thus, our correlatives in the Idasanutlin arm will be aimed at ascertaining whether Idasanutlin activates these transcriptional programs in p53-wildtype tumors, whether this associates with increased T cell homing, and finally, whether these effects correlate with patient response.

3.6.1. Proposed Correlative Studies

Tissue and blood

The comprehensive correlative studies proposed within this trial were designed to provide further understanding of both tumor and immune factors that predict response or resistance. Our main goals are to determine the therapeutic predictive role of the biomarkers proposed on clinical outcome, and to determine if the cfDNA results will discriminate pseudoprogression from true progression. Results will be compared before and after single agent therapy, and immune cell phenotyping in blood will be evaluated during therapy. The following correlative studies will be included:

1. TIL analysis from H&E

2. CD8, CD4, Foxp3, PD-L1, MHC-I and II expression via multiplexed IHC
3. DNA exomes: to identify neoantigens, neoantigen load and mutations/copy number changes.
4. HLA haplotyping for neoantigen prediction
5. RNA-seq: to identify gene expression patterns for the following purposes:
    a. Molecular subtype (PAM50)
    b. MEK activation signatures[68]
    c. Immune cell composition by CIBERSORT[69]
    d. SASP gene expression profile (CCL5, CXCL9,10,11,13)
    e. Expression level of potential neoantigens
6. CyTOF for T cell subsets in peripheral blood
7. Collection of plasma for future cfDNA based analyses.

We expect Cobimetinib treatment to result in the following changes in paired tumor biopsies:

- DECREASE in MEK activation signature (transcriptionally defined[68]), demonstrating on-target pharmacodynamics activity of Cobimetinib. This will be performed as we have previously published[1,32,70]. A paired T-test (or non-parametric equivalent) will be used to test the hypothesis.
- INCREASE in TILs, CD8,CD4, PD-L1, MHC-I and MHC-II IHC expression, which we expect will also be associated with a higher likelihood of response. A paired T-test (or non-parametric equivalent) in patients WITH clinical benefit versus patients WITHOUT clinical benefit will be used.
- INCREASE in IFNγ-response transcriptional signatures[71], which is a marker of both the activity of the local immune environment, and a marker of the robustness of the tumor response to IFNγ.
- DECREASE in *PTGS2* mRNA expression and transcriptional signatures[46]
- EXPANSION of effector T cell compartments in the peripheral blood (CyTOF) which we expect will also be associated with a higher likelihood of response.

We expect Idasanutlin treatment to result in the following changes in paired tumor biopsies:

- INCREASE in mRNA expression of CCL5, CXCL9, CXCL10, CXCL11, CXCL13. A paired T-test (or non-parametric equivalent) in patients WITH clinical benefit versus patients WITHOUT clinical benefit will be used. We will correct for multiple comparisons with a Bonferroni adjustment.
- INCREASE in mRNA expression of SASP/SIRS and senescence-associated markers
- INCREASE in TILs, CD8, and CD4 IHC expression, which we expect will also be associated with a higher likelihood of response. A paired T-test (or non-parametric equivalent) in patients WITH clinical benefit versus patients WITHOUT clinical benefit will be used.

At PRE-Bx or POST-Bx, we expect the following associations in both arms (Cobimetinib and Idasanutlin):

- HIGHER expression of mutations AND/OR predicted neoantigens to be associated with higher likelihood of response, as analyzed by a 2-sample one-tailed T-test in patients WITH clinical benefit versus patients WITHOUT clinical benefit.

3.7. Investigational Agents

3.7.1 Cobimetinib

Cobimetinib (GDC-0973) is a potent and highly selective inhibitor of MEK1/2, which is a MAPK kinase that activates ERK1/2. Inhibition of the RAS/RAF/MEK/ERK pathway affects tumor-cell proliferation and survival. Cobimetinib is a next-generation inhibitor of MEK1/2 with the previous generation represented by the comparator compound PD0325901 (PD901; Pfizer). Observations from the clinical experience with PD0325901[72] indicate a significant occurrence of AEs in the central nervous system (CNS) that may be mechanistically related to the RAS/RAF/MEK/ERK signaling pathway in the brain. Therefore, Cobimetinib was selected for possessing anti-tumor activity while sparing significant brain exposure.

Cobimetinib is currently approved, in combination with vemurafenib as a treatment for adult patients with unresectable or metastatic BRAFV600 mutation–positive melanoma who have been diagnosed with the cobas® 4800 BRAF V600 Mutation Test in a number of countries worldwide, including the United States, Canada, members of the European Union, and several other countries worldwide.

3.7.1.1 Clinical experience with Cobimetinib

Please refer to Cobimetinib Investigator's Brochure for full safety profile of cobimetinib. Study MEK4592g is a multicenter, Phase I, non-randomized, open-label, dose-escalation study. The study consisted of five treatment stages:

- Stage I: Dose-escalation cohorts; patients were treated on a 21 days on, 7 days off (21/7) schedule to determine the maximal tolerated dose (MTD). The MTD for the 21/7 schedule was found to be 60 mg.
- 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. The MTD for the 14/14 schedule was found to be 100 mg.
- Stage II: Expansion cohort with the MTD determined in Stage I (60 mg qd 21/7) in approximately 20 patients using fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scans of avid tumors that harbored a BRAF, NRAS, or KRAS mutation and with FDG-PET–avid disease.
- Stage IIA: Expansion cohort with the MTD determined in Stage IA (100 mg qd 14/14) in approximately 20 patients with FDG-PET–avid tumors that harbored a BRAF, NRAS, or KRAS mutation.
- Stage III: A dedicated DDI study at the MTD determined in Stage I (60 mg qd 21/7) in approximately 20 patients with solid tumors.

The primary objectives of Stages I, IA, II, and IIA of this study were to evaluate the safety and tolerability of Cobimetinib administered orally as repeated doses in patients with solid tumors and to determine the MTD of daily oral administration of Cobimetinib in patients with solid tumors. The primary objective of Stage III of this study was to evaluate the possible effect of Cobimetinib on the pharmacokinetics of dextromethorphan and midazolam. Study MEK4592g has been completed; a total of 115 subjects were treated.

3.7.1.2 Dose-Limiting Toxicities

Four DLTs were observed in Stage I (21/7 dosing schedule) of Study MEK4592g. At the 40-mg dose level, a DLT of Grade 4 hepatic encephalopathy was reported, which resolved following lactulose therapy, routine supportive care, and discontinuation of Cobimetinib. At the 60-mg dose

level, a DLT of Grade 3 rash was reported that improved with skin toxicity management and drug holiday. At the 80-mg dose level, two DLTs were reported: Grade 3 diarrhea despite treatment with anti-diarrheal medications and Grade 3 rash. Two DLTs were observed in Stage IA (14/14 dosing schedule) of Study MEK4592g. At the 125-mg dose level, 1 patient had Grade 3 rash and another had Grade 3 blurred vision associated with neurosensory detachment of the retina.

3.7.1.3 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 qd 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%).

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%), diarrhea, and hypokalemia (6.1% each). Grade 5 adverse events, which in Study MEK4592g included disease progression reported as an adverse event, are discussed separately below.

3.7.1.4 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 ≥ 2 patients among all patients in the study were anemia, bile duct obstruction, dehydration, syncope, and respiratory arrest (3 patients each [2.6%]).

3.7.1.5 Deaths

Study MEK4592g accrued a patient population with metastatic or unresectable solid tumors for which standard curative or palliative measures did not exist or were no longer effective. In addition, in Study MEK4592g disease progression was reported as an adverse event (Grade 5) instead of an outcome measure.

As of the clinical data cutoff date (20 September 2013), a total of 29 patients (25.2%) had died, including 11 patients in the Cobimetinib 60 mg qd 21/7 group.

A total of 14 deaths were reported for patients treated in Stage I of the study. With the exception of 1 patient who died of cardiopulmonary arrest secondary to progressive disease, all deaths in Stage I occurred because of progressive disease, and no death was considered by the investigator to be related to the study drug.

During Stages IA, II, and IIA of the study, 12 deaths were reported, all of which occurred ≥30 days after the last dose of study drug. Of these, 2 deaths were considered by the investigator to be possibly related to study drug. In both cases, the investigator considered the metastatic cancer to be a contributing etiologic factor to the patient's death.

Three deaths were reported in Stage III of this study. None of the deaths were assessed by the investigator as treatment related. Other etiologic factors that contributed to the deaths included the patients' underlying diseases and malignant tumor progression.

3.7.1.6 Clinical Efficacy

Assessment of responses was an exploratory endpoint in Study MEK4592g. Best overall response was assessed for 74 of 97 patients in Stages I, IA, II and IIA of the study who had measurable lesions and at least 1 post-baseline tumor assessment. Overall, 6 patients (all of whom had melanoma; 6.2%) had a confirmed partial response, 28 patients (28.9%) had stable disease, and 40 patients (41.2%) had progressive disease. Twenty-three patients had non-measurable lesions or measurable lesions with no post-baseline tumor assessments.

In Stage III of Study MEK4592g, 18 patients were accrued. Best overall response was assessed for 14 of 18 patients in Stage III with measurable lesions and at least 1 post-baseline tumor assessment. Overall, 4 patients (22.2%) had stable disease as their best overall response, 8 patients (44.4%) had disease progression, and 2 patients (11.1%) had unconfirmed tumor response.

3.7.1.7 Rationale for Cobimetinib and Atezolizumab Dosing

A recent phase Ib dose escalation trial combining Cobimetinib and Atezolizumab in patients with advanced solid tumors was conducted (NCT01988896)[44]. No dose-limiting toxicities were observed, and expansion occurred at Atezolizumab 800 mg q2w and Cobimetinib 60 mg. The most common treatment-related adverse events included diarrhea (69.6%), fatigue (52.2%), dermatitis acneiform (43.5%), rash (34.8%), maculopapular rash (26.1%), pruritus (26.1%) and nausea (26.1%). Incidence of treatment-related G3-4 adverse events was 34.8%. The only treatment-related G3-4 adverse event in ≥ 2 pts was diarrhea (8.7%). No G5 adverse events were reported. Results from the serial biopsy cohort showed enhanced PD-L1 upregulation, CD8 T-cell infiltration and MHC I expression while on treatment, providing mechanistic rationale for the combination. Responses were not associated with baseline PD-L1 expression.

Currently, a phase III, multicenter, open-label, three-arm, randomized study of regorafenib versus Cobimetinib plus Atezolizumab versus Atezolizumab monotherapy has been initiated in participants with unresectable locally advanced or metastatic colorectal cancer who have received at least two prior regimens of cytotoxic chemotherapy for metastatic disease (NCT02788279).

Because Atezolizumab is formulated at a concentration of 60 mg/mL, 800 mg corresponds to a volume of 13.33 mL. In the interest of simplifying administration, the exact dose being used on all studies moving forward will be 840 mg, corresponding to a volume of 14 mL, which can be accurately administered with a single seringe. The 840 mg dose is not expected to result in meaningful different exposures compared to the 800 mg dose.

3.7.2 Idasanutlin

The tumor suppressor protein 53 (p53) is a powerful growth suppressive and pro-apoptotic protein that plays a central role in protection from tumor development and is frequently inactivated in human cancer. Some tumors overproduce the negative p53 regulator, murine double minute 2 (MDM2), to disable its function. Idasanutlin (RO5503781) is a selective inhibitor of the p53-MDM2 binding that frees p53 from negative control and activates the p53 pathway in cancer cells, which leads to cell cycle arrest and apoptosis *in vitro* and *in vivo*. In view of the existing unmet medical need in advanced cancers and the frequency of p53/MDM2 pathway abnormalities in cancer, idasanutlin represents a first-in-class MDM2 antagonist anticancer therapy with a unique mechanism of action and is believed to be a promising agent that may offer a new therapeutic

option.

3.7.2.1 Clinical Experience with Idasanutlin

Two Phase I studies in patients with solid tumors (Studies NP27872 and NP28902) and a Phase I/Ib study of idasanutlin monotherapy or combination therapy with cytarabine in AML patients (Study NP28679) are complete. A Phase Ib/II study in combination with venetoclax in AML patients (Study GH29914), and a Phase III study in patients with AML (Study WO29519) are ongoing. In addition, a Phase Ib/II study (Study BH29812) in combination with obinutuzumab in patients with relapsed or refractory follicular lymphoma (FL) and in combination with obinutuzumab or rituximab in relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and a Phase Ib/II study (BH39147) evaluating the safety and efficacy of obinutuzumab in combination with idasanutlin and venetoclax in patients with relapsed or refractory FL and obinutuzumab or rituximab in combination with idasanutlin and venetoclax in patients with relapsed or refractory DLBCL are ongoing. Another Phase I Study NP29910 investigating the excretion balance, PK, metabolism and absolute oral bioavailability of a single oral dose of [$_{14}$C]- labeled idasanutlin and an intravenous tracer dose of [$_{13}$C]-labeled idasanutlin in a single cohort of patients with solid tumors has completed enrollment and is undergoing clinical study report preparation.

3.7.2.2 Clinical Safety in Solid Tumors

A total of 168 patients with advanced malignancies (excluding leukemia) received idasanutlin in Study NP27872 (99 patients), Study NP28902 (61 patients) and Study NP29910 (8 patients). All patients in Study NP27872 experienced at least one adverse event (AE), with diarrhoea, nausea, vomiting, decreased appetite, and thrombocytopenia being the most frequent. Grade 3–5 AEs were reported in 63.6% of patients treated with idasanutlin in Study NP27872, most commonly within the system organ classes (SOCs) of blood and lymphatic system disorders, gastrointestinal disorders, and metabolism and nutrition disorders. In Study NP28902, the five most frequent AEs reported were diarrhoea, nausea, vomiting, fatigue, and constipation. In this study, gastrointestinal events were the most common related AEs across all these treatment groups. In study NP29910, the most frequent AEs of any grade of gastrointestinal disorders were vomiting, diarrhoea, nausea, and constipation; and general disorders and administration site conditions were pain and pyrexia. Grade 3-5 AEs were supraventricular tachycardia, jaundice, sepsis, and hypertonia. Serious adverse events (SAEs) were reported in 32.3% of patients in Study NP27872, most commonly thrombocytopenia, febrile neutropenia, neutropenia, anaemia, and leukopenia. SAEs were reported in 21.3% of patients in Study NP28902, most commonly pyrexia and cellulitis. One SAE (Sepsis) was reported in 1 of 8 patients (12.5%) in Study NP29910. Seven patients died in Study NP27872, 3 patients died in
Study NP28902, and 2 patients died in Study NP29910. Of the 7 deaths reported in Study NP27872, 5 were attributed to disease progression, one was due to intra-abdominal haemorrhage with pulmonary embolism (considered unrelated), and one was due to pulmonary embolism (remotely related). In Study NP28902, the cause of death for 2 patients was disease progression. The cause of death for the other patient in Study NP28902 was pneumonia aspiration, considered unrelated to study drug. In Study NP29910, the cause of death for both patients was disease progression.

3.7.2.3 Dose-Limiting Toxicities

In Study NP27872, 31 dose-limiting toxicity (DLT) AEs were reported and 21 of 99 patients (21.2%) experienced at least one DLT AE. The SOCs affected by DLT AEs were blood and lymphatic system disorders (19 patients, 19.2%), gastrointestinal disorders (3 patients, 3%), and investigations (1 patient, 1%). The most frequently reported DLT AE was thrombocytopenia or

platelet count decreased (17 patients, 17.2%). Additionally, neutropenia (5 patients, 5.1%), febrile neutropenia (3 patients, 3.0%), and nausea (2 patients, 2%) were reported. Three of thirty-six patients (8.3%) on the weekly schedule experienced DLT AEs, whereas 6 of 15 patients (40%) and 11 of 34 patients (32%) on the daily schedules for 3 days and 5 days, respectively, experienced DLT AEs. DLTs from the blood and lymphatic system disorder were more frequently reported with the daily dosing schedules than with the weekly dosing schedule. DLTs were not assessed in Study NP28902 and Study NP29910.

3.7.2.4 Adverse Events

In Study NP27872, 1432 AEs were reported by 99 patients enrolled in the study. The five most frequent AEs of any grade were diarrhoea, nausea, vomiting, decreased appetite, and thrombocytopenia. Overall, 976 of 1432 AEs were considered by the investigator to be related to idasanutlin, and all patients (100%) experienced at least one AE. Grade 3-5 AEs were reported in 63 of 99 patients (63.6%), and the most frequent SOCs affected were blood and lymphatic system disorders, gastrointestinal disorders, and metabolism and nutrition disorders. Overall, 137 of 193 AEs with Grade ≥ 3 were considered by the investigator to be related to idasanutlin. Among the AEs of Grade ≥ 3, platelet count decrease was reported in 4 patients (4%), thrombocytopenia was reported in 29 patients (29.3%), neutrophil count decrease was reported in 5 patients (5.1%), and neutropenia was reported in 16 patients (16.2%). Two Grade 5 events were reported in a patient in the dose-escalation cohort who received QW dosing for 3 weeks (intra- abdominal haemorrhage with pulmonary embolism) and a patient in the biomarker cohort who received daily dosing for 5 days (pulmonary embolism).

In Study NP28902, 374 AEs were reported by 61 patients enrolled in the study. The five most frequent AEs of any grades reported by the patients were diarrhoea, nausea, vomiting, fatigue, and constipation. Overall, 194 of 374 AEs were considered by the investigators to be related to study drug. Grade 3-5 AEs were reported in 21 of 61 patients (34.4%), and the most frequent SOCs affected were infections and infestations, metabolism and nutrition disorders, blood and lymphatic system disorders, and gastrointestinal disorders. Among the AEs of Grade ≥ 3, platelet count decrease or thrombocytopenia were reported in 5 of 61 patients (8.2%) and neutrophil count decrease or neutropenia were reported in 3 of 61 patients (4.9%). One Grade 5 AE of aspiration pneumonia was reported in optional treatment extension part of this study.

In Study NP29910, 40 AEs were reported by the 8 patients enrolled in the study as of 1 August 2017. The most frequent AEs (≥ 2 patients) of any grade of SOC gastrointestinal disorders were vomiting, diarrhoea, nausea, and constipation; and SOC general disorders and administration site conditions were pain and pyrexia. Overall, 18 of 40 AEs were considered by the investigators to be related to study drug. Grade 3-5 AEs were reported in 4 of 8 patients (50%) as supraventricular tachycardia, jaundice, sepsis, and hypertonia.

3.7.2.5 Serious Adverse Events and Deaths

Seven patients died in Study NP27872, 3 patients died in Study NP28902 and 2 patients died in Study NP29910. In Study NP27872, the cause of death was disease progression for 5 patients; intra-abdominal haemorrhage with concurrent pulmonary embolism, considered unrelated to study drug for 1 patient; and pulmonary embolism, considered remotely related to study drug for 1 patient. In Study NP28902, the cause of death was disease progression for 2 patients and pneumonia aspiration, considered unrelated to study drug for 1 patient.

In Study NP27872, 53 SAEs were reported in total and 32 of 99 patients (32.3%) reported at least one SAE. The 5 most frequent SAEs were thrombocytopenia or platelet count decrease (14 patients each, 14.1%), febrile neutropenia (5 patients, 5.1%), neutropenia or neutrophil count decrease (5 patients, 3%), leukopenia (2 patients, 2%), and anaemia (3 patients, 3%). Thirty-six SAEs (67.9%) were assessed as either remotely, possibly, or probably related to study treatment by the Investigator. Related SAEs were reported in a higher percentage of patients on Schedule

B who receivedtreatmentdaily (7 of 15 patents, 46.7%, for daily dosing for 3 days; 13 of 34 patients, 38.2%, for daily dosing for 5 days, excluding the apoptosis-imaging cohort) than patients on Schedule A who received weekly treatment (4 of 36 patients, 11.1%, excluding the food-effect cohort).

In Study NP28902, 15 SAEs were reported in total and 13 of 61 patients (21.3%) reported at least one SAE. The SAEs reported in D 1 patient were pyrexia (3 of 61 patients, 4.9%) and cellulitis (2 of 61 patients, 3.3%). Three of the 15 SAEs (20.0%) were assessed as relatedto study treatment by the Investigator. These were thrombocytopenia, nausea, and dehydration.

In Study NP29910, 1 SAE was reported in 1 of 8 patients (12.5%).The SAE was reported as sepsis and was assessed as unrelated to study treatment by the Investigator.

3.7.2.6 Clinical Efficacy in Solid Tumors

No patients with solid tumors achieved an objective responseaccording to Response Evaluation Criteria in Solid Tumors (RECIST) in Study NP27872 and Study NP28902. The best overall response was stable disease in both studies. In Study NP27872 30.6% of patients had stable disease as the best tumor response. The median overall duration of stable disease was 72.5 days with a wide range lasting from 8- 696 days. In Study NP28902, the combined rate of stable diseaseacross Part 1 to Part 3 was 41.1%.

3.7.2.7 Dose rationale for this study

Based on the new SDP formulation, all ongoing and future studies of idasanutlin will utilize the SDP formulation, which correspondsto 50% of the older MBP formulation. Therefore, the MTD for solid tumors on the 5 day schedule was 500 mg daily on the original formulation, and 250 mg of the current SDPformulation. Therefore, the doses tested in this study will range from 50 - 200 mg from D1 - 5 of each 28-day cycle.

3.7.3 Atezolizumab

Atezolizumab is a human immunoglobulin (Jg) G 1 mo n o cl onal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fe-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fe receptors and preventsFe-effector function at expected concentrations in humans. Atezolizumab targets human programmed death-ligand 1 (PD-L1) and inhibits its interaction with its receptor, programmed death-1 (PD-1). Atezolizumab also blocks the binding of PD-L1 to 87.1, an interaction that is reported to provide additional inhibitory signals to T cells. Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans.

3.7.3.1 Clinical Experience with Atezolizumab

Onging Clinical Studies

Currentstudies of Atezolizumab include one ongoing Phase la monotherapy study, three ongoing combination studies, five Phase Jl stud i es, a n d one Phase III study. Details of all ongoing studies can be found in the Atezolizumab Investigator's Brochure.

3.7.3.2 Clinical Safety

For further details, see the Atezolizumab Investigator's Brochure. As of 10 May 2016,

Atezolizumab has been administered to approximately 6053 patients with solid and hematologic malignancies. Safety findings of single-agent atezolizumab across multiple tumor types in the clinical development program are consistent with the known mechanism of action of atezolizumab and the underlying disease. Overall, treatment with atezolizumab is well tolerated, with a manageable adverse event profile. Currently, no maximum tolerated dose, no dose limiting toxicities, and no clear dose-related trends in the incidence of adverse events have been determined. Across all studies and tumor types, the most commonly reported adverse events with single-agent atezolizumab include fatigue, nausea, decreased appetite, diarrhea, constipation, and cough.

3.7.3.3 Immune-Related Adverse Events

Given the mechanism of action of Atezolizumab, events associated with inflammation and/or immune-mediated AEs have been closely monitored during the Atezolizumab clinical program. These include potential dermatologic, hepatic, endocrine, and respiratory events as well as events of hepatitis/elevated liver function tests (LFTs) and influenza-like illness.

Immune-related adverse events are consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-related adverse events are closely monitored during the atezolizumab clinical program. As of this IB update, immune-related adverse events associated with atezolizumab include hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, and meningoencephalitis.

3.7.3.4 Clinical Activity in Patients with TNBC

As of 2 September 2014, clinical activity analyses have been performed on 21 patients with PD-L1−selected (IC2/3) TNBC in Study PCD4989g who received Atezolizumab treatment by 21 July 2014. Unconfirmed responses were recorded for 5 patients. Two of these patients experienced a complete response and 3 patients experienced a partial response. As of 2 September 2014, 4 of these 5 patients were still responding and 1 patient experienced disease progression. The median duration of response has not been reached. The Kaplan-Meier estimated overall 24-week PFS rate was 33% (95% CI: 12%, 53%).

4. PARTICIPANT SELECTION

4.1. Inclusion Criteria

1. Signed and dated written informed consent.
2. Subjects ≥ 18 years of age.
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
4. Clinical stage IV invasive mammary carcinoma or unresectable locoregional recurrence of invasive mammary carcinoma that is:
   - ER/PR-positive (> 1% cells) by IHC and HER2 negative per ASCO guidelines (by IHC or FISH)

- Previously exposed to an aromatase inhibitor (AI) or a selective estrogen-receptor modulator/ downregulator (SERM; SERD) + a CDK4/6 inhibitor
- Appropriate candidates for chemotherapy
- Amenable to biopsy at the time of study entry

5. Adequate organ function including:
   - Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L
   - Platelets ≥ 100 × 10^9/L
   - Hemoglobin ≥ 9/g/dL (may have been transfused)
   - Total serum bilirubin ≤ 1.5 times upper limit of normal (ULN)
   - Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤ 2.5 × ULN (or ≤ 5 × ULN if liver metastases are present)
   - Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance ≥ 50 mL/min as calculated using the Cockcroft-Gault (CG) equation
   - Thyroid Stimulating Hormone (TSH) ≤ 1 x ULN
   - Amylase ≤ 1 x ULN
   - Lipase ≤ 1 x ULN
   - CPK ≤ 1.5 x ULN
   - LVEF (echo) ≥ LLN (Cobi arm only)

6. Female patients of childbearing potential must agree to use at least two methods of acceptable contraception with a failure rate of < 1% per year from 15 days prior to first trial treatment administration until at least 5 months after study participant's final dose of study drugs. See appendix C for details.

   Note: Females of childbearing potential are defined as those who are not surgically sterile or post-menopausal (i.e. patient has not had a bilateral tubal ligation, a bilateral oophorectomy, or a complete hysterectomy; or has not been amenorrheic for 12 months without an alternative medical cause). Post-menopausal status in females under 55 years of age should be confirmed with a serum follicle-stimulating hormone (FSH) level within laboratory reference range for postmenopausal women.

7. Patients unable to read/write in English are eligible to participate in the overall study but will not participate in the Patient-Reported Outcome questionnaires throughout the trial

8. Re-enrollment of a subject that has discontinued the study as a pre-treatment screen failure (i.e. a consented patient who did not receive study drugs) is permitted. If re-enrolled, the subject must be re-consented. Only the screening procedures performed outside of protocol-specified timing must be repeated.

4.2. Exclusion Criteria

1. Prior therapy with anti-PD-L1 and anti-PD1 antibodies, MEK inhibitors or MDM2 antagonists.

2. No more than 3 lines of chemotherapy in the metastatic setting

3. No concurrent anticancer therapy. Required washout from prior therapy:
   - Endocrine therapy: no required wash-out
   - Chemotherapy: 14 days
   - Major surgery: 14 days (provided wound healing is adequate)
   - Radiation: 7 days
   - Investigational/Biologic Therapy (half –life ≤ 40 hours): 14 days
   - Investigational/Biologic Therapy (half –life > 40 hours): 28 days
   - Use of corticosteroids or immunosuppressive medication is exclusionary, except the following in the absence of active autoimmune disease:
     - Subjects are permitted the use of corticosteroids with minimal systemic absorption (e.g. topical, ocular, intra-articular, intranasal, and inhaled);
     - Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent are permitted;
     - Adrenal replacement steroid doses including doses > 10 mg daily prednisone are permitted;
     - A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g. CT scan premedication against contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

4. Previous malignant disease other than breast cancer within the last 5 years, with the exception of basal or squamous cell carcinoma of the skin, cervical carcinoma in situ, or low-risk cancers considered curatively treated (i.e. complete remission achieved at least 2 years prior to first dose of study drugs AND additional therapy not required while receiving study treatment).

5. All subjects with brain metastases, except those meeting the following criteria:
   - Brain metastases that have been treated locally and are clinically stable for at least 2 weeks prior to enrollment
   - No history of intracranial or spinal cord hemorrhage
   - No evidence of interim CNS disease progression
   - Metastasis to the midbrain, pons, and medulla
   - No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable.
   - Subjects must be either off steroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent)

6. Receipt of any organ transplantation including allogeneic stem-cell transplantation.

7. Significant acute or chronic infections including, among others:
   - Known history of testing positive for human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS).
   - Active tuberculosis
   - Positive test for hepatitis B virus (HBV) surface antigen (and/or core antibody) and/or confirmatory hepatitis C virus (HCV) RNA (if anti-HCV antibody tested positive).

8. Active autoimmune disease with reasonable possibility of clinically significant deterioration when receiving an immunostimulatory agent:
   - Subjects with Type 1 diabetes mellitus, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
   - Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or 10 mg equivalent prednisone per day.
   - Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable.

9. Interstitial lung disease that is symptomatic or which may interfere with the detection or management of suspected drug-related pulmonary toxicity.

10. Uncontrolled asthma [defined as having 3 or more of the following features of partially controlled asthma within 28 days prior to starting study treatment: Daytime symptoms more than twice per week, any limitation of activities, any nocturnal symptoms/awaking, need for reliever/rescue inhaler more than twice per week, or known lung function (PEF or FEV1) without administration of a bronchodilator that is < 80% predicted or personal best (if known)].

11. Current symptomatic congestive heart failure (New York Heart Association > class II), unstable cardiac arrhythmia requiring therapy (e.g. medication or pacemaker), unstable angina (e.g. new, worsening or persistent chest discomfort), or uncontrolled hypertension (systolic > 160 mmHg or diastolic > 100mmHg). Or any of the following occurring within 6 months (180 days) prior to first dose of study drugs: Myocardial infarction, coronary/peripheral artery bypass graft, cerebrovascular accident or transient ischemic attack. (Use of antihypertensive medication to control blood pressure is allowed.)

12. Concurrent treatment with a non-permitted drug (**refer to prohibited medication list**) as well as foods or supplements that are strong or moderate CYP3A4 enzyme inducers or inhibitors. Any of the above has to be discontinued at least 7 days prior to Cycle 1/ Day 1 of study treatment.

13. Requirement of anticoagulant therapy with oral vitamin K antagonists such as Coumadin (warfarin). Low-dose anticoagulants for the maintenance of patency in a central venous access device or the prevention of deep vein thrombosis or pulmonary embolism is

allowed. Therapeutic use of low molecular weight heparin is allowed provided patients are safely able to interrupt it prior to biopsy procedures.

14. Persisting toxicity related to prior therapy that has not reduced to Grade 1 [National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 5.0]; however, alopecia and sensory neuropathy Grade ≤ 2 are acceptable and Grade ≤ 2 non-hematological toxicities well controlled with medical management are allowed (for example: hypomagnesemia well controlled on magnesium replacement).

15. Known severe (Grade ≥ 3 NCI-CTCAE) hypersensitivity reactions to monoclonal antibodies, or history of anaphylaxis.

16. Vaccination within 28 days of the first dose of study drugs and while on trial is prohibited, except for administration of inactivated vaccines (for example, inactivated influenza vaccine).

17. Pregnant or breastfeeding females.

18. Known current alcohol or drug abuse

19. Prisoners or subjects who are involuntarily incarcerated.

20. Known psychiatric condition, social circumstance, or other medical condition reasonably judged by the patient's study physician to unacceptably increase the risk of study participation; or to prohibit the understanding or rendering of informed consent or anticipated compliance with scheduled visits, treatment schedule, laboratory tests and other study requirements.

21. Known risk factors for ocular toxicity, consisting of any of the following (Cobi arm only):
    - presence of serous retinopathy within 6 months of protocol enrollment
    - presence of retinal vein occlusion (RVO) within 6 months of protocol enrollment

4.3. Inclusion of Underrepresented Populations

Individuals of all races and ethnic groups are eligible for this trial. There is no bias towards age or race in the clinical trial outlined.

5. REGISTRATION PROCEDURES

5.1. Guidelines for VICC and Participating Institutions

Prior to registration, a copy of the IRB approval at the site will be requested and kept on file at the Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center. Eligible participants will be entered on study centrally at the VICC Coordinating Center. All sites should email the Coordinating Center at coordinating.center@vumc.org to verify treatment availability prior to enrollment.

All patients MUST be registered with the VICC prior to the start of protocol treatment. Registration can only be conducted during the business hours of 8AM – 5PM Monday through Friday.

1) All sites should email the VICC CTSR Coordinating Center at coordinating.center@vumc.org to notify of upcoming registration and slot availability.
2) If a subject ID number is required prior to patient enrollment (i.e. screening tissue to be collected), the site must submit the following documents with their email notification to the Coordinating Center:
    - Copy of the patient's signed and dated Informed Consent including documentation of the consent process.
    - HIPAA authorization form (if separate from the main consent form)
    - VICC Patient Enrollment Form

    The Coordinating Center will then provide a subject ID number via email.
3) After following your site's eligibility verification procedures, email the following documents to the VICC Coordinating Center for sponsor eligibility review and patient enrollment (coordinating.center@vumc.org):
    - Copy of the patient's signed and dated Informed Consent, including documentation of the consent process.
    - HIPAA authorization form (if separate from the main consent form)
    - VICC Patient Enrollment Form
    - Copies of laboratory, imaging and pathology reports
    - Tissue Block Registration Form (see the **Lab Manual**)
    - Completed Eligibility Checklist, including all supporting source documents. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criterion listed in the eligibility checklist.**

Note: VICC Coordinating Center requests 24-48 hours to review all documents and confirm eligibility. Same day treatment registrations will only be accepted with prior notice and discussion with the Coordinating Center. Please email the Coordinating Center if enrollment is needed sooner.

Once registration/enrollment confirmation from Coordinating Center is received, proceed with protocol procedures.

Please contact the assigned Project Manager or Regulatory Coordinator with any questions regarding this process. You can also reach out to your assigned CRA once the study is activated.

The VICC Coordinating Center will assign sequence numbers to all patients in screening. Only patients deemed eligible will be registered to investigational treatment. Sequence numbers will not be re-used if a patient screen fails unless the same patient re-screens at a later point. Following registration, eligible participants should begin study treatment consistent with the protocol no later than 3 weeks after registration/enrollment by the VICC Coordinating Center. If a participant does not receive protocol therapy following registration within the allowed time period (2 weeks), the participant's registration on the study may be canceled. The assigned CRA should be notified of cancellations as soon as possible.

Issues that would cause treatment delays should be discussed with the Protocol Chair. If a participant does not receive protocol therapy following enrollment within allowed time period (2 weeks), the participant will become ineligible and will be removed from the study. Such patients will have to undergo re-screening in order to participate in the study.

As is generally accepted, standard of care procedures performed prior to consent, but within the protocol defined screening window for each assessment, can be used for study purposes. All research-only procedures must be performed after the consent date.

6. STUDY CALENDAR

Parameter	Pre-Treatment[1]	Week/Cycle											End of Treatment[6]
		C1 D1	C1D8	C1 D15	C1 D1,8, 15, 22[12]	C2 D1	C2 D15	C3D1	D1 Every Cycle	D15 Every Cycle	Day 1 of Every Odd Cycle except Cycle 1	Every 12 weeks from C2D1 onwards	
Demographics	X												
CLINICAL EVALUATIONS:													
History and Physical	X				X		X[12]		X				X
Height	X												
Vital signs and Weight[3]	X				X		X[12]		X	X			X
Performance status	X				X		X[12]		X				X
Ophthalmologic evaluation[11]	X					X						X	
LABORATORY/RADIOLOGIC EVALUATIONS:													
Hematology (CBC/diff, plt)	X				X		X[12]		X				
Comprehensive Metabolic Panel[2]	X			X	X		X[12]		X				
Pregnancy Test[13]	X										X		
Phosphorus		X							X				
Uric Acid		X							X				
CPK	X								X				
Amylase/ Lipase	X										X		
Echocardiogram[14]	X					X						X	
Thyroid Stimulating Hormone (TSH)	X								X				
HCV antibody and HBV surface antigen	X												
TP53 status[15]	X												
Tumor Assessments through Imaging Studies[4,7]	X										X		

Parameter	Pre-Treatment[1]	Week/Cycle											End of Treatment[6]
		C1 D1	C1D8	C1 D15	C1 D1,8, 15, 22[12]	C2 D1	C2 D15	C3D1	D1 Every Cycle	D15 Every Cycle	Day 1 of Every Odd Cycle except Cycle 1	Every 12 weeks from C2D1 onwards	
TREATMENT ADMINISTRATION													
Atezolizumab				IV once every 2 weeks starting on Cycle 1 Day 15									
Cobimetinib (*TP53*-mut arm)		PO once daily from Day 1 – 21 starting on Cycle 1 Day 1											
Idasanutlin (*TP53*-wt arm)		PO once daily from Day 1 – 5 starting on Cycle 1 Day 1											
CORRELATIVE STUDIES:													
Tumor Biopsy[5,8, 10]	X			X									
Blood collection[8, 9]		X		X				X					X
ADDITIONAL INFORMATION:													
Concomitant Medications Review		X							X	X			X
Adverse Events Assessment		X (AE will be assessed throughout the study)											

Note:

- Additional tests may be performed at the discretion of the treating investigator as clinically indicated.
- The sample collection schedules outlined above are based on an ideal subject. The sample schedule should be followed as closely as is realistically possible; however, the schedule may be modified (± 4 business days) due to problems such as scheduling delays or conflicts (e.g., clinic closure, poor weather conditions, vacations, etc.).
- Items highlighted in grey are performed for research purposes (not standard of care)

1. Within 4 weeks prior to starting treatment, unless otherwise noted.
2. Serum chemistry includes measurement of sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total bilirubin, calcium, total protein, albumin, AST, ALT, and alkaline phosphatase.
3. On days of Atezolizumab treatment, Pre-Dose vitals should respectively be recorded ≤ 60 minutes prior to the start of the Atezolizumab infusion. Post-Dose vitals should be recorded during and after infusion only if clinically indicated.
4. Baseline evaluation of disease status by CT or MRI within 28 days prior to first dose of study drugs. Baseline and subsequent scans to include imaging of the chest, abdomen and pelvis. The first scheduled re-scan should be performed and evaluated 7 to 8 weeks after Cycle 1, Day 1 treatment, with subsequent scheduled scans intended every ~ 8 thereafter. Scanning on the same day as dosing is discouraged but allowed, provided scan results receive appropriate evaluation prior to study

treatment. Additional disease evaluations or increased scan frequency may be performed according to the medical judgment of the patient's study physician.

5. Fresh biopsy in consenting patients (including those with pre-existing archival tissue) with primary or metastatic lesion judged amenable to medically safe excisional, incisional or core needle biopsy.
6. A 1-month follow-up clinic visit is intended 28 days (±7 days) after the preceding End-of-Treatment visit. Documented attempt(s) should be made for patient return to the study clinic. It will not be considered a protocol deviation if the patient is physically unable to return for the follow-up visit; such circumstance should be recorded in the study documents, and as much of the follow-up information as possible should be obtained via feasible patient contact and from local and outside facilities.
7. If a patient discontinues the study for reason other than progressive disease confirmed by CT or MRI (e.g. adverse event), then CT or MRI scans of the chest, abdomen and pelvis should be continued every 8-9 weeks until disease progression is confirmed by imaging.
8. For tissue collection, refer to **Lab Manual** for details of collection, processing and shipping.
9. For peripheral blood, refer to **Lab Manual** for details of collection, processing and shipping
10. Please note on **Section 10** and **Lab Manual** that both FFPE and fresh tissue should be obtained.
11. Complete ophthalmologic exams will be performed prior to treatment initiation, cycle 2 day 1 (± 1 week), and every 12 weeks from then on (± 2 weeks) on patients in the cobimetinib arm only. Complete ophthalmologic examination will be performed and interpreted by a qualified ophthalmologist, including visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography. Ophthalmologic examination may be performed up to 42 days prior to starting study treatment.
12. For patients on the phase Ib portion of the study only (idasanutlin arm only)
13. Only for women of childbearing potential
14. Evaluation of LVEF by Echocardiogram should be performed prior to treatment initiation, cycle 2 day 1 (± 1 week), and every 12 weeks from then on (± 2 weeks) on patients in the cobimetinib arm only. The treatment discontinuation visit evaluation of LVEF does not need to be performed at the treatment discontinuation visit if an evaluation has been performed within the last 12 weeks and there are no clinically significant findings and/or changes from baseline. All patients restarting treatment with a dose reduction 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 of LVEF every three treatment cycles. Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment.
15. *TP53* mutation status may be known based on previously checked NGS or cfDNA commercially available assays. If not known, an archival FFPB should be sent to the Sponsor (see Section 10 and **Lab Manual**) for *TP53* mutation status determination.

7. TREATMENT PLAN

7.1. Overview

This is a multicenter, open-label, 2-arm phase Ib/II trial that will evaluate the anti-tumor effect of Atezolizumab (an anti- PD-L1 mAb) in combination with Cobimetinib (a MEK inhibitor) in patients with *TP53*-mutated ER+ mBC, or Idasanutlin (an MDM2 antagonist) in patients with *TP53*-wt ER+ mBC. In the phase Ib portion of the trial we will determine the safety and tolerability [Dose Limiting Toxicity (DLT), Maximum Tolerated Dose (MTD) and Recommended Phase II Dose (RP2D)] of Atezolizumab and Idasanutlin in patients with ER+ mBC. With three possible dosing cohorts, a minimum of 9 and a maximum of 18 subjects may be recruited for the dose escalation portion of the study. In the phase II portion of the trial we will determine the anti-tumor effect and adverse event profile of Atezolizumab with Cobimetinib or Idasanutlin in patients with ER+ mBC [Progression Free-Survival (PFS), Overall Response Rate (ORR; by RECIST 1.1) and/or Clinical Benefit Rate (CBR; percentage of patients without disease progression at 6 months); immune-related Response Criteria (irRC), Percentage of patients alive at 12 months (% OS), and Adverse Event profile]. All participants will have targeted Next Generation Sequencing (NGS) performed prior to treatment arm allocation for *TP53* mutation status determination and assess tumor mutation burden. We would expect about ~ 40% of all patients with ER+ mBC to have a *TP53* mutation (*TP53*-mut) in their tumor[3]. For the phase II portion of the trial, a minimum of 33 and a maximum of 66 patients (total in both arms) will be receive study drugs (atezolizumab with cobimetinib or idasanutlin, based on *TP53* mutation status) until disease progression, unacceptable adverse event(s), concurrent illness that prevents further administration of treatment, patient withdrawal from study, or significant non-compliance with protocol. To assess the anti-tumor effect of therapy, we will estimate the overall tumor burden at baseline to which subsequent measurements (performed every 8 weeks using the Solid Tumor Response Criteria [RECIST] v1.1) will be compared. Tumor biopsies (fixed for IHC analysis and snap-frozen for RNA extraction) and peripheral blood will be collected prior to initiating Cobimetinib/Idasanutlin (PRE-Bx), and after 15 days of Cobimetinib/Idasanutlin, prior to adding Atezolizumab (POST-Bx).

7.2. Screening Phase

At screening, the patient will provide a signed informed consent form prior to any study related activities. Patients with known *TP53* mutation status (by NGS or cfDNA) will not be required to wait to initiate study treatment provided all other screening requirements have been met. For patients without known *TP53* mutation status, archival tissue (FFPB from primary or metastatic lestion) should be sent to the Coordinating Center (see Section 10 for details on tissue submission requirements and testing procedures), and once tissue is received at the Coordinating Center, results for *TP53* status will take an average of 2 weeks. Once patients are deemed eligible and *TP53* mutation status is known, participants should begin study treatment consistent with the protocol, as soon as possible, but no later than 2 weeks after authorization to start treatment is given by the VICC Coordinating Center.

7.3. Allocation Procedures

Once eligibility is confirmed and *TP53* mutation status is known, patients will then be allocated to receive:

- Arm 1 (*TP53*-mut) –Atezolizumab 840 mg IV, on Days 1 and 15, and Cobimetinib 60 mg PO daily, on Days 1 - 21, every 28 days; or

- Arm 2 (*TP53*-wt) –Atezolizumab 840 mg IV, on Days 1 and 15, and Idasanutlin (final dose to be determined by the phase Ib portion of the trial) PO daily, on Days 1 - 5, every 28 days,

Note that on cycle 1 (in both arms) Atezolizumab will start on Cycle 1 Day 15 instead of Day 1.

7.4. Agent Administration

The investigator will instruct the patient to take the study drugs exactly as specified in the protocol. A pill diary will be given to all patients enrolled in the study. A cycle will last 28 days.

1 cycle = 28 days				
N of pts.	**Dose Level**	**Atezolizumab (IV q15 days)**	**Cobimetinib (PO daily x 21 out of 28 days)**	**Idasanutlin (PO daily x 5 out of 28 days)**
Phase Ib				
3-6	3	840 mg	-----	200 mg
3-6	2	840 mg	-----	150 mg
3-6	1	840 mg	-----	100 mg
3-6	–1	840 mg	-----	50 mg
Phase II				
40	----	840 mg	60 mg	-----
40		840 mg	-----	TBD

7.4.1 Atezolizumab

Patients will receive Atezolizumab 840 mg IV, on Days 1 and 15 of a 28-days cycle, and its first dose will be started on Cycle 1 Day 15. Administration of Atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Atezolizumab infusions will be administered per the instructions outlined below:

<u>First Infusion:</u>

- 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.

Subsequent Infusions:

- 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 and 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.

7.4.2 Cobimetinib

Patients will receive and self-administer Cobimetinib at 60 mg PO daily, on Days 1 – 21 of a 28-days cycle.

Patients will be given a sufficient number of tablets to last until the next visit. In some cases, extra tablets may be dispensed if there is a possibility that the patient's next visit may be delayed (e.g., due to holiday, inclement weather, or distance of patient's home from study center).

Study drugs should be taken at approximately the same time each day, preferably in the morning, and no earlier than 1 hour and no later than 4 hours after the scheduled time. Each dose of Cobimetinib should be taken with a glass of water. Cobimetinib may be dosed with or without food. Cobimetinib tablets should never be chewed, cut, or crushed.

If a dose is missed (i.e., not taken within 4 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. These events should be noted in the medication diary.

Patients will be asked to record the time and date they take each dose in a medication diary (**located in the supplemental packet**). Patients will also be given instructions for self-administration as to the number and strength of the tablets to take. Patients will be instructed to bring all unused tablets and their medication diary to each study visit for assessment of compliance and medication disposal.

7.4.3 Idasanutlin

Patients will receive and self-administer Idasanutlin at (TBD) mg PO daily, on Days 1 – 5 of a 28-days cycle.

Patients will be given a sufficient number of tablets to last until the next visit. In some cases, extra tablets may be dispensed if there is a possibility that the patient's next visit may be delayed (e.g., due to holiday, inclement weather, or distance of patient's home from study center).

Study drugs should be taken at approximately the same time each day, preferably in the morning, and no earlier than 1 hour and no later than 4 hours after the scheduled time. Each dose of Idasanutlin should be taken with a glass of water. Idasanutlin may be dosed with or without food. Idasanutlin tablets should never be chewed, cut, or crushed.

If a dose is missed (i.e., not taken within 4 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. These events should be noted in the medication diary.

Patients will be asked to record the time and date they take each dose in a medication diary (**located in the supplemental packet**). Patients will also be given instructions for self-administration as to the number and strength of the tablets to take. Patients will be instructed to bring all unused tablets and their medication diary to each study visit for assessment of compliance and medication disposal.

7.5. Definition of Dose-Limiting Toxicity (DLT) – for patients on idasanutlin arm only

Any of the following events that occur during cycle 1 (**first 6 weeks**) will be considered a DLT when classified as possibly, probably or definitively related to study treatment (according to NCI CTEP Adverse Event Reporting Requirements). Apart from the criteria listed below, if a lower grade AE leads to a dose interruption of more than 14 consecutive days of study drugs for the first 4 weeks of Cycle 1, this AE will be considered a DLT; patients must receive at least 75% of study drug during cycle 1 in order to be evaluable for the DLT observation period. Whenever a patient experiences toxicity that fulfills the criteria for a DLT, treatment with the study drug responsible for the toxicity will be interrupted (patient may continue the remainder study drugs) and the toxicity will be followed up. The Protocol Chair must be notified immediately of any DLT:

TOXICITY	DLT CRITERIA
Blood and lymphatic system disorders	Anemia CTCAE Grade ≥ 3 > 14 consecutive days
	Febrile neutropenia CTCAE Grade ≥ 3
	ANC CTCAE Grade 3 for > 14 consecutive days
	ANC CTCAE Grade 4
	Platelet count CTCAE Grade 3 for > 7 consecutive days and/or with signs of bleeding
	Platelet count CTCAE Grade 4
Ocular disorders	CTCAE Grade ≥ 2 for > 14 days CTCAE Grade ≥ 3
General disorders and administration site conditions	Fatigue CTCAE Grade 3 for > 14 consecutive days
Skin and subcutaneous tissue disorders	Skin, mucosal or nail toxicity CTCAE Grade ≥ 3 for > 14 consecutive days despite treatment
GI disorders[a]	Diarrhea CTCAE Grade ≥ 3 for ≥ 48 hrs, despite the use of anti-diarrhea therapy
	Nausea/vomiting CTCAE Grade ≥ 3 for ≥ 48 hrs, despite the use of anti-emetic therapy

TOXICITY	DLT CRITERIA
	Constipation CTCAE Grade ≥ 3 for ≥ 48 hrs, despite the use of anti-constipation therapy
Investigations[b]	Blood bilirubin[c] CTCAE Grade 2 for > 7 consecutive days
	Blood bilirubin[c] CTCAE Grade ≥ 3
	AST or ALT CTCAE Grade ≥ 3 in conjunction with blood bilirubin[c] CTCAE Grade ≥ 2 of any duration
	AST or ALT CTCAE Grade 3 for > 7 consecutive days
	AST or ALT CTCAE Grade 4
	Alkaline phosphatase CTCAE Grade 4
Other hematologic and non-hematologic toxicities	Any other CTCAE ≥ Grade 3 toxicity except for: • Decreased lymphocyte count [lymphopenia] that is not clinically significant • Grade 3 fatigue for less than 7 days • Grade 3 diarrhea, nausea/ vomiting, or constipation for less or equal to 48 hours with appropriate supportive medication

[a] Patients will not initially receive prophylactic treatment for nausea/vomiting during Cycle 1. However, prophylactic treatment may be initiated in all patients at the dose level where these toxicities have been observed and in all further patients if at least 1 patient has experienced nausea/vomiting CTCAE Grade ≥ 3 or if at least 2 patients experienced nausea/vomiting CTCAE Grade ≥ 2. However, anti-emetics may be applied for treatment if the patient has experienced nausea/vomiting CTCAE Grade ≥ 1 at the discretion of the treating physician.

[b] For any hepatic toxicity CTCAE Grade 4, or CTCAE Grade 3 that does not resolve within 7 days to CTCAE Grade ≤ 1 (or CTCAE Grade ≤ 2 if liver infiltration with tumor present), an abdominal CT scan should be performed to assess if it is related to disease progression.

[c] Refers to total bilirubin.

Apart from the criteria listed above, if a lower grade AE leads to a dose interruption of more than 14 consecutive days of Idasanutlin, this AE **may** be considered as DLT (the determination will be based on clinical significance and patient risk; discussion with the Protocol Chair will determine if the event should or should not count as a DLT).

Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed as outlined in the table below, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. Patients that require a dose delay of > 28 days due to a cause unrelated to study participation will have the opportunity to continue study if deemed eligible to do so by the Protocol Chair of the study.

TOXICITY	FOLLOW-UP EVALUATION
Hematology	If 2: CTCA E grade 3 neutropenia, anemia or thrombocytopenia have been demonstrated, these parametersmust be repeated at least once a **week** until resolution to s CTCAE grade 1 to allow for initiation of re-treatment.
Renal	If creatinine 2: 2 x ULN has been demonstrated, this parameter must be evaluated at least twice a week until resolution to s CTCAE grade 1 to allow for initiation of re-treatment, and then at least weeklv until either resolution or until stabilization.
	Creatinine 2: 2.0 x ULN and 3+ proteinuria or hematuria 2: CTCAE grade 2 has beendemonstrated, a 24-hour urine collection for total protein and total creatinine must be repeated at least weekly until either parameter returns to baseline value or until stabilization. Whenever a measured CrCl is obtained, a creatinine should be obtained within s 72 h of the urine collection.
Hepatic	If total bilirubin 2: 2 x ULN or 2: CTCA ED grade 3 AST/ALT has beendemonstrated, these parameters mustbe repeated daily until resolution to s CTCAE grade 1 (orsgrade 2 for AST or ALT, if liver metastasis are present) to allow for initiation of re-treatment, and then at least **weeklv** until either resolution or until stabilization
	Patients with total bilirubin > ULN (any duration) should have fractionation of bilirubin into total/direct or indirect/direct components and any additional work-up as clinically indicated by these results. Follow-up of hyperbilirubinemia should proceed as per the guidelines above, irrespective of the results of fractionation.
Metabolic/Laboratory	Parameters of metabolic/ laboratory abnormalities 2: CTCA E grade 3 must be assessed once at 2 to 4 days and once again at 7 days (± 1 day) and be repeatedtwice a week until resolution to s CTCAE grade 2 to allow for initiation of re-treatment, and then at least weekly until either resolution to s CTCAE grade 1 or until stabilization.
	A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of anv 2: CTCA E arade 3 of amylase or lipase levels.
	In patients with triglycerides 2: 500 mg/dL, urine amylase needs to be tested in addition.
Ocular toxicity	Patients who experience ocular toxicity should be followed as per Dose Modification auidelines (Section 8)

TOXICITY	FOLLOW-UP EVALUATION
Non-Laboratory	Patients who experience non-laboratory DLTs must be evaluated at least once a week following demonstration of the toxicity until resolution of the toxicity to allow for re-treatment, stabilization of the toxicity, or study treatment completion.

7.6. Definition of Maximum Tolerated Dose (MTD) – for patients on idasanutlin arm only

The MTD will be defined as the highest dose tested in which a DLT is experienced by 0 out of 3 or 1 out of 6 patients among the dose levels. The first cohort of patients (3 patients) will be started at dose level 1, and each patient will be observed for 6 weeks on the specified dose:

- If no patient in the first cohort of 3 experiences a DLT, accrual will continue to test the next dose level
- If 1 patient experiences a DLT any given cohort/ dose level, an additional cohort of 3 patients will be treated at the same dose level
- If 1 patient has a DLT out of 6 patients treated at this same dose, accrual will continue to test the next dose level
- If 2 or more patients in 3 or 6 patients treated at a given dose experience DLT, the dose will be de-escalated to the next lower dose level. If the current dose level is at -1, the regimen will be considered too toxic and the corresponding cohort within the study will be discontinued
- If 0 out of 3 or 1 out of 6 patients has a DLT treated at dose level 3, accrual will continue to the phase II portion of the study

No new cohort of patients will be treated until the previous cohort has been fully evaluated for toxicity and a dose escalation decision has been made. Routine updates regarding patient and study status will be conducted.

Once the MTD is reached, the expansion component of the study will be completed to assess tolerability and efficacy. Patients in the phase II portion of the study will initiate study treatment at the MTD defined in the escalation component of the trial. Note that dose reduction within patients (individually) is allowed after the 4 week DLT observation period in the escalation and in the expansion components of the study (see Dose Modification guidelines, Section 8). Intrapatient dose escalation will not be allowed. Dose reduction will be required for a given patient in case of:

- Grade 3 or 4 toxicities
- Grade ≥ 2 elevation of creatinine, bilirubin, AST, or ALT lasting more than 14 days despite medical treatment, or
- Grade ≥ 2 ocular, skin or nail toxicity for more than 28 days in a row despite optimal medical treatment, or
- Grade ≥ 2 GI toxicity lasting more than 14 days despite medical treatment.

7.7. Concomitant Treatment and Supportive Care Guidelines

There is a potential for interaction of cobimetinib with other concomitantly administered drugs through the cytochrome P450 system, and should not be used with strong inhibitors or inducers of CYP3A4. The case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. Patients taking any of the prohibited medications on the Prohibited Medications list are excluded from entering the study. This list can be found in the supplemental packet. Patients already enrolled in the study that initiate and persist taking any of the medications on the **Prohibited Medications list** (except for weak inhibitors) will be discontinued from the study. No apparent drug interactions have been identified for idasanutlin, but strong inhibitors and/or inducers of CYP2C8 and CYP3A4/5 may affect idasanutlin exposure. For idasanutlin, CYP2C8 inhibitors should be avoided when CYP3A4 inhibitors are allowed, since the risk of simultaneous administration of CYP3A4 and CYP2C8 inihibitors is unknown.

Patients on chronic medications that can be given concomitantly with Cobimetinib or Idasanutlin should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. Caution should be used in patients on antiplatelet or anticoagulant therapy due to the risk of bleeding with cobimetinib. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug, and any changes in dosing should be recorded.

All supportive measures consistent with optimal patient care can be given throughout the study at the discretion of the treating physician, as long as they are not part of the list of prohibited medications (**located in the supplemental packet**). In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted with the following considerations:

- Prophylactic anti-emetics should be started only once the patient experienced nausea or vomiting at the discretion of the investigator.
- G-CSF support will be allowed at the treating physician's discretion. Hematopoietic growth factors may be used according to ASCO guidelines (when applicable, we would suggest pegfilgrastim 6 mg subcut on Day 6 of the cycle for the idasanutlin arm; and filgrastim 300 – 480 mcg subcut [based on body weight] on days 22, 23 and 24 of the cycle for the cobimetinib arm)
- Bone directed therapy to prevent skeletal related events (SRE's) or to treat osteoporosis with bisphosphonates or denosumab is permitted. While the use of bisphosphonates has been found to reduce the incidence of new bone metastases in patients with metastatic breast cancer, we do not anticipate this to affect the results of this trial. Thus, treatment initiated prior to registration or after registration with these agents is permitted. The time of initiation of bone directed therapy should be clearly recorded on the case report forms
- Local radiotherapy required for life-threatening situations (e.g., superior vena cava syndrome, spinal cord compression, central nervous system metastases) will require the patient to discontinue protocol treatment due to symptomatic deterioration. However, limited palliative radiotherapy (i.e., to bone metastasis) in subjects who are otherwise benefiting from study treatment will be allowed during the study but must be discussed with the Protocol Chair. Study treatment should be withheld until palliative radiotherapy is terminated. This treatment break should not be considered as treatment interruption. Palliative radiation is permitted if done solely for bone pain relief. It should not be delivered to a target lesion and it should not encompass more than 25% of irradiated bone marrow. If palliative radiotherapy is initiated

after the start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out

- Other investigational therapies must not be used while the patient is on the study
- Anticancer systemic therapy other than the study treatments must not be given to patients while on the study. If such agents are required for a patient then the patient must be discontinued from the study
- Herbal preparations are not allowed throughout the study. These herbal preparations include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal preparations 7 days prior to first dose of study drug

7.8. Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of criteria in Section 7.11 applies.

7.9. Duration of Follow-Up

- Patients will be followed until 28 days (± 7days) following discontinuation of study treatment due to disease progression
- Patients removed from study treatment for unacceptable treatment related adverse event(s) will be followed weekly until resolution or stabilization of all treatment related adverse events to Grade 1 or lower
- Patients who have discontinued study treatment for any reason other than disease progression will be followed until disease progression

7.10. Criteria for Removal from Study

Participants will be removed from study treatment when any of the criteria listed in Section 7.11 applies. All patients who initiate protocol treatment will be included in the safety analysis, and all patients who initiate protocol treatment and receive at least 8 weeks of treatment will be included in overall evaluation of response. All reasons for discontinuation of therapy should be documented clearly in the medical record.

7.11. Discontinuation of Treatment

The reasons for discontinuation or protocol treatment include:

- Evidence of disease progression during treatment as deemed by the treating investigator
- Non-compliance with the study protocol, including, but not limited to not attending the majority of scheduled visits. The Protocol Chair will determine when non-compliance should lead to removal from study. Note: These patients will still be included in the overall evaluation of safety and response
- Unacceptable major toxicity. Note: These patients will still be included in the overall evaluation of safety and response
- Intercurrent illness or condition that would, in the judgment of the treating investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment

- At subject's own request. Note: The reason for discontinuation from the study must be documented. These patients will be included in the overall evaluation of safety and response if any protocol therapy was administered prior to withdrawal
- Study is closed for any reason (e.g. new information shows that the patient's welfare would be at risk if she continued study treatment)
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator
- Patients that require a dose delay of > 28 days. If the delay is due to a cause unrelated to study participation, the patient will have the opportunity to continue study if beyond the first 8 weeks of treatment, if clinical benefit is seen, and if deemed eligible to do so by the Protocol Chair of the study
- If the patient requires dose reduction below dose level -1, the patient should be discontinued from the study unless deemed to have clinical benefit that would outweigh the risk. A discussion with the Protocol Chair should be carried out prior to final decision on discontinuation

7.12. Replacement of Patients Who Discontinue Early

In general, the study intends that patients would be treated until disease progression or intolerable toxicity. If a patient discontinues study treatment for reasons clearly not related to study treatment, after completing fewer than one planned cycle of study, and/or receiving <75% of the total intended dose of study drugs over the first cycle of treatment, then that patient will be considered not evaluable for efficacy analysis (will still be included in the safety analysis though) and may be replaced with a new patient.

7.13. Withdrawal from Study

The reasons for withdrawal from the study include:

- Subject withdraws consent for follow-up.
- Subject is lost to follow-up.
- Study is terminated for any reason.

8. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

8.1. Cobimetinib

8.2. Anticipated Toxicities

Most common adverse events from Cobimetinib include:

- Rash
- Diarrhea
- Nausea and vomiting
- Anorexia
- Fatigue
- Peripheral edema
- Visual disturbances
- Hemorrhage
- Elevation of CPK and rhabdomyolysis

8.2.1. Toxicity Considerations

8.2.1.1. Dermatologic toxicity

Skin toxicities of rash have been reported in patients treated with Cobimetinib as a single agent or in combination with other therapies. In the Phase III study (GO28141), combined rash events of all types and grades were reported more frequently in patients treated with vemurafenib + Cobimetinib than vemurafenib + placebo (71.7% vs. 65.7%), although Grade ≥ 3 events (approximately 16%) and types of rash reported were similar between study arms. Specific events in patients treated with vemurafenib + Cobimetinib included rash (39% all grades, 5.9% Grade ≥ 3, 1.6% serious events) and rash maculo-papular (14.6% all grades, 6.3% Grade ≥ 3, 1.2% serious events). In the Phase I single-agent study (MEK4592g), reported rash events included rash (49.6% all grades, 4.3% Grade≥3 events) and rash maculo-papular (1.7% all grades, 0.9% Grade≥3 events).

The appearance of rash and other dermatologic events will be specifically closely monitored. Patients and investigators will be instructed to monitor closely for the development of rash. Patients will also be instructed to avoid sun exposure and to use sunscreen regularly while receiving study treatment. Prophylactic therapy for rash is not allowed prior to a first event of rash in this study; exceptions may be granted with the approval of the Medical Monitor. Patients must seek further evaluation promptly if rash develops.

Patients who develop Grade 1-2 skin toxicity may be treated with concomitant medications (e.g., topical agents, oral antibiotics, topical moisturizers for dry skin) at the discretion of the investigator. Patients who experience clinically significant acneiform rash should be treated with standard therapies for EGFR-related toxicity, for example topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine or a similar antihistamine, and/or oral antibiotics (e.g., tetracycline, doxycycline, minocycline). Treatment of rash should be initiated early (i.e., at onset of symptoms).

General recommendations to avoid skin toxicities:

- Avoid unnecessary exposure to sunlight and excessive use of soap.
- Avoid bathing in excess; use tepid rather than hot water.
- Use moisturizers regularly; apply thick, alcohol-free and oil-in-water based emollient cream on exposed and dry areas of the body.
- Avoid perfumed products, bubble bath, perfumed soaps, and take breaks from shaving.
- Use broad-spectrum sunscreen with a skin protection factor (SPF) ≥15.
- Wear cotton clothes next to skin rather than wool, synthetic fibers, or rough clothing.
- Use occlusive alcohol-free emollient creams (jar or tub) for treatment of mild/moderate xerosis.
- For scaly areas, use exfoliants (ammonium lactate 12% or lactic acid cream 12%).

8.2.1.2. Diarrhea

Diarrhea has been reported in all Cobimetinib clinical studies in cancer patients. In the Phase I single-agent study (MEK4592g), diarrhea of any grade was reported in 67.0% of patients, 6.1% of patients experienced Grade 3 diarrhea, and no Grade 4 or 5 events were reported as of the data cutoff date. Serious events of diarrhea were reported in 1.7% of patients. In the Phase III study (GO28141), diarrhea was the most common adverse event reported. Diarrhea events of all grades were reported in 56.7% of patients, and Grade 3 or 4 events were reported in 6.3% of patients treated with vemurafenib + Cobimetinib. No Grade 5 events of diarrhea were reported as of the data cutoff date. Serious events of diarrhea were reported in 1.2% of patients treated with

vemurafenib + Cobimetinib.

Diarrhea can frequently be managed with anti-diarrheal agents but can also progress to clinically significant dehydration and/or electrolyte imbalances **with** effects on other organs, possibly resulting in renal, hepatic, and/or cardiac failure. Patients should be instructed to promptly contact the investigators if they develop diarrhea. Investigators should treat diarrhea and intervene promptly for patients who appear to be at increased risk of developing significant dehydration, electrolyte imbalances, and/or multi-organ failure. Patients should receive maximum supportive care per institutional guidelines.

Patients should be instructed to promptly report and seek medical evaluation for severe GI signs and symptoms (e.g., sudden onset of severe abdominal pain and fever, hematemesis, hematochezia, melena), and investigators will monitor patients closely for severe GI toxicity, perform appropriate medical evaluation and treatment, and promptly refer to a specialist, if applicable. Patients with known severe ulcer disease should not be administered Cobimetinib.

8.2.1.3. Nausea and vomiting

For nausea and/or vomiting, maximum supportive care, including ondansetron and aprepitant, should be administered at the discretion of the investigator or per institutional guidelines.

8.2.1.4. Alteration in Liver Functions

Liver laboratory test abnormalities, including elevationsin AST and/or ALT, have been reported as adverse events and serious adverse events in patients treated with vemurafenib+Cobimetinib. In the Phase III study (G0 28141), liver laboratory test abnormalities reportedas Grade 3 adverse events occurred more frequently in patients treated with vemurafenib+Cobimetinib than vemurafenib+placebo (20.5% vs. 15.1%). Liver laboratorytest abnormalities reportedas Grade 3 adverse eventsat frequencies 2% higher in patients treated with vemurafenib+Cobimetinib than vemurafenib+placebo includedincreased ALT (11.4% vs. 6.3%), increased AST (8.3% vs. 2.1%), and increasedalkaline phosphatase (4.3% vs. 1.7%).

In Study MEK4592g, there were no reported adverse events or serious adverse events for clinically significant Grade 4 elevations in liver laboratory tests, and no patient experienced findings suggestive of drug-induced liver injury or liver failure. Generally, elevations in liver laboratory tests were managed effectively with dose modification guidelines. In both study arms of G028141, the majority of Grade 3 liver laboratory test abnormalities resolved.

8.2.1.5. Visual Disturbances

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed with MEKi, including Cobimetinib. The majority of events in Cobimetinib-treated patients were reported as chorioretinopathy or retinal detachment. In the Phase I single-agent study (MEK4592g), also **with** ocular examinations prescribed for patients reporting visual disturbance, 2.6% of patients (including 1 patient with a Grade 2 event that was not coded at the time of the data cutoff date) experienced serous retinopathy events, all of which were Grade 1 or 2.

In the Phase III study (G028141), **with** prospective serial ocular examinations, serous retinopathy events were reported more frequently in patients treated with vemurafenib+Cobimetinib than vemurafenib+placebo (24% vs. 2.1%), and approximately 50% were asymptomatic Grade 1 events. Few patients treated with vemurafenib+Cobimetinib experienced Grade 3 ocular events (2.8%); the majority of these were managed with dose modification of both Cobimetinib and vemurafenib, and all were resolved or resolving as of the data cutoff date.

Patients with neurosensory detachment of the retina typically present with visual disturbances

such as blurred vision, seeing spots, and photophobia; however, some patients have been asymptomatic. These cases have been reversible and most patients are able to continue treatment at the same or reduced dose, but some have experienced recurrence upon re-challenge and have discontinued study drug. It should be noted that these events of neurosensory detachment have occurred only with doses at or above the MTD.

To address the potential ocular toxicity, patients with a history of RVO or glaucoma, visible retinal pathology, intraocular pressure > 21 mmHg, and predisposing factors to RVO (e.g., uncontrolled hypertension, diabetes, or hyperlipidemia, coagulopathy) within 6 months of protocol enrollment will be excluded. Patients will be asked about any vision changes at each symptom-directed physical examination. All new patients will have complete ophthalmologic examinations performed and interpreted by a qualified ophthalmologist, including visual acuity testing, intraocular pressure measurements by tonometry, slit lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography. These complete ophthalmologic examinations will be performed at baseline.

For any treatment emergent onset of Grade ≥ 2 visual symptoms or ocular toxicity, Cobimetinib must be interrupted pending diagnostic evaluation, which will include a complete ophthalmologic examination. If RVO is diagnosed, Cobimetinib dosing should be permanently discontinued and the RVO treated per institutional guidelines.

- General considerations: Avoid unnecessary exposure to sunlight, use sunglasses in bright light.
- Prophylactic management: Frequent use of artificial tear substitutes is strongly recommended.

8.2.1.6. Cardiac Effects

Left ventricular dysfunction may occur with signs and symptoms of cardiac failure, or reduction in left ventricular ejection fraction (LVEF) may be asymptomatic. Without active surveillance for reduction in LVEF, there were no events in this risk category reported in the Phase I single agent study (MEK4592g). In the Phase III study (GO28141), with active surveillance, reductions in LVEF were reported more frequently in patients treated with vemurafenib+Cobimetinib than vemurafenib+placebo (6.7% vs. 2.9%). Of the patients treated with vemurafenib+Cobimetinib, two patients (0.8%) had symptomatic reduction in LVEF and the remaining patients were asymptomatic. One patient in each arm (0.4% each) experienced serious events; these were symptomatic. Most events in patients treated with vemurafenib+Cobimetinib (88%) improved or resolved with management according to the dose modification guidelines. No Grade 4 or 5 events of reduction in LVEF have been reported in Cobimetinib clinical studies as of the data cutoff dates. Reduction in LVEF has also been observed in patients treated with MEKi other than Cobimetinib.

8.2.1.7. 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, GI tract hemorrhage, reproductive tract hemorrhage, and hematuria have been reported. Caution should be used in patients with additional risk factors for bleeding, such as brain metastases, and in patients that use concomitant medications that increase the risk of bleeding (including antiplatelet or anticoagulant therapy).

8.2.1.8. CPK elevations and rhabdomyolysis

CPK elevations have been observed in patients who received cobimetinib monotherapy, as well as in patients administered cobimetinib in combination with other agents. The majority of CPK elevations reported were asymptomatic, non-serious, and resolved with or without study drug

interruption. One event of rhabdomyolysis was reported in the Phase III Study GO28141 (cobimetinib + vemurafenib), and rhabdomyolysis has been reported in postmarketing experience. In Study GO28141, CPK elevations was reported as an AE more frequently in patients treated with cobimetinib + vemurafenib (32.4% all grades, 11.3% Grade 3 events) than with placebo + vemurafenib (8.1% all grades, 0% Grade 3 events).

8.2.1.9. Potential embryofetal toxicities

The effect of cobimetinib on human fertility is unknown. No dedicated fertility studies in animals have been performed with cobimetinib. In repeat-dose toxicology studies, degenerative changes were observed in reproductive tissues including increased apoptosis/necrosis of corpora lutea and seminal vesicle, epididymal and vaginal epithelial cells in rats, and epididymal epithelial cells in dogs.

There are no data regarding the use of cobimetinib in pregnant women. When administered to pregnant rats, cobimetinib caused embryolethality and fetal malformations of the great vessels and skull at systemic exposures approximately 0.9 to 1.4 times the human clinical plasma AUC exposure. Therefore, teratogenicity and developmental toxicity is a potential risk for cobimetinib, and cobimetinib use is not recommended during pregnancy. The use of effective forms of contraception (as defined in appendix C) during treatment with cobimetinib and for the duration after the last dose as described in the protocol is mandated.

8.3. Idasanutlin

8.3.1. Anticipated Toxicities

The majority of AEs recorded for idasanbutlin are transient in nature and reversible.

- Diarrhea
- Nausea
- Vomiting
- Anorexia
- Fatigue/ asthenia
- Thrombocytopenia
- Neutropenia and febrile neutropenia
- Anemia
- Pyrexia
- Sepsis
- Pneumonia
- Fungal Infections
- Electrolyte Disorders (most commonly Hypokalemia)
- Tumor Lysis Syndrome

8.3.2. Toxicities Considerations

8.3.2.1. Gastrointestinal Toxicities

Gastrointestinal toxicity has early onset and occurs frequently within hours from dosing. Prophylactic antidiarrheal has shown efficacy in moderating symptoms. **Antidiarrheal prophylaxis is recommended, but not mandatory, for patients who will be treated with idasanutlin.** If necessary, an oral loading dose of 4 mg loperamide 30 minutes before the administration of study medication has been successfully used to reduce the frequency and severity of diarrhea. If diarrhea occurs, 2 mg loperamide should be administered orally every 4

hours or after every unformed stool to a maximum dose of 16 mg per 24 hours. It is recommended to monitor concomitant causes of GI toxicity, including Clostridium difficile infection, malabsorption/lactose intolerance, fecal impaction, dietary supplements high in fiber, and medications (e.g., stool softeners, laxatives, and antacids). Additional dietary measures could help to minimize risk. It is advised to discontinue all lactose-containing products, alcohol, and high osmolar supplements. Patients should be instructed to eat frequent small meals that include food with anti-diarrheal properties such as bananas, rice, apples, and toast. If diarrhea ≥ Grade 2 occurs, electrolytes need to be monitored at least daily and adequate hydration may be achieved if necessary through IV fluids for electrolyte correction.

Treatment to mitigate emesis may be given prophylactically and is strongly encouraged. The risk of nausea/vomiting should be managed symptomatically throughout treatment with idasanutlin. From 30 to 60 minutes before administration of study, 5-HT3-receptor antagonist administration with or without dexamethasone orally or IV may be sufficient to control symptoms. Rescue medication may include blockers of neurokinin 1 receptor (NK-1 RA). It is recommended to administer IV fluids and correct electrolytes as clinically required.

8.3.2.2. Hematological Toxicities

Patients treated with idasanutlin are at increased risk for infections for the effect on bone marrow progenitors and the related cytopenia. Patients should be closely monitored for infection, and prompt therapy and diagnostic procedures need to be performed as necessary. Idasanutlin has exposure-dependent suppressive effects on bone marrow progenitors. Prophylactic platelet transfusion is recommended when platelet count is < 10 x109/L or local institutional guidelines, and therapeutic transfusions are recommended when clinically indicated (any platelet value in the presence of hemorrhagic symptoms). The hemoglobin level should be maintained at > 9 g/dL in patients with documented cardiac insufficiency (ejection fraction < 50%). Growth factor support may be given per local guidelines for hematologic or solid tumor malignancies.

8.4. Atezolizumab

8.4.1. Anticipated Toxicities

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events, specifically the induction or enhancement of autoimmune conditions. Adverse events with potentially immune-mediated causes include:

- Fatigue
- Arthralgia
- Asthenia
- Anorexia
- Diarrhea
- Dyspnea
- Urinary Tract Infection
- Cough
- Pruritis
- Nausea
- Fever
- Rash
- Vomiting
- Musculoskeletal pain
- Chills

- Dysphagia
- Hypotension
- Nasal congestion
- Hypoxia
- Flu-like symptoms
- Thrombocytopenia
- Abdominal pain
- Diabetes
- Nephritis
- Endocrinopathies including hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency
- Hepatitis/transaminitis
- Pneumonitis
- Colitis
- Neurological disorders such as Myasthenia gravis, Guillian-Barre syndrome, and meningoencephalitis
- Infusion-related reactions
- Myocarditis
- Pancreatitis

8.4.2. Toxicity Considerations

Toxicities associated or possibly associated with Atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Although most immune-related adverse events (irAEs) 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, mycophenolate, or TNFα inhibitors.

The primary approach to Grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with Atezolizumab; for higher-grade irAEs, Atezolizumab should be withheld and oral and/or parenteral steroids administered. Recurrent Grade 2 irAEs may also mandate withholding Atezolizumab or the use of steroids. Assessment of the benefit-risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of Atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening irAEs.

8.4.2.1. Infusion-related reactions (IRRs)

The management of infusion-related reactions (IRRs) will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) IRR, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.
- In the event that a patient experiences a moderate IRR (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the

symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the IRR.

- For severe or life-threatening IRRs (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening IRRs will not receive further infusion and will be further managed as clinically indicated until the event resolves.

8.4.2.2. Gastrointestinal Toxicity

Immune-mediated colitis has been associated with the administration of Atezolizumab. Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild.

If the event is of significant duration or magnitude, or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP or platelet count or bandemia), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with three to five specimens for standard paraffin block be performed. If possible, one or two biopsy specimens should be snap frozen and stored.

Treatment may be restarted following the resolution of colitis. In addition, if the patient is being managed with corticosteroids, treatment should not be restarted until the steroids have been tapered down to a prednisone dose $\leq$ 10 mg/day. Patients who resume treatment should be monitored closely for signs of renewed diarrhea.

8.4.2.3. Hepatotoxicity

Immune-mediated hepatitis has been associated with the administration of Atezolizumab. While in this study, patients presenting with right upper-quadrant abdominal pain felt by the investigator to be possibly related to study treatment and/or unexplained nausea or vomiting should have LFTs performed immediately, and LFTs (AST/ALT) should be reviewed before administration of the next dose of study drug.

In the presence of LFT abnormalities, neoplastic, concurrent medications, viral hepatitis, and toxic 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 of increased LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is suspected.

8.4.2.4. Dermatologic Toxicity

Treatment-emergent rash has been associated with Atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus.

A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be performed unless contraindicated. Low-grade rash and pruritus irAEs have been treated with symptomatic therapy (e.g., antihistamines). Topical or parenteral corticosteroids may be required for more severe symptoms.

8.4.2.5. Endocrine Toxicity

Hypothyroidism has been associated with the administration of Atezolizumab. Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies, as well as for hyponatremia or hyperkalemia.

An endocrinologist should be consulted if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T4 levels should be obtained to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

8.4.2.6. Pulmonary Toxicity

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of Atezolizumab and have primarily been observed in patients with underlying NSCLC.

Mild-to-moderate events of pneumonitis have been reported with 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 (COPD), or pulmonary hypertension and the following should be performed:

- Measurement of oxygen saturation (i.e., arterial blood gas)
- High-resolution CT scan of the chest
- Bronchoscopy with bronchoalveolar lavage and biopsy
- Pulmonary function tests (with diffusion capacity of the lung for carbon monoxide [DL_{CO}])

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

8.4.2.7. Systemic Immune Activation

Systemic immune activation (SIA) is a rare condition characterized by an excessive immune response. Given the mechanism of action of Atezolizumab, SIA is considered a potential risk when given in combination with other immunomodulating agents. SIA 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 SIA is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

8.4.2.8. Pancreatic Toxicity

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with administration of other immunomodulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for obstruction, as well as serum amylase and lipase tests.

8.4.2.9. Potential Eye Toxicity

An ophthalmologist should evaluate visual complaints. Uveitis or episcleritis 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.

8.4.2.10. Immune-mediated Nephritis

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 nonsteroidal 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. If no alternative cause of acute kidney injury is identified, patients with signs and symptoms of acute kidney injury, in the absence of an identified alternate etiology, should be treated according to the management guidelines for immune-related renal events in the table below.

Event	Management
Grade 1 Renal Event	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Grade 2 Renal Event	• 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 Study Chair.[c]
Grade 3 or 4 Renal Event	• Permanently discontinue atezolizumab and contact Study Chair. • 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.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[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 Study Chair.

[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 Study Chair.

8.4.2.11. Immune-related Myositis

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are amongst the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatinine-kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle-biopsy. One etiology of myositis is immune-mediated, which is the current concern with atezolizumab.

It is recommended that atezolizumab should be withheld for moderate or severe (Grade 2 or 3) immune-related myositis and permanently discontinued for recurrent severe or life-threatening myositis (recurrent Grade 3 and Grade 4). Please refer the patient to rheumatologist and/or neurologist and consider muscle biopsy and supportive measures as clinically indicated. Corticosteroids treatment with 1-2 mg/kg/day IV methylprednisolone or higher-dose bolus if severely compromised (weakness severely limiting mobility, cardiac function, respiratory function, dysphagia) and/or additional immunosuppressive agents should be administered for ≥ Grade 2 events or if the event does not improve after initial corticosteroids. Please refer to the table below for detailed management guidelines for immune-mediated myositis.

Management Guidelines for Immune-Related Myositis:

Event	Management
Immune-related Myositis Grade 1	• Continue atezolizumab • Refer patient to a rheumatologist or neurologist • Initiate treatment per institutional guidelines
Immune-related Myositis Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset and contact the Study Chair • Refer patient to a rheumatologist or neurologist • Initiate treatment per institutional guidelines • Consider treatment with corticosteroid equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab • If event does not improve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Study Chair.

Event	Management
Immune-related Myositis Grade 3	□ Withhold atezolizumab for up to 12 weeks after event onset and contact the Study Chair □ Refer patient to a rheumatologist or neurologist □ Initiate treatment per institutional guidelines □ Respiratory support may be required in more severe cases. □ Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone or higher-dose bolus if patient is severely compromised (e.g. cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisolone or equivalent upon improvement □ If event does not improve within 48 hours after initating coritosteroids, consider adding an immunosuppressive agent □ If event resolves to Grade 1 or better, resume atezolizumab □ If event does not improve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Study Chair. □ For recurrent events, treat as a Grade 4 event
Immune-related Myositis Grade 4	□ Permanently discontinue atezolizumab and contact the Study Chair □ Refer patient to rheumatologist or neurologist. □ Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. □ Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone or higher-dose bolus if patient is severely compromised (e.g. cardiac or respiratory symptoms, dysphagia, or weakness that severely limiting mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. □ If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

8.5. Dose Modifications/ Delays and Toxicity Management

Atezolizumab

- There will be no dose reduction for Atezolizumab in this study.
- If atezolizumab is withheld and corticosteroids are initiated for an atezolizumab-related toxicity, corticosteroids must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- Atezolizumab may be withheld for a period of time up to 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. If Atezolizumab is held because of AEs for > 12 weeks beyond the scheduled date of infusion, the patient will be discontinued from Atezolizumab and will be followed for safety and efficacy as specified in the protocol.
- 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.
- Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the Protocol Chair.
- Patients should be assessed clinically (including review of laboratory values) for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to Atezolizumab occurs at any time during the study, treatment with Atezolizumab should be discontinued.

Cobimetinib

- All dose modifications should be based on the worst preceding toxicity. Once a dose has been reduced it will not be increased at a later time even if there is no toxicity. Patients who require dose reductions of Cobimetinib past the lowest dose level will be discontinued from study drugs treatment.
- If a patient requires a dose delay of > 28 consecutive days from the intended day of the next scheduled dose of Cobimetinib, due to study related interventions, then the patient must be discontinued from the study treatment.
- Patients that require a dose delay of > 28 days due to a cause unrelated to study participation will have the opportunity to continue study if deemed eligible to do so by the Protocol Chair of the study.
- Patients who discontinue from the study for a study-related adverse event (AE) or an abnormal laboratory value must be followed at least once a week for 4 weeks and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first, except specifically mentioned.

Cobimetinib dose level reductions

Starting dose	First reduction	Second reduction	Third reduction
60 mg	40 mg	20 mg	Discontinue

Idasanutlin

- All dose modifications should be based on the worst preceding toxicity. Once a dose has been reduced it will not be increased at a later time even if there is no toxicity. Patients who require dose reductions of Idasanutlin past the lowest dose level will be discontinued from study drugs treatment.
- If a patient requires a dose delay of > 28 consecutive days from the intended day of the next scheduled dose of Idasanutlin, due to study related interventions, then the patient must be discontinued from the study treatment.
- Patients that require a dose delay of > 28 days due to a cause unrelated to study participation will have the opportunity to continue study if deemed eligible to do so by the Protocol Chair of the study.

- Patients who discontinue from the study for a study-related adverse event (AE) or an abnormal laboratory value must be followed at least once a week for 4 weeks and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first, except specifically mentioned.

Idasanutlin dose level reductions

Starting dose	First reduction	Second reduction	Third reduction	Fourth reduction
200 mg	150 mg	100 mg	50 mg	Discontinue
150 mg	100 mg	50 mg	Discontinue	
100 mg	50 mg	Discontinue		

Cardiac (Cobimetinib or Atezolizumab)	
Ejection fraction decrease or congestive heart failure	<u>Management of Asymptomatic LVEF Decrease from Baseline:</u> • Withhold cobimetinib dosing for at least 2 weeks for either: – A drop in LVEF to < 40% or – LVEF of 40% to 49% with a ≥ 10% absolute decrease below pretreatment values • If LVEF improves to ≥ 40% or to < 10% absolute decrease below pre-treatment values, resume cobimetinib at: – 1st dose level down for first appearance of LVEF decline – 2nd dose level down for second appearance of LVEF decline – Permanently discontinue cobimetinib for a third episode of LVEF decline – In patients restarting cobimetinib after a dose reduction or interruption, evaluate LVEF at approximately 2, 4, 10 and 16, and then as clinically indicated • If LVEF remains < 40% or ≥ 10% absolute decline below pretreatment values after withholding cobimetinib for at least 2 weeks, consider permanently discontinuing cobimetinib • Continue atezolizumab as clinically indicated <u>Management of Symptomatic LVEF Decrease from Baseline:</u> • Consider holding atezolizumab; discuss with Medical Monitor regarding resumption of atezolizumab • Cardiology consultation strongly recommended • Withhold cobimetinib dosing for at least 4 weeks for symptomatic LVEF decrease. • Permanently discontinue cobimetinib if after 4 weeks patient continues to have symptomatic heart failure despite maximal supportive care or if LVEF has not recovered to ≥ 40% or to < 10% absolute decrease below pretreatment values. • If heart failure symptoms have resolved following treatment break and LVEF has recovered to ≥ 40% or to < 10% absolute decrease below pretreatment values, resume cobimetinib at: – 1st dose level down for first appearance of LVEF decline – 2nd dose level down for second appearance of LVEF decline – Permanently discontinue cobimetinib for a third episode of LVEF decline
Hematology (Cobimetinib or Idasanutlin)	
ANC decreased (Neutropenia)	
Grade 1 / 2	Maintain dose level of Cobimetinib or Idasanutlin.
Grade 3	Omit dose of Cobimetinib or Idasanutlin until ANC ≥ 1000/mm^3, then - If resolved in ≤ 7 days, then maintain dose level of Cobimetinib or Idasanutlin. - If resolved in > 7 days, then ↓ 1 dose level of Cobimetinib or Idasanutlin.
Grade 4	Omit dose of Cobimetinib until ANC ≥ 1000/mm^3, then ↓ 1 dose level of Cobimetinib or Idasanutlin.

Anemia	
Grade 1 / 2	Maintain dose level of Cobimetinib or Idasanutlin.
Grade 3	Omit dose of Cobimetinib or Idasanutlin until resolved to CTCAE Grade ≤ 1 or baseline
Grade 4	Discontinue Cobimetinib or Idasanutlin.
Febrile neutropenia	
Grade 3	Omit dose of Cobimetinib or Idasanutlin, then - If resolved by ≤ 7 days, then, ↓ 1 dose level of Cobimetinib or Idasanutlin. - If not resolved within 7 days discontinue Cobimetinib or Idasanutlin.
Grade 4	Discontinue Cobimetinib or Idasanutlin.
Platelet count decreased (Thrombocytopenia)	
Grade 1 / 2	Maintain dose level of Cobimetinib or Idasanutlin.
Grade 3	Omit dose of Cobimetinib or Idasanutlin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then ↓ 1 dose level of Cobimetinib or Idasanutlin. - If resolved in > 7 days and/or with signs of bleeding, then discontinue patient from Cobimetinib or Idasanutlin.
Grade 4	Discontinue Cobimetinib or Idasanutlin.
Pulmonary (Cobimetinib or Atezolizumab)	
General guidance	Mild-to-moderate events of pneumonitis have been reported with atezolizumab and cobimetinib. 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.
Pneumonitis, grade 1 (asymptomatic)	• Continue atezolizumab and cobimetinib. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For recurrent pneumonitis, treat as Grade 3 or 4 event.
Pneumonitis, grade 2	• Withhold atezolizumab and cobimetinib. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-related etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • Resume atezolizumab and cobimetinib if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. • For recurrent events, treat as a Grade 3 or 4 event.
Pneumonitis, grade 3/4	• Permanently discontinue atezolizumab and cobimetinib.[c] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-related etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If pulmonary event does not improve within 48 hr or worsens, consider adding an immunosuppressive agent (e.g., infliximab, cyclophosphamide, IV Ig, or mycophenolate mofetil). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Hepatic (Cobimetinib or Atezolizumab)	
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin < 2 × ULN (Grade 1)	• Continue atezolizumab and cobimetinib. • Continue with the standard monitoring plan (i.e., LFTs q4w before dosing).

AST/ALT > 3 × baseline values to < 5 × ULN with total bilirubin < 2 × ULN (Grade 2)	• Continue all study treatment.
	• Monitor LFTs at least weekly.
	• Consider referral to a hepatologist and liver biopsy.
	• For suspected immune related events of > 5 days duration
	  ○ Consider withholding atezolizumab
	  ○ Consider administering 1-2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper
	  ○ Restart atezolizumab if event resolves to Grade 1 or better within 12 weeks
	  ○ Permanently discontinue atezolizumab and cobimetinib if event does not resolve to Grade 1 or better within 12 weeks

AST/ALT > 5 × baseline values to < 10 × ULN with total bilirubin < 2 × ULN (Grade 3)	• Continue all study treatment.
	• Monitor LFTs at least weekly.
	• Consider referral to a hepatologist and liver biopsy.
	• For suspected immune related events
	  ○ Withhold atezolizumab
	  ○ Consider administering 1-2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper
	  ○ 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.
	  ○ Permanently discontinue atezolizumab and cobimetinib if event does not resolve to Grade 1 or better within 12 weeks Continue all study treatment.

AST/ALT > 3 × ULN with bilirubin > 2 × ULN	• Withhold atezolizumab and cobimetinib. • Consult hepatologist and consider liver biopsy. • Consider administering 1-2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper (for possible autoimmune hepatitis). • If LFTs do not decrease within 48 hr after initiation of systemic steroids, consider adding an immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist). • Monitor LFTs every 48–72 hr until decreasing and then follow weekly. • Restart atezolizumab at fixed dose and cobimetinib at 1 dose reduction after discussion with medical monitor if AST/ALT < 3 × ULN with bilirubin < 2 × ULN and steroid dose < 10 mg oral prednisone equivalent per day. • Permanently discontinue atezolizumab and cobimetinib for life-threatening hepatic events, and contact the Protocol Chair.

AST/ALT > 10 × ULN	• Permanently discontinue atezolizumab and cobimetinib. • Consult hepatologist and consider liver biopsy. • Consider administering 1–2 mg/kg/day oral prednisone or equivalent (for possible autoimmune hepatitis). If event resolves to Grade 1 or better, taper corticosteroids over ≥ _1 month. • If LFTs do not decrease within 48 hr after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) or dose escalation of corticosteroids may be considered. • Monitor LFTs every 48–72 hr until decreasing and then follow weekly.
Endocrine (Atezolizumab)	
Asymptomatic hyperthyroidism	• Withhold Atezolizumab • Resume Atezolizumab at the same doses when symptoms are controlled and thyroid function is improving. • TSH < 0.1 mU/L: Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold Atezolizumab • Resume Atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue Atezolizumab for life-threatening immune-related hyperthyroidism.
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• Withhold Atezolizumab • Resume Atezolizumab if event resolves to Grade 1 or better within 12 weeks • Permanently discontinue Atezolizumab if event does not resolve to Grade 1 or better within 12 weeks
Hyperglycemia, Grade 3 or 4	• Withhold Atezolizumab • Resume Atezolizumab when symptoms resolve and glucose levels are stable.
Ocular (Cobimetinib or Atezolizumab)	
General guidance	• An ophthalmologist should evaluate visual complaints. • 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-related ocular event that is unresponsive to local immunosuppressive therapy. • 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 ≤1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation. • Retinal vein occlusion (RVO) has been reported in patients treated with MEK inhibitors other than cobimetinib.
Serous retinopathy Severity grade assessment based on NCI CTCAE v4 "Eye Disorders – Other" scale	Serous retinopathy, Grade 1 or 2 (tolerable): • Continue cobimetinib and atezolizumab without dose change. • Continue ophthalmology follow-up as clinically indicated.

	Serous retinopathy, Grade 2 (intolerable) or 3/4: • 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.
Potential immune-related ocular toxicity (e.g., uveitis, iritis, episcleritis, or retinitis)	Grade 1: continue atezolizumab (if symptoms persist, treat as grade 2) Grade 2: • hold atezolizumab • resume atezolizumab if event resolves to grade 1 or better within 12 weeks • permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks Grade 3 or 4: permanently discontinue atezolizumab
CK/ CPK elevation (Cobimetinib or Atezolizumab)	
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 and atezolizumab dosing does not need to be modified or interrupted to manage asymptomatic Grade ≤ 3 creatine phosphokinase (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 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. • If CPK elevations do not improve to Grade ≤3 within 4 weeks following dose interruption, permanently discontinue cobimetinib treatment. • Resumption of atezolizumab may be considered in patients who are deriving benefit.
Rhabdomyolysis or symptomatic CPK elevations	• Interrupt cobimetinib and atezolizumab treatment. • If severity is improved by at least one grade and symptoms resolve within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. • If rhabdomyolysis or symptomatic CPK elevations do not improve within 4 weeks, permanently discontinue cobimetinib treatment • Resumption of atezolizumab may be considered in patients who are deriving benefit after discussion with the Protocol Chair.

Gastrointestinal (Cobimetinib or Atezolizumab or Idasanutlin)	
Diarrhea	
General Guidance	• 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 (Lomotil and loperamide). • <u>Suggested regimen:</u> o Loperamide: Initiate dose with 4 mg, then 4 mg/6 hr around the clock, alternating with Lomotil. o Lomotil (diphenoxylate and atropine): 2 tablets (diphenoxylate 5 mg, atropine 0.05 mg) every 6 hr around the clock o Continue Lomotil and loperamide until no loose stools for 24 hours. o If Grade ≤ 2 diarrhea persists after 48 hr total treatment with Lomotil and loperamide, consider second-line agents (e.g., octreotide, budesonide, tincture of opium). • <u>Oral supplementation:</u> o Initiate oral supplementation of potassium and/or magnesium if serum levels are < LLN. o Consider oral rehydration therapy (e.g., Pedialyte®) for Grade ≥ 1 diarrhea or vomiting. • <u>Dietary modifications:</u> o Stop all lactose-containing products and eat small meals. o The BRAT (banana, rice, apples, toast) diet, without fiber (other vegetables and fruits), may be helpful. o Encourage adequate hydration with salt-containing liquids, such as broth or Gatorade.
Diarrhea, Grade 1 or Grade 2 (tolerable)	• Continue atezolizumab, idasanutlin and cobimetinib. • Initiate supportive care and monitor patient closely. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis if appropriate.
Diarrhea, Grade 2 (intolerable) or Grade 3	• Withhold atezolizumab, idasanutlin and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab, idasanutlin and cobimetinib. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib and idasanutlin with dose reduced by one level. If not, permanently discontinue cobimetinib and idasanutlin.

Diarrhea, Grade4	• Permanently discontinueatezolizumab, idasanutlin and cobimetinib, andcontact Medical Monitor.c • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. • Rule out bowel perforation. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.
Colitis, Grade 1	• Continue atezolizumab, idasanutilin 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, idasanutilin 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. • For recurrent events or events that persist D 5 days, initiate treatment with 1- 2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab, idasanutilin and cobimetinib • If event resolves to Grade 1 or better within 28 days, resume cobimetinib and idasanutilin with dose reduced by one level. If not, permanently discontinue cobimetinib and idasanutilin.
Colitis, Grade 3	• Withhold atezolizumab, idasanutlin 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 at fixed dose. If not, permanently discontinue atezolizumab, cobimetinib and idasanutlin • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib and idasanutlin.
Colitis, Grade 4	• Permanently discontinue atezolizumab, idasanutlin and cobimetinib, and contact Medical Monitor. • 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.

Nausea and Vomiting (Cobimetinib or Idasanutlin)	
Grade 1 / 2	Continue Cobimetinib or Idasanutlin at same doses. Begin maximum supportive care and adequate anti-emetic treatments
Grade 3 / 4	Begin maximum supportive care and adequate combination anti-emetic treatments, including ondansetron and aprepitant. May delay Cobimetinib or Idasanutlin dosing (up to 28 days) until Grade ≤ 1 on maximum supportive care and then restart but decrease dose one level. Permanently discontinue if after restarting, the patient experiences persistent nausea and/or vomiting despite prophylaxis and treatment requiring need to withhold treatment.
Pancreatic toxicity (Atezolizumab)	
Amylase or lipase elevation, Grade 3 or 4	• Withhold Atezolizumab. • Resume Atezolizumab if event resolves to Grade 1 or better within 12 weeks • Permanently discontinue Atezolizumab if event does not resolve to Grade 1 or better within 12 weeks • For recurrent events, permanently discontinue Atezolizumab
Immune-related pancreatitis, Grade 2 or 3	• Withhold Atezolizumab • Resume Atezolizumab if event resolves to Grade 1 or better within 12 weeks • Permanently discontinue Atezolizumab if event does not resolve to Grade 1 or better within 12 weeks • For recurrent events, permanently discontinue Atezolizumab
Immune-related pancreatitis, Grade 4	Permanently discontinue Atezolizumab.
Skin and subcutaneous (Cobimetinib or Atezolizumab)	
General guidance	A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.
Dermatologic event, Grade 1/2	• 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 and cobimetinib. • Refer patient to dermatologist. A biopsy should be performed if appropriate. • Consider initiating treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 2 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib • Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. • 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 atezolizumab and cobimetinib, and contact Medical Monitor.
General (Cobimetinib or Idasanutilin)	
Fatigue/ asthenia	
Grade 1 / 2	Maintain dose level of Cobimetinib or Idasanutlin.
Grade 3	Omit dose of Cobimetinib or Idasanutlin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, maintain dose level of Cobimetinib or Idasanutlin. - If resolved in > 7 days, discontinue patient from Cobimetinib or Idasanutlin.
Neurologic (Atezolizumab)	
Immune-related neuropathy, Grade 2	• Withhold Atezolizumab. • Resume Atezolizumab if event resolves to Grade 1 or better within 12 weeks • Permanently discontinue Atezolizumab if event does not resolve to Grade 1 or better within 12 weeks
Immune-related neuropathy, Grade 3 or 4	Permanently discontinue Atezolizumab
Myasthenia gravis and Guillain-Barré, all grades	Permanently discontinue Atezolizumab
Immune-related meningoencephalitis, all grades	Permanently discontinue Atezolizumab
Other AEs	
Grade 1 / 2	Maintain dose level of Atezolizumab, Cobimetinib or Idasanutlin
Grade 3	Omit dose of Atezolizumab, Cobimetinib or Idasanutlin until resolved to CTCAE Grade ≤ 1 within 28 days, then ↓ dose level of Cobimetinib. If adverse event persists > 28 days, permanently discontinue Cobimetinib or Idasanutlin
Grade 4	Discontinue Atezolizumab, Cobimetinib or Idasanutlin.

8.6. Special Considerations

- For toxicities which are considered by the treating investigator unlikely to develop into serious or life–threatening events (e.g. alopecia, altered taste etc.), treatment may be continued at the same dose without reduction or interruption.
- The treating investigator may reduce a subject's dose for a toxicity of any grade/duration where s/he believes it to be in the best interests of the subject.
- Any consideration to modification of the above dose modification guidelines should be discussed with the Principal Investigator for approval or disapproval in advance.
- If a toxicity requiring Cobimetinib or Idasanutlin permanent drug interruption occurs, Atezolizumab can be continued as a single-agent
- If a toxicity requiring Atezolizumab permanent drug interruption occurs, patients will come off both study drugs

Diagnostic Criteria and Recommended Management for Systemic Immune Activation (applicable only when alternative etiologies have been excluded)	
Major Criteria	**Minor Criteria**
• Fever ≥ 38.5°C on more than one occasion • Ferritin ≥ 3000 ng/mL • Cytopenias (Grade ≥ 2 in two or more lineages) • Age-adjusted soluble IL-2 receptor elevated by ≥ 2 standard deviations • Severe dysfunction in two or more organs • Decreased fibrinogen	• Splenomegaly • Hemophagocytosis in bone marrow, spleen, or lymph nodes • Elevated GGT or LFTs (AST, ALT, or total bilirubin) • Elevated triglycerides • Elevated LDH • Decreased natural killer cell activity

Diagnosis and Management of Systemic Immune Activation		
Number of Criteria	**Diagnosis**	**Action to Be Taken**
≥ 4 major criteria	Consistent with systemic immune activation	• Permanently discontinue atezolizumab. • Consider treatment with an immunosuppressive agent (i.e., tocilizumab, infliximab, cyclosporine A, or etoposide) and IV corticosteroids (i.e., methylprednisolone 1 g once daily or equivalent). • Consider HLH-94 protocol if there is no clinical improvement.
3 major criteria OR 2 major plus ≥ 3 minor criteria	Probable systemic immune activation	• Depending on clinical severity, follow guidelines for "Consistent with systemic immune activation" or "Possible systemic immune activation" diagnosis.
2 major plus ≤ 2 minor criteria OR 1 major plus ≥ 4 minor criteria	Possible systemic immune activation	• Withhold atezolizumab. • Consider treatment with IV corticosteroids. • Follow guidelines for "Consistent with systemic immune activation" diagnosis if there is no clinical improvement or if clinical worsening occurs. • If clinical improvement occurs, atezolizumab may be resumed following a benefit-risk assessment.

9. DRUG FORMULATION/STORAGE/SUPPLY

9.1. Cobimetinib

9.2. Supply

Cobimetinib is an investigational agent and will be supplied free-of-charge from Genentech.

9.2.1. Formulation

The 20-mg Cobimetinib drug product is a film-coated, immediate release tablet. The white tablet is round with the engraving “ROCHE” on one side. Cobimetinib will be packaged in both bottles and 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. For further details, see the Cobimetinib Investigator’s Brochure.

9.2.2. Dosage, Administration, and Storage

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 Coordinating Center (who will contact Genentech, the drug supplier). The dose level of Cobimetinib to be tested in this study is 60 mg PO by self-administration daily on days 1 – 21 of each cycle, every 28 days.

9.3. Idasanutlin

9.3.1. Supply

Idasanutlin is an investigational agent and will be supplied free-of-charge from Genentech.

9.3.2. Formulation

The 50 mg, 200 mg, 300 mg, and 400 mg film−coated tablets with idasanutlin (SDP) that have been optimized for use in current and future studies and as market formulation contain the excipients copovidone, microcrystalline cellulose, croscarmellose sodium, crospovidone, colloidal silicon dioxide, magnesium stearate, and a film coat. The film coat of the 50 mg as well as 200 mg tablets consists of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, iron oxide red, and iron oxide black. The film coat of the 300 mg dose strength consists of polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc. The film coat of the 400 mg dose strength consists of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow.

9.3.3. Dosage, Adminitration, and Storage

Idasanutlin should not be stored above 25°C (77°F). The dose levels of Idasanutlin to be tested in this study are 300 - 500 mg PO by self-administration daily on days 1 – 5 of each cycle, every 28 days.

9.4. Atezolizumab

9.4.1. Supply

Atezolizumab (MPDL3280A) is an investigational agent and will be supplied free-of-charge from Genentech.

9.4.2. Formulation

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 ~20 mL (1200 mg) of Atezolizumab solution. 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 direct sunlight. For further details on the storage and preparation of Atezolizumab, see the Investigator's Brochure.

9.4.3. Dosage, Administration, and Storage

The dose level of Atezolizumab to be tested in this study is 840 mg administered by IV infusion every 2 weeks (14 [± 2] days). Atezolizumab will be delivered in infusion bags with IV infusion lines that have product contacting surfaces of polyvinyl chloride (PVC) or polyolefin and 0.2 μm in-line filters (filter membrane of polyethersulfone [PES]). No incompatibilities have been observed between Atezolizumab and PVC or polyolefin infusion materials (bags or infusion lines).

9.5. Drug Accountability

Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation. Accountability for the drug at all study sites is the responsibility of the principal investigator and designated Pharmacy representative. The investigator will ensure that the investigational drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and destruction/disposal per institutional policy will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates, and patient numbers.

At the conclusion of the study, and, as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to Genentech.

10. CORRELATIVE/SPECIAL STUDIES

10.1. Overview

The correlative studies will focus on:

1) Pharmacodynamic evaluation of the effect of Cobimetinib and Idasanutlin using paired biopsies;
2) Evaluation of the effects of MEK and MDM2 inhibition on the tumor-immune microenvironment prior to initiating Atezolizumab;
3) Evaluation of the effects of MEK and MDM2 inhibition on the peripheral blood T cell repertoire and immunophenotype before and after initiating Atezolizumab; and
4) Correlation of items (1 - 3) with clinical response of the combination.

10.2. Blood Samples

Tubes should be packed according to the **Lab manual** and sent immediately (within 24 h).

10.2.1. Specimen collection

Peripheral blood will be collected in patients prior to initiating Cobimetinib or Idasanutlin (PRE-Bx), and after 7-14 days of Cobimetinib or Idasanutlin, prior to adding on Atezolizumab (POST-Bx). The molecular correlates for each biological sample/time point are listed below.

Parameter	Cycle 1 Day 1 (PRE)	Cycle 1 Day 15 (POST)	Cycle 3 Day 1	End of Treatment
cfDNA	X	X	X	X
Flow Cytometry	X	X	X	X
HLA Typing	X			
Exome-seq (germline)	X			

Details on specimen handling can be found in the **Lab Manual.**

10.2.2. Specimen processing

Correlate	Sample Source	Test	Needs immediate specialized processing	Needs immediate shipping
Exome-seq	Buffy coat	WBC DNA/NGS	NO	NO
HLA-typing		WBC DNA/NGS		
CyTOF/Flow cytometry	Cyropreserved Ficoll-separated blood	PBMCs	YES (refer to **Lab Manual**)	
cfDNA	Blood, platelet poor plasma (PPP)	Cell free DNA/NGS		

10.2.3. Specimen shipment

Ship specimens along with Tissue/Blood Registration Form directly to:

Justin M. Balko, Pharm.D. Ph.D
658 Preston Research Building
Vanderbilt Ingram Cancer Center
2220 Pierce Avenue
Nashville, TN 37232-6307
Office Phone: 615-875-8666
Research Lab Phone: 615-936-2205

****Specimens should be mailed to arrive from Monday 8AM through Friday 1PM****

10.3. Tissues Samples

At screening: patients will provide a signed informed consent form prior to any study related activities. Patients with known *TP53* mutation status (by previously performed NGS or cfDNA) will not be required to wait to initiate study treatment provided all other screening procedures have been completed. For patients without known *TP53* mutation status, an archival tissue (FFPE from primary or metastatic lesion) should be sent to the Sponsor (see sections 10.3.1 – 10.3.3 for details on tissue submission requirements and testing procedures), and once tissue is received, results for *TP53* status will take an average of 2 weeks and will be communicated to the site.

On study: Fresh tumor biopsies will be collected in patients (a) prior to initiating Cobimetinib or Idasanutlin (PRE-Bx), and (b) after 15 days of Cobimetinib or Idasanutlin but prior to adding on Atezolizumab (POST-Bx). One tumor core will be fixed for IHC analysis, while two additional cores will be snap-frozen for RNA and DNA extraction where feasible. The fresh biopsies will follow guidelines as listed in the **Lab Manual**. The molecular correlates for each biological sample/time point are listed below.

Correlate	Sample Source	Test	Needs immediate specialized processing	Needs immediate shipping
TILs	FFPE tumor biopsy	IHC/multiplexed IF	NO	NO
CD8				
CD4				
HLA-A (MHC-I) IHC				
HLA-DR (MHC-II) IHC				
FoxP3				
PD-L1				
RNA-seq	Fresh frozen tumor biopsy	RNA		
Exome-seq		DNA		

Parameter	Prior to Cycle 1 Day 1	Cycle 1 Day 15
Immunohistochemistry (IHC) Analysis	X	X
RNA-seq	X	X
Exome-seq (tumor)	X	
TCR Sequencing	X	X

Tissue specimen labeling, documentation and shipment

- Label ALL specimens before freezing
- If sample comes in contact with contaminate, make note in information section of paperwork.
- Enter time core biopsy was collected on paperwork.
- Label each collection containers with Patient ID sequence number/code letter, Medical Record #, site and location of biopsy, date and time.
- Ship specimens along with Tissue/Blood Registration Form directly to:

Justin M. Balko, Pharm.D. Ph.D
658 Preston Research Building
Nashville, TN 37232-6307
Office Phone: 615-875-8666
Research Lab Phone: 615-936-2205

The specimens will be logged in as a consented specimen and either be stored frozen or as paraffin-embedded tissue and available for molecular pathology studies.

***All frozen tissue should be sent in a cooler with ample volume of dry ice.**

****All formalin-fixed paraffin embedded tissue and/or slides should be sent in a cooler with cold packs (except in winter months) to avoid melting of the paraffin leading to the tissue falling off the slides.**

****These procedures are essential to prevent compromise of the tissue analyses.**

****Specimens should be mailed to arrive from Monday 8AM through Friday 1PM****

10.4. Quality control

First, Dr. Melinda Sanders or her designee (Pathology) will be examining tumor content of the frozen tissue by cutting a frozen H&E section from the tissue. To be adequate for the correlative studies, the invasive tumor area should be at least 5 mm x 5 mm and contain 20% tumor cellularity. If the biopsy contains tumor/immune content >40%, entire 10um sections will be used for RNA purification using the Promega Maxwell 16 automated method.

Purified RNA will be subjected to RNA-sequencing for whole-transcriptome profiling. Biopsies containing <40% will be macrodissected from sequential slides to enrich for the tumor portion, and RNA purified as above.

For DNA extraction, there are no expected tumor changes at the exome level, and so only one time point will be analyzed, preferably PRE-Bx. Tumor content >80% will be targeted, using the whole section/macrodissection scheme above.

10.5. Genetic Testing

Participants will be given information as part of the informed consent process that samples will be used for research tests that will include genetic studies and testing. The intent is not to give participants (or his/her medical providers) the results of any testing done for research purposes; however, incidental germline (heritable) mutations may be identified of which a participant may or may not already be aware. In the case that an incidental genetic finding is identified, the Protocol Chair of this project will be notified. The possible decisions for handling incidental findings may include notification of the participant (and provider); recommendation for genetic counseling, which may or may not include genetic testing (e.g., if the finding was not done in a CLIA certified laboratory); or, neither. In general, a member of the participant's treating team will be given the information to help with notification. In all cases, the current policy of the local/participating site IRB, as applicable, will be followed and any additional approvals that may be required prior to participant notification will be secured in advance.

11. SPECIMEN BANKING

The study Protocol Chair and collaborators have approval to use all research bio-specimens collected during the conduct of this trial to address the research questions described in the protocol document. All future use of residual or repository specimens collected in this trial for purposes not prospectively defined will require review and approval by the Protocol Chair, whether the specimens are stored in a central site or at a local institution in a virtual repository.

12. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be re-evaluated for response after every two cycles. Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1)[73]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

12.1. Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first administration of study treatment drugs.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

12.2. Disease Parameters

12.2.1. Measurable

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 CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which 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 ≥15mm in 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.

12.2.2. Non-measurable

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes of ≥10 to <15 mm in the 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, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

12.2.3. Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

12.2.4. Bone lesions:

- Bone scan, 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 as measurable lesions if the soft tissue component meets the definition of measurability described above
- Blastic bone lesions are non-measurable

12.2.5. Cystic lesions:

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

12.3. 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 disease progression there has been demonstrated

12.3.1. 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.

12.3.2. 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 follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but is/are assessable by clinical exam.

- 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. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
- 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. Guidelines have defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm 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 (e.g. for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy, laparoscopy: The utilisation of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response.
- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with taxanes or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered, if measurable lesions have met criteria for response or stable disease, in order to differentiate between response (or stable disease) and progressive disease.

12.4. Response Criteria

12.4.1. Target lesions

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

12.4.1.1. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) 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 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 (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must

also demonstrate an absolute increase of at least 5 mm. (Note: 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 of diameters while on study.

12.4.2. Non-target lesions:

All other lesions (or sites of disease) including pathological lymph nodes should be identified as **non-target 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'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

12.4.2.1. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10 mm in their short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker levels above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

12.4.3. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocol must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one as the 'best overall response'.

Target Lesions	Non-Target 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, PR=partial response, PD=progressive disease, SD=stable disease, NE=not evaluable.
* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: 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*". In these patients, every effort should be made to document the objective progression even after discontinuation of treatment.

13. Immune-Related Response Criteria (irRC)

13.1. Introduction

Increasing clinical experience indicates that traditional response criteria (e.g., Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1] and World Health Organization [WHO]) may not be sufficient to characterize fully activity in the new era of target therapies and/or biologics. In studies with cytokines, cancer vaccines, and monoclonal antibodies, complete response, partial response, or stable disease has been shown to occur after an increase in tumor burden as characterized by progressive disease by traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long-term effect on the target disease must also be captured. The immune-related response criteria (irRC) are criteria that attempt to do that by enhancing characterization of new response patterns that have been observed with immunotherapeutic agents (i.e., ipilimumab). (Note: The irRC only index and measurable new lesions are taken into account.)

13.2. Glossary

Term	Definition
SPD	sum of the products of the two largest perpendicular diameters
Tumor burden	$SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$
Nadir	minimally recorded tumor burden
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irSD	immune-related stable disease
irBOR	immune-related best overall response

13.3. Baseline Assessment Using irRC

Step 1. Identify the index lesions (five lesions per organ, up to ten visceral lesions and five cutaneous lesions).

Step 2. Calculate the SPD of all of these index lesions: SPD = Σ (Largest diameter of lesion i) $\times$ (Second largest diameter of lesion i).

13.4. Post-baseline Assessments using irRC:

Step 1. Calculate the SPD of the index lesions.

Step 2. Identify new, measurable lesions (≥ 5 × 5 mm; up to five new lesions per organ: five new cutaneous lesions and ten visceral lesions).

Step 3. Calculate the SPD of the new, measurable lesions.

Step 4. Calculate the tumor burden: Tumor burden = $SPD_{index\ lesions} + SPD_{new,\ measurable\ lesions}$

Step 5. Calculate the change in tumor burden relative to baseline and the change in tumor burden relative to nadir.

Step 6. Derive the overall response using the table below.

Overall Response	Criterion
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment ≥ 4 weeks from the date first documented
irPR	Decrease in tumor burden ≥ 50% relative to baseline confirmed by a consecutive assessment ≥ 4 weeks from the date first documented
irSD	Criteria for irCR, irPR, and irPD are not met; does not require confirmation
irPD	Increase in tumor burden ≥ 25% relative to nadir confirmed by a consecutive assessment ≥ 4 weeks from the date first documented

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

13.5. Determination of Immune-Related Best Overall Response (irBOR)

Once a patient has completed all tumor assessments, his/her irBOR may be determined:

Condition	irBOR
At least one irCR	irCR
At least one irPR and no irCR	irPR
At least one irSD and no irCR and no irPR	irSD
At least one irPD and no irCR, no irPR, and no irSD	irPD

irBOR = immune-related best overall response; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

14. Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

15. ADVERSE EVENT REPORTING REQUIREMENTS

15.1. General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) that is available at http://ctep.cancer.gov/reporting//ctc.html.

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 28 days (+/- 7 days) of the last dose of study medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 28 days (+/- 7 days) will continue to be contacted by a member of the study team weekly until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB (as per institutional guidelines) and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study drugs.

15.2. Definitions

15.2.1. Adverse Event (AE)

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with metastatic ER+ breast cancer that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

15.2.2. Serious adverse event (SAE)

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

15.3. Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

15.3.1. Adverse Event Reporting Period

The study period during which AEs and SAEs as described in ***section 13.2*** where the patient has been exposed to Genentech product must be reported. Reporting period begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

15.3.2. Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to atezolizumab, cobimetinib or idasanutlin (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of atezolizumab, cobimetinib or idasanutlin, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to atezolizumab, cobimetinib or idasanutlin; and/or the AE abates or resolves upon discontinuation of atezolizumab, cobimetinib or idasanutlin or dose reduction and, if applicable, reappears upon re- challenge.

No

Evidence exists that the AE has an etiology other than atezolizumab, cobimetinib or idasanutlin (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to atezolizumab, cobimetinib or idasanutlin administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B. or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

15.3.3. Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment
- Unlikely - The AE is doubtfully related to the study treatment
- Unrelated - The AE is clearly NOT related to the study treatment

16. Adverse Events of Special Interest (AESI - Immediately Reportable)

All AESIs must be reported to the Coordinating Center according to the SAE reporting guidelines. Coordinating Center will be responsible for reporting to Genentech within 24 hours of the Coordinating Center becoming aware of it.

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

16.1. Non-drug specific AESI

- 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 and based on the following observations:
  - Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which > 35% is direct bilirubin)
  - Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice

16.2. Cobimetinib

The following events are adverse events of special interest and will need to be reported to Genentech expeditiously (i.e. no more than 1 business day after learning of the event), irrespective of regulatory seriousness criteria:

- Retinal vein occlusion
- Any retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment or central serous chorioretinopathy
- Rhabdomyolysis or Grade 3+ CPK elevation
- Grade 3+ hemorrhage or any grade cerebral hemorrhage
- Grade 3+ rash
- Grade 3+ diarrhea
- Significant liver toxicity: AST and/or ALT > 10 x upper limit of normal, potential drug-induced liver injury as defined by Hy's law
- Symptomatic heart failure or Grade 2+ left ventricular ejection fraction reduction
- Pneumonitis

16.3. Idasanutlin

The following events are adverse events of special interest and will need to be reported to Genentech expeditiously (i.e., no more than 1 business day after learning of the event), irrespective of regulatory seriousness criteria:

- TLS of any grade, irrespective of causality
- Febrile neutropenia, Grade ≥ 3 neutropenia, Grade ≥ 3 thrombocytopenia or Grade 2 thrombocytopenia if associated with hemorrhage/bleeding
- Diarrhea (Grade ≥ 3)
- Grade ≥ 2 Clostridium difficile infection
- Grade ≥ 3 infection
- Grade ≥ 3 vomiting
- Grade ≥ 2 thromboembolic event
- Supraventricular arrhythmias (any grade)

16.4. Atezolizumab

Adverse events of special interest are required to be reported by the investigator to Genentech immediately (i.e., no more than 24 hours after learning of the event). Adverse events of special interest for this study include the following conditions which may be suggestive of an autoimmune disorder:

- Pneumonitis
- Colitis

- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Vasculitis
- Hepatitis
  - Grade ≥ 2 transaminitis (AST or ALT > 3 ×ULN and bilirubin > 2 ×ULN or AST/ALT > 10 ×ULN)
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade > 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Events suggestive of hypersensitivity, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome (SIRS), or infusion-reaction syndromes, systemic immune activation
- Autoimmune Hemolytic Anemia
- Severe cutaneous reactions (e.g. Stevens-Johnson Syndrome, dermatitis bullous, toxic epidermal necrolysis)

17. Reporting Procedures

17.1. General Considerations

All adverse events will be captured on a centralized electronic case report form called ON-line Clinical Oncology Research Environment = Oncore

(http://www.vicc.org/ct/research/oncore.php).

Oncore is a highly secure, web based, cancer specific, and customizable system that provides fully integrative clinical data management and study administration capabilities developed in an ongoing collaborative effort with NCI designated Comprehensive Cancer Centers. It fully integrates study administration functionality including protocol tracking, patient registration, NCI reporting, review committee tracking, and SAE tracking, with clinical data management functionality including electronic case report forms (eCRF) design, clinical data capture, protocol and regulatory compliance monitoring. Specified members at each participating site will submit all regulatory documents to the Coordinating Center.

17.2. Procedures for Eliciting, Recording and Reporting Adverse Events

17.2.1. Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

17.2.2. Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs.

Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported 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, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section I), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. W hen reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

e. Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

f. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 5 months after the last dose of study drug, (add the following if applicable or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within *five months* after the last dose of study drug), a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

17.3. Serious Adverse Events

All serious adverse events, regardless of causality to study drug, will be reported to the Principal Investigator and/or the Study Coordinator at each institution, and also to the Coordinating Center.

All serious adverse events must be reported to the Coordinating Center within 1 business day after the investigator becomes aware of the event. Events should be reported using the Vanderbilt SAE form.

The Vanderbilt Coordinating Center SAE form is part of the packet of supplemental forms and must be fully completed and emailed (preferred), faxed, or scanned to:

ATTN: VICC CTSR Personnel
EMAIL: coordinating.center@vumc.org

FAX: (615) 875-0040

If SAE documents are faxed, the Coordinating Center must be notified via email as well. Follow-up information must also be reported within 1 business day of receipt of the information by the investigator.

The Coordinating Center will disseminate information regarding serious adverse events to the participating sites as described in FDA guidance only in the case that the event(s) is/are believed to be related (i.e., possibly, probably or definitely) to the study medication. The Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

17.3.1. Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification of the study protocol, these modifications will be provided to the IRB as soon as is possible.

17.3.2. Food and Drug Administration (FDA)

In this trial, unexpected serious adverse events believed to be definitely, probably, or possibly related to the study treatment will be reported to the FDA via MedWatch 3500A (available at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf. Submissions by the sponsor can also be submitted via fax or email and must be addressed to Regulatory Project Manager and the Chief, Project Management Staff in the FDA review division that has responsibility for review of the IND. The Coordinating Center will be responsible for correspondence regarding adverse events with the FDA for all participating sites.

17.3.3. Genentech

The Sponsor will be responsible for collecting all protocol-defined Adverse Events (AEs) and Special Situation Reports (including pregnancy reports) originating from the Study for the Product.

The Sponsor must report all Adverse Events/Serious Adverse events (SAEs), AEs of Special Interest (AESIs) and Special Situation Reports (including pregnancy reports) adequately to Genentech within the timelines described below. The completed MedWatch or CIOMS I form or Genentech approved reporting forms should be faxed immediately upon completion to Genentech Drug Safety at:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

All SAEs, pregnancy reports (if applicable, including pregnancy occurring in the partner of a male study subject), AESI reports, and other Special Situation Reports where the patient has been exposed to the Genentech Product(s), shall be transmitted to Genentech on the Vanderbilt Coordinating SAE form or Medwatch or CIOMS I form within 1 business day of the Awareness Date.

- All non-serious Atezolizumab, Idasanutlin or Cobimetinib AEs originating from the study will be forwarded Genentech quarterly by the Sponsor.

Note: Investigators should also report events to their IRB as required.

17.4. Other Special Situation Reports

In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected and transmitted to the Coordinating Center even in the absence of an Adverse Event within 1 business day of the Awareness Date:

- Data related to product usage during breastfeeding
- Data related to overdose, abuse, misuse ormedication error (including potentially exposed or intercepted medication errors)
- Drug interaction
- Use of a Medicinal Product in a Pediatric and Elderly population (in addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population)
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), 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

The Coordinating Center will transmit to Genentech within 1 business day of Awareness.
In addition, reasonable attempts should made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

Occasionally Genentech may contact the Coordinating Center for additional information, clarification, or current status of the patient for whom an adverse event was reported.

It is understood and agreed that the Sponsor will perform adequate due diligence with regardto obtaining follow-up information on incomplete AE, Special Situations and pregnancy reports.

17.5. Aggregate Reports

17.5.1. IND Annual Reports

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech.

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

17.5.2. Other Reports

The Sponsor will forward a copy of the Final Study Report to Genentech/Roche upon completion of the Study.

OR

Sponsor will forward a copy of the Publication to Genentech/Roche upon completion of the Study.

17.6. Safety Reconciliation

17.6.1. Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via Sponsor emailing Genentech a Quarterly line-listing documenting single case reports sent by Sponsor to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Sponsor to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

17.6.2. MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (item 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the AE to each investigational product and suspect medication

17.6.2.1. Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

- Summarizing new information and submitting it with a cover letter including patient identifiers (i.e., date of birth, initial, patient number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted. (The patient identifiers are important so that the new information is added to the correct initial report.)

MedWatch 3500A (Mandatory Reporting) form is available at:

http://www.fda.gov/downloads/AboutFDA/ReportsManualsFo rms/Forms/UCM048334.pdf

17.7. Reporting to Regulatory Authorities, Ethics Committees and Investigators

Vanderbilt University Medical Center, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

Vanderbilt University Medical Center will be responsible for the distribution of safety information to its own investigators, where relevant

17.7.1. Additional Reporting Requirements for IND Holders (if applicable):

For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

- **7 Calendar Day Telephone or Fax Report:**

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of atezolizuma, cobimetinib, or idasanutlin. An unexpected adverse event is one that is not already described in the atezolizuma, cobimetinib, and idasanutlin Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genen within 7 calendar days of first learning of the event.

- **15 Calendar Day Written Report**

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of atezolizumab,cobimetinib, or idasanutlin. An unexpected adverse event is one that is not already described in the atezolizumab,cobimetinib, and idasanutlin investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA,

Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

And Vanderbilt University Medical Center will be responsible for the distribution of safety information to the participating sites for submission to their IRBs per their local IRB reporting requirements.

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

17.8. STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech/Roche. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech/Roche. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Anti-pdl-1-mpd3280a-gsur@gene.com

Attention: Heather Ronemus

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

17.9. QUERIES

Queries related to the Study will be answered by the Vanderbilt Coordinating Center. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. The Vanderbilt Coordinating Center agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

17.10. Safety Crisis Management

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech shall have the final say and control over safety crisis management issues relating to the Product. Vanderbilt University Medical Center agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech.

18. DATA AND SAFETY MONITORING

18.1. Data Management and Reporting

Data will be collected using a centralized electronic case report form called ON-line Clinical Oncology Research Environment (Oncore), located at

< **http://www.vicc.org/ct/research/oncore.php** >.

Oncore allows the investigator to define specific protocol requirements and generate data collection forms. Creation of the data collection form is done with a single button click after the parameters of an individual protocol have been specified. Oncore also permits specification of study protocols, management of patient enrollment, clinical data entry and viewing, and the generation of patient or study-specific reports based on time stamping. OnCore is embedded with a comprehensive domain repository of standard reference codes and forms to promote standardization. The sources for the repository include CDUS, CTC, CDEs from NCI, ICD, MedDRA and various best practices from contributing NCI-designated Comprehensive Cancer Centers. OnCore provides several reporting features specifically addressing NCI Summary 3 and Summary 4 and other reporting requirements. Data may also be exported in a format suitable for import into other database, spreadsheets or analysis systems (such as SPSS). This system will be used to manage all VICCC clinical trials data. OnCore is maintained and supported in the VICC Clinical and Research Informatics Resource.

Specified site members will submit all pertinent regulatory documents to the Coordinating Center Data Manager, who will store it in a secure location.

The Principal Investigator or designee will inform Genentech as defined in established Safety and Data Exchange Agreement (SDEA) of any serious adverse event, and will inform the Vanderbilt IRB in accordance with IRB policy. The Principle Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as specified in this protocol. Whenever there is a safety evaluation during the study, the treating investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs, as detailed in the protocol. If any problem is identified related to the conduct of this research, the VICC Data Safety and Monitoring Committee (DSMC) will be formally asked to review the study and the situation that required DSMC intervention.

19. Data Handling and Record Keeping

An electronic case report form (Oncore eCRF) is required and must be completed for each included participant.

The investigator or designee may maintain records separate from the case report forms in the forms of clinic charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The investigator will document in the clinic chart or medical record the date on which the patient signed informed consent prior to the patient's participation in the trial. Source documents must completely reflect the nature and extent of the patient's medical care, and must be available for source document verification against entries in the case report forms. Source documents regarding procedures such as scans and laboratory evaluations performed as part of the standard of care prior to consent, but within the protocol specified screening period can be used to fulfill certain screening and baseline assessments. All information obtained from source documents will be kept in strict confidentiality. Source data sent as supporting documentation to regulatory authorities for serious adverse events will be de-identified to preserve confidentiality.

To enable evaluations and/or audits from Health Authorities and Vanderbilt the investigator agrees to keep records including: The identity of all participants (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

19.1. Data Verification

Data will be collected via eCRFs and entered into the database per Coordinating Center guidelines. The Coordinating Center will check data accuracy by performing source data verification. Source data verification is a direct comparison of the entries made on the CRFs against the appropriate source documentation. This will be conducted remotely, with the possibility of on-site verification periodically. Discrepancies in the data will be brought to the attention of the Investigator and/or the Investigator's staff. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated and transmitted to the site by the assigned monitor. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or the Investigator's staff. This will be done on an ongoing basis.

20. Meetings

This trial will be monitored by the VICC Breast Cancer Research Team. The Breast Cancer Research Team is composed of the Clinical Core Director of the Breast Cancer Program and Team Leader, surgical oncologists, radiation oncologists, medical oncologists, research nurses, data managers, and our regulatory specialist. The Breast Cancer Research Team meets *informally* weekly and *officially* on a monthly basis to discuss all AEs/SAEs, accrual, compliance, safety issues, adherence to protocol, data reviews, etc. pertaining to all breast cancer clinical trials. This particular study will be thoroughly reviewed during these meetings. The monthly meetings have minutes recorded each time, those are also reviewed on a monthly basis by the Breast Cancer Research Team Physician Leader.

Teleconferences between participating sites and the Breast Cancer research team at Vanderbilt will be held monthly, to discuss all issues related to the trial (AEs/SAEs, accrual, compliance, safety issues, adherence to protocol, data reviews, etc.).

21. Monitoring and Quality Assurance

This trial will be monitored continuously by the Protocol Chair and the Breast Cancer Research Team (weekly and monthly). Additionally, the Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.

The VICC DSMC meets on a quarterly basis and ad hoc to discuss data and safety monitoring of clinical trials and to oversee the VICC DSMP. Internal audits for compliance with adverse event reporting, regulatory and study requirements, and data accuracy and completion are conducted according to the VICC DSMP according to study phase and risk. The committee reviews all serious adverse events (SAE) on Vanderbilt sponsored, investigator-initiated studies on a quarterly basis and provides DSMC SAE review reports to the Vanderbilt IRB.

The investigator will allow the VICC-DSMC designee access to all pertinent medical records, as required by federal regulations, in order to allow for the verification of data gathered in the electronic data case report forms (eCRFs) and for the review of the data collection process. The VICC-DSMC designee will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff. The investigator and the investigational site staff must be available to meet with the VICC-DSMC designee in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the Research Compliance Coordinator.

Additionally, the Coordinating Center has responsibilities to health authorities to take all reasonable steps to ensure the proper conduct of the study as regards to ethics, protocol adherence, integrity, validity of the data recorded on the CRFs, and adherence to regulations regarding Good Clinical Practice (GCP) and the protection of human subjects.

In accordance with applicable regulations, GCP, and Coordinating Center procedures, sites will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Coordinating Center requirements.

During the course of the study, the Coordinating Center will routinely monitor sites for protocol compliance, compare CRFs with individual subjects' original source documents, assess drug accountability, and ensure that the study is being conducted according to the pertinent regulatory requirements. The review of subjects' medical records will be performed in a manner to ensure that subjects' confidentiality is maintained. Monitoring visits will primarily be conducted remotely, and sites are required to provide the appropriate source documentation in order to allow for proper oversight per GCP. Investigators must agree to cooperate with the Coordinating Center to ensure that any problems detected are resolved.

In addition to the above, the FDA may review the conduct or results of the study at the investigational site.

In accordance with HIPAA and associated privacy regulations, a subject's authorization to use personally identifiable health information may be required from each subject before commencement of research activities. This authorization document must clearly specify what

parties will have access to a subject's personal health information, for what purpose and for what duration.

22. REGULATORY CONSIDERATIONS

22.1. Pre-Study Documentation

Prior to initiating the trial, the sponsor will collect all relevant regulatory documents, including but not limited to the following documents:

- A copy of the signed FDA Form 1572
- A current *curriculum vitae* of the Principal Investigator and each sub-investigator listed on the FDA Form 1572
- A copy of the current medical licenses of the Principal Investigator and all sub-investigators listed on the FDA 1572
- A copy of the Protocol Acceptance Page signed and dated by the Principal Investigator
- A letter from the IRB stipulating approval of the protocol, the informed consent document and any other material provided to potential trial participants with information about the trial (e.g. advertisements)
- A copy of the informed consent document approved by both the sponsor and local IRB
- The current IRB membership list for the reviewing IRB
- A completed financial disclosure form for the investigator and all sub- investigators listed on the FDA 1572
- Current laboratory certification for the reference laboratory and *curriculum vitae* of the laboratory director
- A list of current laboratory normal values for the reference laboratory
- A copy of the signed Delegation of Authority Log
- Protocol training documentation for study staff
- The drug destruction SOP for each participating site
- A copy of the fully executed contract must be on record

22.2. Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards of each participating center. Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB of each institution prior to implementation at that institution. Documentation of these approvals must be sent to the Coordinating Center upon receipt.

The Protocol Chair (or his designee) is responsible for the coordination and development of all protocol amendments, and will disseminate this information to the participating centers.

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC/REB). Any amendments to the protocol, other than administrative ones, must be approved by this committee.

Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes.

22.3. Informed Consent

The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the signed document. No subject will enter the study or have study-specific research procedures performed before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

22.4. Confidentiality and Disclosure

The investigator agrees to keep all information provided by this study in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided (protocols, investigators' brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality.

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. This medical information must be made available to the IRB and DSMC, upon request, for source verification of study documentation. Data generated by this study must be available for inspection upon request by representatives of the U.S. Food and Drug Administration, the Federal Government Office for Human Research Protections, National Cancer Institute, the Vanderbilt University Institutional Review Board, local health authorities, Dr. Ingrid Mayer and her authorized representative(s), collaborators and licensees, Genentech and its authorized representatives, and the IRB for each study site, if appropriate. We will make all reasonable efforts to keep patient's protected health information (**PHI**) private and confidential. We will only utilize or relinquish this kind of information according to federal privacy guidelines. There are many safeguards in place to prevent the unintentional disclosure of information obtained for or produced by this study. Research data, including the data collected from the medical charts will be entered into a password-protected database. Any publications or public disclosure of data relating to the patient's tumor will be done without any identifying information.

PHI will be collected and stored in the ONCORE research database. The coordinating center will have access to all research data, which will be kept for at least 2 years after the study is completed. Any research data entered in a patient medical record will be stored for an indefinite amount of time. There are no plans to destroy data at this time.

Confidentiality and security will be maintained for the tissue collection within this study. All tissue samples obtained for this study will be assigned a code and this code used to identify the sample. The samples will not be labeled with the patient's name, address or other information that would identify them. All information will be coded to maintain privacy. Research data, including the data

collected from the medical charts will be entered into a password-protected database. The database (Breast Cancer Program Database) in which this study data are going to be stored has a firewall (in addition to the institutional firewall) with the highest level of protection, i.e. the same level of protection as the on-line hospital information system at Vanderbilt. This means that users must log on to a web server that sits between the institutional firewall and the firewall to the database, and only this application server is allowed to query the database. Information, including the identifier and password for the authorized users, is transmitted via a secure shell protocol using 128k encryption. Only Dr. Ingrid Mayer, the PI, and the Breast Team Data Manager, approved through our IRB will be allowed access to patient identifiers. Other levels of authorization may exist for approved users, e.g. access to de-identified data. This database will store a de-identified link to the patient data and will not otherwise store patient data, even de-identified data. The safety monitoring will be performed by the groups deemed appropriate by the Vanderbilt University Medical Center IRB for reviewing the clinical trials procedure. Safety monitoring for the database is also performed by the Networking and Security Services of the Vanderbilt University Medical Center. Audit trails for access to the web server and the databases behind the dual firewall system are maintained in accordance with the practices of the Networking and Security Services of the Vanderbilt University Medical Center.

The investigator agrees to keep all information provided by Genentech in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Genentech (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Genentech to the investigator may not be disclosed to others without direct written authorization from Genentech, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

22.5. Records Retention

The investigator will retain the records of the clinical trial (including, but not necessarily limited to, CRFs, source documents, informed consent forms, drug accountability records, IRB correspondence, etc.) for at least 2 years after all investigations have been discontinued. Study records must be stored in a safe and secure location permitting timely retrieval, if necessary.

Study records that must be retained include case report forms, signed informed consents, correspondence with the IRB, study drug dispensing and inventory records, source documents (clinic charts, medical records, laboratory results, radiographic reports) and screening/ enrollment logs.

22.6. Study Termination

The investigator reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to, the following:

- Investigator non-compliance with the protocol, GCP or regulatory requirements
- Insufficient enrollment
- Safety concerns
- Decision by Genentech to modify or discontinue the development or manufacturing of erdafitinib
- A request to discontinue the study by the IRB or FDA

The investigator will promptly notify Genentech, the IRB and FDA if the study is terminated for any reason.

22.7. Ethics and GCP

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described in:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations)
- Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996)

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice to which it conforms.

22.8. Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

23. MULTI-CENTER GUIDELINES

23.1. Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), each participant's informed consent, enrollment form, eligibility checklist and tissue block registration, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

The requirements for data management, submissions, and monitoring are outlined below. The participating sites will submit all the research related information (source documents and research records – IRB approval documents, patient registration list, CRF info, toxicity assessments, tumor measurements/ responses, etc.) within 2 weeks of the patient's visit to the assigned Coordinating Center Monitor. The Coordinating Center Monitor will check if data was entered into Oncore within 1 week of receiving the information. Personnel from the VICC Clinical Trial Shared Resource will monitor the trial and may periodically visit the investigative site to assure proper conduct of the trial and proper collection of the data. The investigators at other sites will allow the monitor to review all source documents used in the preparation of the case reports.

23.2. Records Retention

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms,

laboratory test results, and medication inventory records, must be retained by each Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

23.3. Publication

It is understood that any manuscript or releases resulting from the collaborative research will be circulated to all participating sites prior to submission for publication or presentation.

Any formal presentation or publication of data from this trial may be published after review and comment by Genentech and prior to any outside submission. Genentech will receive copies of any intended communication in advance of publication (at least twenty-one working days for presentational materials and abstracts and thirty working days for manuscripts). Principal Investigator/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Genentech and, in accord with the trial contract shall not permit disclosure of Genentech confidential or proprietary information.

24. STATISTICAL CONSIDERATIONS

This two-part study consists of 1) a Phase Ib dose-escalation study of Idasanutlin in combination with Atezolizumab to determine an RP2D in patients with *TP53*-wt ER+ mBC, followed by 2) a Phase II open-label, multi-arm, multicenter clinical trial to determine whether whether Cobimetinib or Idasanutlin in combination with Atezolizumab improves anti-tumor effect relative to a historical control of Atezolizumab alone in patients with ER+ mBC.

24.1. Phase Ib Trial of Idasanutlin and Atezolizumab

For the dose-escalation study, a standard 3 + 3 dose escalation scheme will be utilized to evaluate the primary objective of determining a RP2D (Recommended Phase II Dose) for Idasanutlin in combination with Atezolizumab. Three dosing cohorts of Idasanutlin will be evaluated in combination with Atezolizumab (dosage will be held constant at 840 mg) to determine the RP2D and will occur in accordance with the dose escalation rule below.

1 Cycle = 28 days			
N of pts.	**Dose Level**	**Atezolizumab (IV q15 days)**	**Idasanutlin (PO daily x 5 out of 28 days)**
3-6	3	840 mg	200 mg
3-6	2	840 mg	150 mg
3-6	1	840 mg	100 mg
3-6	–1	840 mg	50 mg

DLTs are defined in section 7.5 and will be assessed during a DLT assessment window, which is during the first cycle of therapy. The RP2D from this study will be utilized in the Idasanutlin +

Atezolizumab arm in the Phase II portion of this study. The determination of the MTD and RP2D are reviewed in the following table. Of note, the PI may adjust the RP2D based on overall tolerability after cycle 1 at their discretion after discussion with all study PI's.

Number of Patients with DLT at a given dose level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level. If dose level 3 is reached without DLT, then dose level 3 will be considered the MTD and RP2D.
>= 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered), exceeding the MTD. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose. If this occurs at dose level 1, then 3-6 additional patients will be enrolled on dose level -1, based on toxicity occurring at that dose level. If ≥ 2 patients experience DLT at dose level -1, then the study is considered a failure.
1 out of 3	Enter at least 3 more patients at this dose level. If 0 of these 3 patients experience DLT, proceed to the next dose level. In the event that enrollment is on dose level 3 when this occurs, then dose level 3 is considered the MTD and the RP2D. If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the MTD and RP2D. At least 6 patients must be entered at the recommended phase 2 dose. These patients will also be considered evaluable in the phase II portion of the study.

24.2. Phase II Trial of Atezolizumab with Cobimetinib or Idasanutlin Study Design

Subsequent to the completion of the Phase Ib dose escalation portion for the Idasanutlin arm of this study, the Phase II portion of the Idasanutlin arm of this trial will open. The Phase II portion of the Cobimetinin arm will start once the study is activated, as no Phase I is necessary for that combination. Patients will be allocated based on *TP53* mutational status and treated with a 15 day lead-in of Cobimetinib or Idasanutlin, followed by combination therapy with Atezolizumab until progressive disease or intolerable toxicity. Tumor tissue and blood will be obtained at study start and before initiation of Atezolizumab. Additional blood samples will be obtained after the first cycle of combination therapy and at disease progression.

The primary endpoint of this study is Progression-Free Survival (PFS); imaging will be performed at 8-week intervals. To observe a definitive outcome (success or failure), we will define treatment success as being progression-free at 16 weeks when the subjects will have the second imaging. Patients will be followed for a minimum of 12 months from time of study initiation, and their actual progression-free survival time will be recorded. There will be two treatment groups; however, these two groups will not be compared, rather each arm will be compared to historic control.

Secondary endpoints include ORR defined by iRecist, Clinical benefit rate (lack of disease progression at 6 months), Duration of Response (DOR), Overall Response Rate (ORR by RECIST 1.1), and percentage of patients alive (OS) at 12 months, and will be similarly summarized with 95% CI by arm. Patients will be followed for a minimum of 12 months from time of study initiation.

Safety will be evaluated by estimating the percentage of patients who experience a clinically relevant toxicity (both patient and physician reported) for each arm. Additionally, continuous monitoring for toxicity will be employed.

24.3. Sample Size/ Accrual Rate

24.3.1. Primary Endpoint/ Sample Size

In recently reported trials of PD-L1 therapies, the median progression-free survival (PFS) rates of 8 weeks were observed in ER+ mBC[22]. Assuming an exponential survival model, this corresponds to the hazard rate of 0.0866 and progression-free survival of 25% and 13% at 16 and 24 weeks, respectively. For the new treatment arms, we expect the median PFS to be 16 weeks, which corresponds to the hazard rate of 0.0433. The table below summarizes the two survival curves.

Group	Median Survival	Hazard Rate	Proportion Surviving		
			8 weeks	16 weeks	24 weeks
Historical Control	8 weeks	0.0866	50%	25%	13%
Cobimetinib / Idasanutlin	16 weeks	0.0433	71%	50%	35%

Our proposed phase II trial results will serve as a proof-of-concept for future immunotherapy combination strategies in these patients. In view of the overall low PFS in ER+ mBC treated with single-agent immune checkpoint inhibitors, we opted for an open-label design without an Atezolizumab only control arm, and will use the 16-week PFS (Yes/No) as the primary endpoint. "Response" (16-week PFS and 8-week PFS) will be estimated and reported along with a 95% exact confidence interval. Progression-free survival will be estimated using the Kaplan-Meier method with censoring used as needed (e.g. if a patient is lost to follow-up, or analysis is done before all patients have had the event of interest). Median time to event and corresponding 95% CI will be reported along with Kaplan-Meier curves. The duration of PFS for patients who progress and then subsequently die will be the number of days between initiation of the study treatment and the date of when disease progression is first observed.

We propose to use a Simon's Minimax design with stage I and II sample sizes of 16 and 17, respectively (maximum total of 33 patients per arm), to ensure that the total number of patients exposed to Atezolizumab + Cobimetinib or Idasanutlin is minimized in each of the arms in the trial. The futility boundary at the end of stage I is 4, that is if we have 4 of fewer "responses", then the trial will be terminated. At the end of the trial if there are 13 or more "responses", we will conclude clinical benefit of Cobimetinib or Idasanutlin. This design has 4.5% type I error rate at response rate of 25%, and 90% power if the true "response" rate is 50% or higher. At the end of stage I, patient accrual will not be halted; accrual will be stopped after the data from the 16th patient are available and the number of responders is below the threshold. The patients who are already accrued at the time of interim decision will be followed and their data will be included in all the subsequent analysis.

24.3.2. Accrual Rate

We expect to accrue a minimum of 4 patients per month (all participating sites combined). Assuming a linear increase over the first 6 months to target accrual, approximately 24 months of patient accession is anticipated, with an additional 12 months needed for follow-up.

24.3.3. Secondary Endpoints

Secondary endpoints defined in terms of percentages such as Immune related response criteria (irRC), Clinical Benefit Rate (CBR), Overall Response Rate (ORR), and rate of Overall Survival (OS) at 12 months will be summarized by cohort and 95% CI for each percentage will be reported. Safety will be evaluated by estimating the percentage of patients who experience a clinically relevant toxicity with 95% CI. All adverse events will be tabulated and summarized with descriptive statistics. The distribution of OS per each cohort will be estimated using the Kaplan-Meier method with censoring used as needed (e.g. if a patient is lost to follow-up, or analysis is done before all patients have had the event of interest). Median time to event and corresponding 95% CI will be reported along with Kaplan-Meier curves. Demographic and clinical characteristics will be summarized for all patients overall and by cohort as percentages for categorical variables and as mean, standard deviation, median, minimum and maximum for continuous measures. Data will be collected using a centralized electronic case report form called **ON**-line **C**linical **O**ncology **R**esearch Environment = **Oncore** (http://www.vicc.org/ct/research/oncore.php).

24.3.4. Correlative Science Endpoints

Each biomarker will be compared to each clinical endpoint, particularly the primary endpoint of overall response rate, overall response by iRecist, and PFS. These exploratory analyses will be performed using the baseline biopsy, and also using correlative science assay values obtained from the Cycle 1 Day 1 time point biopsy.

Biomarkers will be categorized as continuous variables (gene expression values, expression signatures, IHC staining intensity, FAC based cell type counts, Neoantigen burden, etc.), or as dichotomous variables (somatic mutation in gene X yes or no, DNA copy number change Y, etc.). Many continuous variable scores will be also examined as dichotomous, but given the exploratory nature of these the precise cut points are not yet determined. Some specific assays are listed below, and when it says response it is understood to mean testing each assay result versus all response endpoints, both using the baseline biopsy and the C1/intermediate time biopsy.

A paired t-test (or the non-parametric equivalent if needed) will be used to determine if the proposed endpoints are significantly increased in paired biopsy in either arm. In exploratory analyses, patients will also be stratified by clinical response to determine if the change in endpoint is associated with patient-specific clinical response.

25. Reporting and Exclusions

All patients included in the study must be assessed for safety, tolerability, and response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in

exclusion from the analysis of clinical endpoints (e.g. overall response rate and clinical benefit rate).

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27. APPENDIX A: ECOG PERFORMANCE STATUS SCALE

Score	Definition	Karnofsky Equivalent
0	Asymptomatic	100
1	Symptomatic, fully ambulatory	80 – 90
2	Symptomatic, in bed less than 50% of day	60 – 70
3	Symptomatic, in bed more than 50% of day, but not bedridden	40 – 50
4	Bedridden	20 – 30

28. APPENDIX B: CONTRACEPTIVE GUIDELINES

Women Not of Childbearing Potential are Defined as Follows:
Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Contraceptive Guidelines for Women of Child-Bearing Potential:
Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use at least two methods of acceptable contraception from 15 days prior to first trial treatment administration until at least 5 months after final dose of study treatment. The highly effective contraception is defined as either:

1. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. [In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.]
2. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomized male partner should be the sole partner for that patient.
3. Use of a combination of two of the following:
   a) Barrier methods **with** spermicide
      - condom (male or female)
      - occlusive cap (diaphragm or cervical/vault caps/shield)
      - use of two barrier methods is acceptable (i.e. male condom + diaphragm or equivalent)
   b) Placement of an intrauterine device (IUD) or intrauterine system (IUS).
   c) Hormonal implants or combined oral contraceptives

The following are **unacceptable** forms of contraception for women of childbearing potential:

- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Abstinence

29. APPENDIX C: PROHIBITED AND CAUTIONARY CONCOMITANT MEDICATIONS

PROHIBITED AND CAUTIONARY CONCOMITANT MEDICATIONS

Herbal preparations are not allowed throughout the study. These herbal preparations include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal preparations 7 days prior to first dose of study drug.

INHIBITORS

Inhibitors compete with other drugs for a particular enzyme thus affecting the optimal level of metabolism of the substrate drug, which in many cases affects the individual's response to that particular medication, e.g. making it ineffective.

■ A **Strong inhibitor** is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.

■ A **Moderate inhibitor** is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.

■ A **Weak inhibitor** is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

FDA preferred[1] and acceptable[2] **inhibitors** for in vitro experiments*.

CYP2C9 (for idasanutlin only)	CYP3A4 (for cobimetinib only)
■ fluconazole[2]	■ indinavir
■ amiodarone	■ nelfinavir
efavirenz	■ ritonavir
fenofibrate	■ clarithromycin
fluconazole	■ itraconazole[1]
fluvastatin	■ ketoconazole
fluvoxamine[2]	■ nefazodone
isoniazid	■ saquinavir
lovastatin	■ suboxone
metronidazole	■ telithromycin
paroxetine	■ aprepitant
phenylbutazone	■ erythromycin
probenicid	■ fluconazole
sertraline	■ grapefruit juice
sulfamethoxazole	■ verapamil[2]
sulfaphenazole[1]	■ diltiazem

teniposide	cimetidine
voriconazole	amiodarone
zafirlukast	NOT azithromycin
	chloramphenicol
	boceprevir
	ciprofloxacin
	delaviridine
	diethyl-dithiocarbamate
	fluvoxamine
	gestodene
	imatinib
	mibefradil
	mifepristone
	norfloxacin
	norfluoxetine
	starfruit
	telaprevir
	voriconazole

INDUCERS

CYP2C9 (for idasanutlin only)	**CYP3A4 (for cobimetinib only)**
Carbamazepine	efavirenz
Enzalutamide	nevirapine
Nevirapine	barbiturates
Phenobarbital	carbamazepine
Rifampin	enzalutamide
Secobarbital	glucocorticoids
St. John's Wort	modafinil
	oxcarbazepine
	phenobarbital[2]
	phenytoin[2]
	pioglitazone
	rifabutin
	rifampin[1]
	St. John's Wort
	troglitazone[1]

OATP INHIBITORS – to be used with caution in patients in the idasanutlin arm

- Statins
- Atazanavir (Reyataz®)
- Clarithromycin (Biaxin®)
- Cobicistat (part of Stribild®)
- Cyclosporine (Neoral®, Gengraf®, Sandimmune®)
- Daclatasvir (Daklinza™)
- Eltrombopag (Promacta®)
- Erythromycin (E-mycin®)
- Gemfibrozil (Lopid®)
- Lopinavir/Ritonavir (Kaletra®)
- Paritaprevir (Viekira Pak™, Technivie™)
- Ritonavir/Lopinavir (Kaletra®)
- Sacubitril (Entresto®)
- Saquinavir (Invirase®)
- Simeprevir (Olysio®)
- Telithromycin (Ketek®)
- Tipranavir (Aptivus®)
- Rifampin
- Velpatasvir (Epclusa®)