

Official Protocol Title:	A Randomized, Open-Label, Phase 2 Trial of CMB305 (Sequentially Administered LV305 and G305) and Atezolizumab in Patients with Locally Advanced, Relapsed, or Metastatic Sarcoma Expressing NY-ESO-1
NCT number:	NCT02609984
Document Date:	08-March-2017



CLINICAL PROTOCOL

A Randomized, Open-Label, Phase 2 Trial of CMB305 (Sequentially Administered LV305 and G305) and Atezolizumab in Patients with Locally Advanced, Relapsed, or Metastatic Sarcoma Expressing NY-ESO-1

Protocol Number	IMDZ-C232
Investigational Agent	CMB305 (LV305 [lentiviral vector expressing NY-ESO-1 gene] and G305 [NY-ESO-1 recombinant protein plus GLA-SE]) in combination with atezolizumab
Sponsor	Immune Design 1616 Eastlake Ave. E, Suite 310 Seattle, WA 98102
Trial Registration Numbers	ClinicalTrials.gov #: NCT02609984 BB IND: 16589
Version and Date	Version 03, 08 March 2017

INVESTIGATOR AGREEMENT PAGE

Investigator: _____
Study Number: IMDZ-C232
Product Name: CMB305 (LV305 and G305) and atezolizumab
Study Title: A Randomized, Open-Label, Phase 2 Trial of CMB305 (Sequentially Administered LV305 and G305) and Atezolizumab in Patients with Locally Advanced, Relapsed, or Metastatic Sarcoma Expressing NY-ESO-1
Document Date: 08 March 2017

As Principal Investigator, I agree to the following:

- Keep all documentation supplied to me or developed by me concerning this study, and that has not been previously published, in the strictest confidence. This documentation includes, but is not limited to, the Investigator's Brochure (IB) and Case Report Forms (CRFs).
- That the study will not commence without prior written approval of a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol or consent forms without prior written approval of Immune Design and the Institutional Review Board, except where necessary to eliminate an immediate hazard to patients.
- Implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices, and all applicable laws and regulations.
- Accurately transfer all required data from each patient's source documentation to the CRFs. The original CRFs will be submitted to the Sponsor in a timely manner at the completion of the trial, or as otherwise specified by the Sponsor.
- Keep a complete and accurate accounting during and at the completion of the trial of all procedures performed with the drug provided by the Sponsor.
- Allow authorized representatives of Immune Design or regulatory authority representatives to conduct on-site visits to receive, review, audit, and copy trial documents. I will personally meet with these representatives at mutually convenient times to answer any trial-related questions.
- Provide the Sponsor with an Investigator's summary within 90 days of completion of the final trial visit for the last patient enrolled, or as designated by Sponsor.
- Maintain all information supplied by the Sponsor in confidence and, when this information is submitted to an IRB, Ethical Review Committee, or another group, it will be submitted with a designation that the material is confidential.

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. federal regulations as well as "Guidance for Good Clinical Practice," International Conference on

Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

I have read this protocol in its entirety, including the preceding statements, and I agree to comply with all aspects of this trial.

Investigator Printed Name

Investigator Signature

Date

Institution Name

STUDY SYNOPSIS

Title	A Randomized, Open-Label, Phase 2 Trial of CMB305 (Sequentially Administered LV305 and G305) and Atezolizumab in Patients with Locally Advanced, Relapsed, or Metastatic Sarcoma Expressing NY-ESO-1
Sponsor	Immune Design
Trial Sites	Up to 20 sites in the United States and Canada
Trial Phase	Phase 2
Investigational Drug Products	<p>CMB305 (LV305 [lentiviral vector expressing NY-ESO-1] and G305 [NY-ESO-1 recombinant protein plus glucopyranosyl lipid A stable emulsion {GLA-SE}]) The dose of LV305 will consist of 1×10^{10} viral genomes (vg) administered intradermally (ID). G305 will consist of GLA-SE (5 µg) mixed with 250 µg of NY-ESO-1 protein administered intramuscularly (IM).</p> <p>Atezolizumab (formerly MPDL3280A, Roche). Anti-programmed death ligand-1 (anti-PD-L1) will be administered at a dose of 1200 mg/day intravenous (IV) every 3 weeks in combination with CMB305 or alone.</p>
Purpose and Study Rationale	This study will investigate adding a prime-boost immunotherapeutic regimen (CMB305) that can induce NY-ESO-1-specific CD8 T cells to complement the blockade of the PD-L1 checkpoint in the treatment of patients with locally advanced, relapsed, or metastatic sarcoma. Preclinical studies have demonstrated that sequential dosing of LV305 followed by G305 can increase anti-tumor cellular immune responses over each agent alone. Treatment combined with an anti-programmed death receptor ligand-1 (anti-PD-L1) product may synergistically increase the effect.
Objectives	<p>Primary Objective</p> <ul style="list-style-type: none"> To evaluate overall survival (OS) and progression-free survival (PFS) with CMB305 (sequentially administered LV305 and G305) in combination with atezolizumab or with atezolizumab alone, in patients with locally advanced, relapsed, or metastatic sarcoma expressing NY-ESO-1 <p>Secondary Objective</p> <ul style="list-style-type: none"> To evaluate the safety of CMB305 in combination with atezolizumab and atezolizumab alone in patients with locally advanced, relapsed, or metastatic sarcoma expressing NY-ESO-1 To evaluate progression-free survival rates at 6 months after start of study treatment (Day 0) To evaluate the immune response and histologic and molecular tissue changes in the tumor tissue and peripheral blood To evaluate the time to next treatment (TTNT) To evaluate the distant metastasis free survival (DMFS) <p>Exploratory Objectives</p> <ul style="list-style-type: none"> To compare efficacy assessments, such as tumor growth rate (TGR), and progression arrest rate (PAR) To compare PFS and OS between treatment arms To evaluate the immunogenicity of CMB305 in combination with atezolizumab compared to atezolizumab alone

	<ul style="list-style-type: none"> • To evaluate available pre-, on-, and post-treatment tumor tissue and blood for histologic, immunohistologic, and genomic markers • To evaluate the best overall response rate (ORR; by Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 modified to use immune-related Response Criteria [irRC]) and duration of response (DOR) • To evaluate the clinical benefit rate (CBR) • To evaluate the quality of life as a composite endpoint including but not limited to the following: while on study, the incidence of hospitalization, transfusions, and laboratory markers (eg. absolute neutrophil count, hemoglobin, and platelets)
<p>Study Design</p>	<p>This is a randomized, open-label, Phase 2 trial of CMB305, a regimen of LV305 and G305, in combination with atezolizumab or with atezolizumab alone in patients with sarcoma who have had an inadequate response, relapse, and/or unacceptable toxicity with one or more prior systemic, surgical, or radiation cancer therapies. This study will investigate whether adding a prime-boost immunotherapeutic regimen can induce NY-ESO-1-specific CD8 T cells to augment the clinical efficacy of PD-1 blockade. For the combined treatment arm, the trial will be conducted in 4 phases: Treatment Phase (study Days 0 to 84), Booster Phase (post Day 84 to 1 year post Day 0), Maintenance Phase (from 1 year to 2 years post Day 0), and Survival Follow-up Phase (quarterly thereafter) (Table 1). For the control arm, the trial will be conducted in 3 phases: Treatment Phase (study Days 0 to 84), Maintenance Phase (post Day 84 to 2 years post Day 0), and Survival Follow-up Phase (quarterly thereafter). While the study will be open-label, tumor responses will be adjudicated by blinded independent centralized review to minimize bias, if requested by the Sponsor.</p> <p>Up to 12 patients will be randomized in 1:1 allocation ratio to receive CMB305 with atezolizumab or atezolizumab alone in a Safety Run-in, then patients will be randomized in a 1:1 allocation ratio. Approximately 80 patients (40 patients per treatment arm) will be enrolled. Randomization will be stratified by disease type. Archival tumor specimens will be obtained from all patients to determine PD-L1 molecular status.</p> <p>All patients will have tumor samples screened for expression of NY-ESO-1 for eligibility. Imaging will be performed approximately every 6 weeks for 12 months, then every 12 weeks for tumor staging until progression. Tumor responses will be assessed by RECIST v1.1 modified to use irRC-specified confirmation and unidimensional tumor measurements. Patients will be followed on study until confirmed radiographic progression to determine ORR and PFS. In addition, OS will be collected. For patient deaths, the date of death will be documented by the local physician and/or registries.</p> <p>In the combination treatment arm, CMB305 treatment consists of 2 doses of LV305 administered on Days 0 and 14, followed every 2 weeks with alternating doses of G305 and LV305 (Figure 1). In total, 4 doses of LV305 and 3 doses of G305 will be administered over a period of 3 months. LV305 will be administered ID at a dose of 1×10^{10} vg and G305 will administered IM at a dose of 5 µg GLA-SE mixed with 250 µg of NY-ESO-1 protein. Atezolizumab (1200 mg/dose) will be administered IV every 3 weeks and may be continued up to 2 years until toxicity develops or confirmed progression. In addition, a G305</p>

booster dose will be given every 6 weeks in the first year until confirmed disease progression (to coincide with the staging follow-up visit).

Peripheral blood will be collected for immunogenicity assays at baseline, then on Days 42 and 70, and on Day 98 (\pm 2 weeks). Tissue biopsies will be taken before treatment and on Day 42, on Day 98 (\pm 2 weeks), at 6 months or longer (for patients with treatment response), and at the time of progression to assess immune cell invasion, including changes in PD-L1, CD4, CD8/Ki-67, and/or CD3/perforin expression. If a patient undergoes a tumor biopsy at any time after disease progression, investigators are strongly encouraged to provide biopsy tissue to the sponsor for immune response and tumor changes analysis.

Blood will be collected to test for LV305 persistence at baseline, and 6, 12, and 24 months (if required) following the first study treatment administration.

Depending on the results from the 12-month sample, annual assessments may continue until 2 consecutive samples show no evidence of LV305 persistence.

All serious adverse events (SAEs) and medical events of interest (MEOIs) deemed potentially related to the study agents will be reviewed by the Sponsor and an independent Data Monitoring Committee (DMC).

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should resume study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record. Patients may continue treatment in the absence of symptomatic progression based on the criteria in [Section 6.3](#).

Safety Run-in

The first 6 patients will be randomized 1:1 to receive CMB305 in combination with atezolizumab or atezolizumab alone (using a block size of 6) to investigate the safety of the sequential combination. The 3 patients in the combination arm will be observed for treatment-emergent dose-limiting toxicities (DLTs) in the first 42 days of therapy. During the safety observation period, all SAE and DLT safety events deemed potentially related to the study agents will be reviewed by the Sponsor and the independent DMC. If no DLTs are observed in the combination arm, enrollment of patients into the remainder of the study will commence.

If 1 of the 3 patients in the combination treatment arm experiences a DLT during the safety "run-in" evaluation, an additional 6 patients will be randomized (1:1).

If 2 or more of the 6 patients in the combination treatment arm experience DLTs, dosing in the CMB305/atezolizumab treatment arm will stop, and the safety of the combination will be reviewed by the Sponsor and the independent DMC.

Based on this review, the DMC may recommend, and the Sponsor may choose, to reduce the dose of one or more components of CMB305 (dose de-escalation) and treat an additional 3 to 6 patients with the combination treatment regimen following the same 3+3 design, or they may recommend stopping the combined treatment. Should a lower dose prove to be safe, patient enrollment in the randomized treatment arms will commence using the lower dose of that component. Following evaluation by the DMC and the sponsor, a modification to the dose/treatment schedule could be recommended.

Duration of Patient Participation	The expected duration of a patient’s participation on study treatment is up to 2.1 years; this includes Screening, Treatment Phase, Booster Phase (for patients in the combined treatment arm), and Maintenance Phase. Once treatment is completed, or once patients have progressed or discontinued treatment for other reasons, patients will enter the Survival Follow-up Phase during which their disease and survival status will be collected every 3 months by telephone until the study is completed (last patient, last death in the study).
Patient Population	Patients with locally advanced, relapsed, or metastatic sarcoma post standard therapy who have measurable disease and whose tumor expresses NY-ESO-1, as detected by immunohistochemistry (IHC).
Inclusion Criteria	<ol style="list-style-type: none"> 1. Locally advanced, relapsed, or metastatic sarcoma with measurable tumor burden following therapy, as defined by RECIST v1.1; the total of all lesions must be ≤ 12 cm (for synovial sarcoma) or ≤ 15 cm (for myxoid/round cell liposarcoma [MRCL]). 2. Tumor histology consistent with synovial sarcoma or MRCL. 3. Tumor specimen positive for NY-ESO-1 expression by IHC. 4. Inadequate response, relapse, and/or unacceptable toxicity with one or more prior systemic, surgical, or radiation cancer therapies. 5. Have resolution of toxic effect(s) of the most recent prior therapy to Grade 1 or less (except Grade 2 or less neuropathy or alopecia). If subject received major surgery or radiation therapy, they must have recovered from the toxicity and/or complications from the intervention. 6. ≥ 18 years of age before the first scheduled dose. 7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 8. ECG without evidence of clinically significant abnormality. 9. If female of childbearing potential (FCBP), willing to undergo pregnancy testing and agrees to use at least 2 adequate barrier contraceptive methods during the dosing period and for 90 days after the last injection of CMB305 or atezolizumab. 10. If male and sexually active with a FCBP, must agree to use highly effective contraception such as latex condom during the dosing period and for three months after last CMB305 injection. Note: Abstinence is acceptable for either gender if this is the established and preferred contraception for the subject.
Exclusion Criteria	<ol style="list-style-type: none"> 1. Investigational therapy within 4 weeks prior to CMB305 dosing. 2. Prior administration of other NY-ESO-1-targeting immunotherapeutics. 3. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti PD-1, and anti PD-L1 therapeutic antibodies, or any other antibody or drug targeting T-cell costimulation. 4. Treatment with systemic immunostimulatory agents (including but not limited to interleukin-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to first dose. 5. Significant immunosuppression from:

	<p>a. Concurrent, recent (≤ 3 weeks prior to the first schedule dosing) or anticipated need for treatment with systemic corticosteroids (the use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor). The use of topical or inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.</p> <p>b. Other immunosuppressive medications (≤ 3 weeks prior to the first scheduled dosing) including but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor (anti-TNF) agents or conditions such as common variable hypogammaglobulinemia.</p> <p>6. Other cancer therapies, including chemotherapy, radiation, biologics or kinase inhibitors within 3 weeks prior to the first scheduled dosing.</p> <p>7. Has received colony stimulating factors (CSFs; including granulocyte [G]-CSF, granulocyte-macrophage [GM]-CSF, or recombinant erythropoietin) within 4 weeks prior to the first scheduled dosing.</p> <p>8. Psychiatric, other medical illness, or other condition that in the opinion of the Investigator prevents compliance with study procedures or ability to provide valid informed consent.</p> <p>9. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix E for a more comprehensive list of autoimmune diseases).</p> <ul style="list-style-type: none"> • Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. • Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study. <p>10. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), risk of pulmonary toxicity, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.</p> <p>11. Significant cardiovascular disease, such as New York Heart Association cardiac disease (\geq Class II), myocardial infarction within the previous 3 months prior to study treatment, unstable arrhythmias, or unstable angina.</p> <p>12. Inadequate organ function, including the following:</p> <p>a. Marrow: absolute neutrophil count (ANC) $\leq 1500/\text{mm}^3$, platelets $< 75,000/\text{mm}^3$, or hemoglobin (Hb) < 10 g/dL.</p> <p>b. Hepatic: alanine aminotransferase (ALT), and aspartate aminotransferase (AST) $> 2.5 \times$ the upper limit of normal (ULN) OR $\geq 5 \times$ ULN for subjects with liver metastases, total serum bilirubin $> 1.5 \times$ ULN (OR direct bilirubin \geq ULN for patients with total bilirubin levels $< 1.5 \times$</p>
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	<p>ULN; patients with Gilbert's Disease may be included if their total bilirubin is < 3.0 mg/dL).</p> <p>c. Renal: creatinine > 1.5 × ULN.</p> <p>d. Other: prothrombin time (PT), international normalized ratio (INR), or partial thromboplastin time (PTT) > 1.5 × ULN.</p> <p>13. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently). Patients with indwelling catheters (e.g., PleurX®) are allowed.</p> <p>14. Uncontrolled tumor-related pain. Patients requiring pain medication must be on a stable regimen at study entry. Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment. Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.</p> <p>15. Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium (Ca) or Ca > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab. Patients who are receiving these agents specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible. Patients who are receiving denosumab prior to enrollment must be willing and eligible to discontinue its use while on study and receive a bisphosphonate instead.</p> <p>16. History of other cancer within 3 years (except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, localized prostate cancer treated with curative intent, ductal carcinoma in situ treated surgically with curative intent, or other cancers with a similar outcome).</p> <p>17. Evidence of active tuberculosis or recent (< 1 week prior to first scheduled dosing) clinically significant infection requiring systemic therapy (prophylactic antibiotics [e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease] are permitted).</p> <p>18. Evidence of active hepatitis B (HepB), hepatitis C (HepC), or Human Immunodeficiency Virus (HIV) infection. Active HepB is defined as having a positive HepB surface antigen (HBsAg) test at screening. Patients with past/resolved HepB infection (defined as having a negative HBsAg test and a positive antibody to HepB core antigen [anti-HBc] antibody test) are eligible. HepB viral DNA must be negative in these patients prior to the first scheduled dosing. Patients positive for HepC antibody are only eligible if polymerase chain reaction (PCR) is negative for HepC viral RNA.</p> <p>19. Administration of a live, attenuated vaccine within 4 weeks prior to the first scheduled dosing or anticipation that such a live attenuated vaccine will be required during the study. Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not</p>
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	<p>receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to the first scheduled dosing or at any time during the study.</p> <p>20. Known active or untreated central nervous system (CNS) metastases. Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:</p> <ol style="list-style-type: none"> No metastases to cerebellum, brain stem, midbrain, pons, medulla, or within 10 mm of the optic apparatus (optic nerves and chiasm). No evidence of interim progression \geq 4 weeks between the completion of CNS-directed therapy and the screening radiographic study and \geq 2 weeks since discontinuation of corticosteroids. No ongoing requirement for dexamethasone as therapy for CNS disease; anticonvulsants at a stable dose allowed. <p>21. Pregnant, planning to become pregnant within 6 months of treatment, or nursing.</p> <p>22. Known allergy(ies) to any component of CMB305, atezolizumab, or severe allergic reactions to monoclonal antibodies, fusion proteins, or CHO cell products.</p>
<p>Safety Monitoring</p>	<p>The safety profiles for CMB305 and atezolizumab are described in their respective Investigator’s Brochures (IBs). Safety will be monitored by evaluating solicited and spontaneously reported adverse events (AEs), including reactogenicity, symptoms, physical examination findings, vital signs, laboratory findings, and discontinuations for AEs. AE severity assessments will be performed using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03. All adverse events, regardless of relationship to study drug, should be reported until 30 days after the last dose of study drug or until initiation of another anti-cancer therapy, whichever occurs first.</p> <p>AEs (both non-serious and serious) associated with exposure to the study drugs may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. The study drugs must be withheld for drug-related toxicities as outlined in Appendix F, as well as severe or life-threatening AEs.</p> <p><u>Data Monitoring Committee</u></p> <p>A DMC will operate in accordance with a signed charter and will consist of 2 experienced oncologists familiar with clinical use of the study drugs and an ad hoc biostatistician who is knowledgeable about statistical methods for clinical trials and sequential analysis of trial data. The DMC will review all cumulative safety information from the Safety Run-in prior to recommendations for further patient enrollment. Thereafter, the DMC will provide independent review of all safety data every 3 months to minimize risks to study patients. All DLTs and SAEs considered at least possibly related to study regimen will be reviewed by the DMC and the Sponsor as they are reported and on an ongoing basis. These reviews may lead to modification or stopping of the treatment program if related, treatment-emergent adverse events indicate a safety profile that is inconsistent or significantly worse than reported with the use of either CMB305 or atezolizumab</p>

	<p>alone. Related SAE reports will be expedited to regulatory authorities, investigators, and DMC members.</p> <p>The preliminary safety of the individual components of CMB305 (LV305 and G305) and of the combinatorial regimen have been studied in separate Phase 1 studies; that of the CMB305/atezolizumab combination will be investigated during the 3-6 patient Safety Run-in. Dosing will be suspended in this study if a DLT is observed in one third or more patients in the combination treatment arm (assuming a minimum of 12 combined regimen patients were enrolled at that point and would represent the initial denominator), pending review and recommendation from the DMC.</p>
<p>Toxicities Associated with Atezolizumab</p>	<p>Atezolizumab can be associated with the following AEs and will be withheld until resolution for any of the following events:</p> <ul style="list-style-type: none"> • Grade ≥ 2 pneumonitis • Grade ≥ 3 symptomatic hepatic toxicities that do not resolve to Grade 2 within 48 hours or Grade ≥ 3 asymptomatic hepatic toxicities that do not resolve to Grade ≤ 1 within 3 weeks of onset with the following exceptions: <ul style="list-style-type: none"> • For patients with Grade 2 AST, ALT, or alkaline phosphatase abnormality at baseline, an increase to $>8x$ ULN that does not resolve to Grade 2 within 48 hours (if symptomatic) or Grade ≥ 3 asymptomatic hepatic toxicities that do not resolve to Grade ≤ 1 within 3 weeks of onset (if asymptomatic) will be considered a DLT. • Grade ≥ 2 diarrhea or colitis • Symptomatic hypothyroidism, hyperthyroidism, pan hypopituitarism, or any Grade ≥ 3 endocrine events • Grade ≥ 3 ocular events • Grade ≥ 3 dermatologic events • Grade ≥ 2 neuropathy • Grade ≥ 4 neutropenia (ANC $<500/\mu\text{L}$) lasting ≥ 7 days, thrombocytopenia, anemia, or Grade ≥ 3 febrile neutropenia • Grade ≥ 3 non-hematologic, non-hepatic organ toxicity, excluding the following: <ul style="list-style-type: none"> • Grade 3 immune related AE that resolves to Grade ≤ 1 within 3 weeks of its onset (may include events that resolve after medical treatment, including immunosuppressant therapy) • Grade 3 nausea or vomiting that resolves to Grade ≤ 1 within 72 hours of appropriate supportive therapy • Grade ≥ 3 fatigue that resolves to Grade ≤ 2 within 7 days • Grade 3 arthralgia that can be adequately managed with supportive care or that resolves to Grade ≤ 2 within 7 days • Grade 3 fever (in the absence of any clinically significant source of fever) that resolves to Grade ≤ 2 within 7 days with supportive care • Grade ≥ 3 laboratory abnormality that is asymptomatic and deemed by the Investigator not to be clinically significant • Grade 3 tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor • Grade 3 infusion reaction that resolves within 6 hours to Grade ≤ 1

	<p>These reactions, along with any DLTs, will be reviewed by the data monitoring committee (DMC) on a case-by-case basis and may be considered DLTs if they meet the criteria outlined above. Atezolizumab treatment can be resumed in patients whose adverse reactions recover to Grade 0-1.</p>
<p>Dose Limiting Toxicity (DLT)</p>	<p>AE severity assessments will be performed using NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Unacceptable toxicity is defined when one third or more of the subjects treated with the combined regimen develop an AE considered Grade 3 or higher and considered at least possibly related to CMB305 or atezolizumab with the exceptions below. Hospitalizations primarily intended to expedite diagnostic evaluations or for elective surgery will not be considered as serious adverse events (SAEs) for the purpose of ascertaining DLT.</p> <p>Any treatment emergent grade 3 or higher AE that occurs in the DLT assessment window, which is the first 42 days after initiation of study drug, that is deemed possibly, probably or definitely related to the combination of CMB305 and atezolizumab will be considered DLTs with the following exceptions:</p> <ul style="list-style-type: none"> • Alopecia or vomiting (unless not controlled by optimal anti-emetics) • Hepatic enzyme elevations associated with the baseline Grade 2 abnormalities that are noted as exceptions above • Grade 3 laboratory AEs that are asymptomatic and return to baseline or to Grade 1 within 3 days, unless identified specifically as DLT by the investigator or the Data Monitoring Committee (DMC) • Grade 3 fatigue • Grade 3 systemic reactions (such as fever, headache, influenza like symptoms, myalgia, malaise, or nausea) that return to baseline or Grade 1 within 3 days of study inoculation <p>Atezolizumab has a recognized safety profile. AEs in the combined treatment arm that are attributed to atezolizumab will be evaluated by the DMC and sponsor, but will not be immediately considered as DLTs except as noted above. All such events should be reported to the Sponsor in an expedited manner (within 24 hours) and will be reviewed by the DMC. Although these events will not contribute automatically to the DLT stopping criteria, these reviews may lead to modification or stopping of the treatment program if related, treatment-emergent AEs indicate a safety profile that is inconsistent or significantly worse than reported with the use of atezolizumab alone.</p> <p>During the safety run-in, the following patients will not be considered evaluable for DLTs and will be replaced:</p> <ul style="list-style-type: none"> • Patients who withdraw or are withdrawn for either study treatment prior to completing the DLT assessment window for any reason other than a DLT • Patients who do not receive the full assigned dose of either study treatment during the DLT assessment window for reactions other than a DLT. <p>Replaced patients will remain on study treatment if they otherwise meet criteria to continue dosing and continue assessment.</p>

Statistical Analysis	<p><u>Endpoints</u></p> <p>Primary</p> <p>The primary endpoints are the following:</p> <ul style="list-style-type: none">• OS and PFS <p>Secondary</p> <p>The secondary endpoints include the following:</p> <ul style="list-style-type: none">• Safety• Progression-free rate (PFR) at 6 months• TTNT• Immune response and histologic and molecular tissue changes in tumor tissue or peripheral blood• DMFS <p>Exploratory</p> <p>The exploratory endpoints are the following:</p> <ul style="list-style-type: none">• TGR• PAR• To compare OS and PFS between treatment arms• ORR as assessed by RECIST (v1.1) modified to use irRC• DOR• CBR• Immune responses as measured by changes from baseline in anti-NY-ESO-1 immunity• Biomarkers• Quality of life <p>Safety</p> <p>The safety endpoints include the nature, frequency, and severity of AEs and MEOIs, laboratory abnormalities, and other safety assessments (including vital signs, LV305 persistence, physical examination findings, electrocardiograms [ECGs], etc.).</p> <p><u>Statistical Analyses</u></p> <p>Efficacy</p> <p>The primary efficacy analysis will be the evaluation of OS and PFS using Kaplan-Meier methodology and will be performed on the ITT Population for each treatment arm. Kaplan-Meier plots and 95% confidence intervals (CIs) for 75%, 50% and 25% survival, if reached, will be provided for each treatment group.</p> <p>A secondary efficacy analysis will be based on the proportion of patients that are progression-free at 6 months after start of study drug treatment (Day 0). Time-to-next-treatment and distant metastasis free survival will be compared between treatment arms based on a stratified log-rank test.</p> <p>The immunologic efficacy in tumor tissue and peripheral blood will be evaluated by changes in concentration of immune cells (e.g., CD8+ T cells) and antibodies.</p>
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	<p>Exploratory comparisons of the OS, PFS, and DOR between treatment arms will be based on stratified log-rank tests. ORR will be compared between treatment groups using a stratified logistic regression model. Weighted log-rank tests will be explored if delayed treatment effect is observed; TGR, PAR, CBR, and quality of life will be evaluated for each group.</p> <p>Safety Descriptive statistics will be performed for all safety information including AEs, SAEs, laboratory findings and discontinuations of patients at all data collection timepoints. No formal statistical hypothesis will be tested.</p> <p>Immunogenicity Descriptive statistics will be performed comparing the baseline and treatment administration peripheral blood NY-ESO-1-responsive T cells between the 2 treatment arms. Analyses will be performed to determine if there are any statistically significant changes from baseline values. Changes from baseline in serial anti-NY-ESO-1 antibodies will be expressed as geometric mean titers.</p> <p>Biomarkers Descriptive statistics will be provided for biomarkers and treatments will be compared using ANOVA, or non-parametric method when appropriate, of specific genes and/or analysis of gene-networks (e.g., signaling of immune cells) and gene modules (e.g., sets of genes [typically 100-200]) that are up- or down-regulated in concert in certain conditions or disease states (e.g., infection, autoimmunity, etc.) will be performed. Data will be used to compare the baseline with responses post-treatment. Additionally, joint models of overall survival and longitudinal biomarker data may be explored.</p>
Sample Size	<p>The median PFS for first-line chemotherapy for patients presenting with or developing metastatic synovial sarcoma has been reported to be 2.5 to 8.3 months; PFS with atezolizumab in the post-chemotherapy setting is unknown. Thus, no power calculations based on comparisons of PFS were made. However, based on an unacceptable and desirable median PFS of 3 months and 5.2 months, respectively, corresponding PFRs at 6 months were derived. With an unacceptable PFR of 25% and an acceptable PFR of 45% at 6 months, a Simon 2-stage design will be used to examine the PFR in 40 patients in each arm ($\alpha=0.1$, $\beta=0.15$). For this study, two groups of approximately 40 patients each (approximately 80 patients for the entire study) will be dosed with CMB305 with atezolizumab or with atezolizumab alone to assess the quartiles (25%, 50%, and 75%) of PFS with 95% CIs and the PFR at 6 months. If favorable results are observed, the study may be expanded to improve the estimates of PFS.</p>
Interim Analysis	<p>An exploratory analysis of the PFR at 6 months after treatment initiation will be used as a non-binding futility analysis for each treatment arm. Upon obtaining the progression status after 6 months on study from the first 36 (18 per arm) and subsequently from all enrolled patients, interim analyses will be performed and presented to the DMC, which will include estimates of PFS and assessment of PFR. Based on the assumptions above, futility guidelines at Stage 1 will be based on 18 patients and will require at least 6 patients to be progression free to continue on to Stage 2. With an additional 22 patients at the end of Stage 2, at least 14 of the total of 40 patients should be progression free at 6 months after initial dosing to recommend further study in this setting. For the purposes of</p>

	<p>safety monitoring, key safety analysis will also be performed quarterly. The DMC will evaluate the available data and make necessary recommendations to the study. Details will be outlined in the DMC charter.</p> <p>A final OS analysis will be conducted when at least 72 deaths have been observed, or sooner if the Sponsor so decides.</p>
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Table 1 Schedule of Events – Combination Treatment Arm

	Screening	Treatment Phase										Booster Phase			Maintenance Phase	Survival Follow-up ^a
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13+			
Timeline – Weeks ^a	-4 to 0	0	2	3	4	6	8	9	10	12	14	15	Every 3 wks ^b	Every 3 wks ^b	Every 3 mos (12 wks)	
Procedures	Timeline – Days	-30 to -1	0	14	21	28	42	56	63	70	84	98	105			
Informed consent/HIPAA ^c	X															
Inclusion/exclusion criteria	X															
Demographics/Medical History	X															
Tumor-specific therapy history	X															
NY-ESO-1 expression on pre-study tumor sample ^d	X															
Enrollment and randomization		X														
Report AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record any previous concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam ^f	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG (12-Lead)	X											X				
Tumor staging, by CT scan ^g	X					X				X			X	X		
ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV, HepB, and HepC (5 mL) ^h	X												X ^h	X ^h		
Blood for cellular immunity (55 mL) ⁱ	X	X				X			X		X ⁱ					
Blood for safety labs (10 mL) ^j	X	X	X	X	X	X	X	X	X	X		X	X	X		
Thyroid function tests ^k	X									X			X ^k	X ^k		
Urinalysis	X															
Urine sample for pregnancy test ^l	X	X	X	X	X	X	X	X	X	X		X	X	X		
Study drug: LV305		X	X			X			X							
Study drug: G305					X		X			X			X ^m			
Study drug: atezolizumab		X		X		X		X		X		X ⁿ	X ⁿ	X ⁿ		
Blood for LV305 persistence (8 mL) ^o	X												X ^o	X ^o		
Tumor biopsy ^p	X					X					X ^p			X ^b		
Survival Status															X ^q	
Blood volume per visit (mL)	78	65	10	10	10	65	10	10	65	10	55	10				
Total blood volume	78	14	15	16	17	23	24	25	32	333	38	398				
		3	3	3	3	8	8	8	3		8					

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CMB305 (LV305 and G305) and Atezolizumab
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Abbreviations: AE = adverse event, CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HepB = hepatitis B; HepC = hepatitis C; HIPAA = Human insurance Portability and Accountability Act; HIV = Human immunodeficiency Virus; meds = medications; mos = months; PBMC = peripheral blood mononuclear cells; SAE = serious adverse event.

- a. A window of ± 3 days is permitted for Visits 3 through 12. Follow-up phase visits (Visits 13+) will be permitted a window of ± 4 days, Tumor assessments will be permitted a window of ± 1 week.
- b. Patients will be followed with visits every 3 weeks (± 4 days) for 2 years (from Day 0) for until progression. Tumor size will be assessed every 6 weeks for the first year, then every 12 weeks until progression. Patients will then have no further staging procedures. Tumor biopsies will be obtained at 6 months or longer for patients with treatment response. Tumor biopsies will also be obtained at time of progression.
- c. Informed consent and HIPAA authorization must be signed before any screening study-related procedures are initiated. Three informed consents will be used: one to screen tumor sample for NY-ESO-1, one to engage in the study protocol, and an agreement to continue in the study and obtain peripheral blood samples and biopsies if the patient meets the criteria for progressive disease but wishes to remain on study.
- d. Documentation of NY-ESO-1 expression in prior tumor samples may have been collected from any procedure performed before baseline activities. There is no time limit for use of the results from the IMDZ-approved central lab.
- e. Vital sign measurements include temperature, pulse, respiratory rate, and resting systolic and diastolic blood pressure. On the day of each dosing, vital signs will be obtained pre-dosing and 30 minutes after dosing. For the first atezolizumab infusion, the patient's vital signs (HR, respiratory rate, BP, and temperature) should be measured within 15 minutes of the infusion, during the 60-minute infusion (every 15 \pm 5 minutes), and 30 minutes after the infusion. For subsequent infusions, vital signs do not need to be obtained during the infusion if the prior infusion was tolerated without symptoms.
- f. Once the baseline physical exam has been conducted, a simple symptom-directed physical exam should be performed for all subsequent visits. Height and weight will be collected at Day 0 only.
- g. Imaging will be performed by CT scan as defined by RECIST/irRC at screening and every 6 weeks after first study injection for the first year, then every 12 weeks for tumor staging until disease progression and includes a confirmatory scan performed at least 4 weeks later. Magnetic Resonance Imaging (MRI), bone scans, or PET/CT at baseline or subsequent visits will be performed only if clinically indicated.
- h. An HIV screening test will be repeated on Day 168 to determine if seroconversion has occurred following LV305 injections. If positive, further testing can demonstrate that the normal complement of HIV proteins is not present (unless the patient has developed a true HIV infection).
- i. Blood for immunogenicity will be collected at clinical sites that are trained in peripheral blood mononuclear cells (PBMC) isolation. Baseline samples will be drawn twice to ensure a good yield. At least 55 mL should be collected in 8 Cell Preparation Tubes (CPT)TM tubes for T-cell response assays. See the Lab Manual for processing details.
- j. Initial safety labs are to be performed within 4 days before treatment initiation. On treatment days during the study dosing period, the hematology and clinical chemistry laboratories must also be performed and reviewed before dosing and may be performed up to 48 hours prior to the planned dosing.
- k. Thyroid function tests (triiodothyronine [T₃], thyroxine [T₄], and thyroid stimulating hormone [TSH]) should be taken at initial screening and at least every 3 months while being treated with atezolizumab. As thyroid disorders could occur at any time as a result of atezolizumab treatment, patients should be monitored for changes in thyroid function for clinical signs and symptoms of thyroid disorders (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation).
- l. Urine pregnancy test must be performed for women of childbearing potential within 72 hours before study drug administration and negative before study drug administration, including during the follow-up period if patients are still receiving booster doses of G305 and/or atezolizumab. Serum pregnancy test may be performed if the site's standard operating procedures allow.
- m. Booster doses of G305 will be given 6 weeks following the Day 84 dose and every 6 weeks thereafter for 1 year (from Day 0) or until disease progression at the staging visits.
- n. Atezolizumab should be continued every 3 weeks for 2 years (from Day 0) or until progression unless toxicity occurs.
- o. Peripheral blood will be collected at screening, Day 168, and 12 and 24 months after initial injection to test for persistence of LV305. Samples will be assayed for presence of the viral genome by polymerase chain reaction (PCR). Depending on the results through 12 months, annual assessments may continue until 2 consecutive samples show no evidence of LV305 persistence.
- p. The pre-treatment biopsy must be completed ≤ 6 months prior to screening; if not available, a fresh biopsy may be included in the screening process. The tissue biopsy taken on Day 98 can be performed ± 2 weeks from this study visit; however, the patient may opt out of the Day 98 biopsy after a discussion with a physician and documentation in the patient's chart. If a tumor biopsy is not feasible, a biopsy may be done at a subsequent visit with approval provided by the Sponsor.

- q. Once patients have progressed and study drugs are discontinued for more than 30 days, their physicians will be contacted by the sites every 3 months by telephone until the study is completed (last patient, last death in the study) to assess OS. The attending physician will be contacted quarterly or database searched until study completion for identification of subsequent treatments and survival status.

Table 2 Schedule of Events – Control Arm

	Screening	Treatment Phase						Maintenance Phase			Survival Follow-up ^a
Visit	1	2	3	4	5	6	7	8	9	10+	
Timeline – Weeks^a	-4 to 0	0	3	6	9	10	12	14	15	Every 3 wks ^b	Every 3 months (12 wks)
Procedures	Timeline – Days	-30 to -1	0	21	42	63	70	84	98	105	
Informed consent/HIPAA ^c	X										
Inclusion/exclusion criteria	X										
Demographics/medical history	X										
Tumor-specific therapy history	X										
NY-ESO-1 expression on pre-study tumor sample screen ^d	X										
Enrollment and randomization		X									
Report AEs and SAEs		X	X	X	X	X	X	X	X	X	X
Record any previous/concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Vital signs ^e	X	X	X	X	X	X	X	X	X	X	
Physical exam ^f	X	X	X	X	X	X	X	X	X	X	
ECG (12-Lead)	X								X		
Tumor staging, by CT scan ^g	X			X			X			X	
ECOG	X	X	X	X	X	X	X	X	X	X	
HIV, HepB, and HepC (5 mL)	X										
Blood for cellular immunity (55 mL) ^h	X	X		X		X		X			
Blood for safety labs (10 mL) ⁱ	X	X	X	X	X		X		X	X	
Thyroid function tests ^j	X						X			X ^j	
Urinalysis	X										
Urine sample for pregnancy test ^k	X	X	X	X	X		X		X	X	
Study drug: atezolizumab		X	X	X	X		X		X	X ^l	
Tumor biopsy ^{m & b}	X			X				X ^m		X ^b	
Survival Status											X ⁿ
Blood volume per visit (mL)	70	65	10	65	10	55	10	55	10		
Total blood volume	70	135	145	210	220	275	285	340	350		

Abbreviations: AE = adverse event, CT = computed tomography; ECG = 12-lead electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HepB = hepatitis B; HepC = hepatitis C; HIPAA = Human insurance Portability and Accountability Act; HIV = Human immunodeficiency Virus; SAE = serious adverse event.

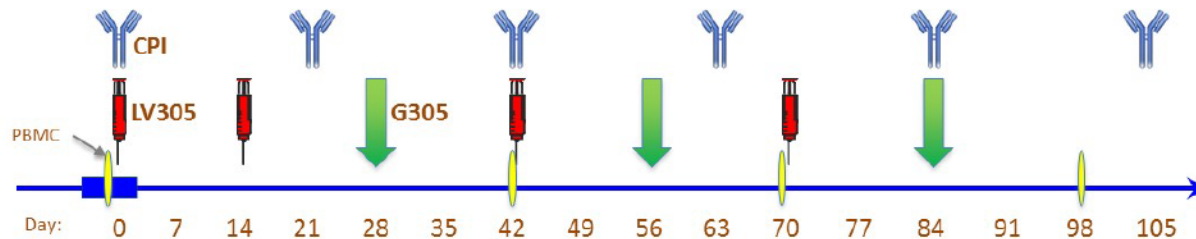
a. A window of ±3 days is permitted for Visits 3 through 9. Follow-up phase visits (Visits 10+) will be permitted a window of ±4 days, Tumor assessments will be permitted a window of ±1 week.

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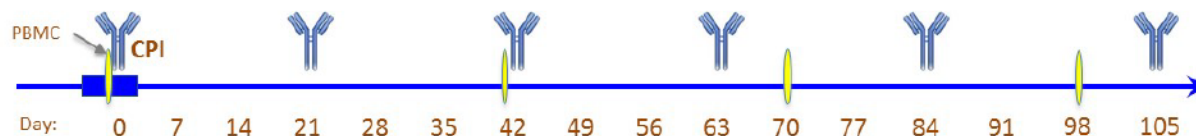
- b. Patients will be followed with visits every 3 weeks (± 4 days) for 2 years (from Day 0) for atezolizumab treatment until progression. Tumor size will be assessed every 6 weeks for the first year, then every 12 weeks until progression. Patients will then have no further staging procedures. Tumor biopsies will be obtained at 6 months or longer for patients with treatment response. Tumor biopsies will also be obtained at time of progression.
- c. Informed consent and HIPAA authorization must be signed before any screening study-related procedures are initiated. Three informed consents will be used: one to screen tumor sample for NY-ESO-1, one to engage in the study protocol, and an agreement to continue in the study if the patient meets the criteria for progressive disease but wishes to remain on study.
- d. Documentation of NY-ESO-1 expression in prior tumor samples may have been collected from any procedure performed before baseline activities. There is no time limit for use of the results from the IMDZ-approved central lab.
- e. Vital sign measurements include temperature, pulse, respiratory rate, and resting systolic and diastolic blood pressure. On the day of each dosing, vital signs will be obtained pre-dosing and 30 minutes after dosing. For the first atezolizumab infusion, the patient's vital signs (HR, respiratory rate, BP, and temperature) should be measured within 15 minutes of the infusion, during the 60-minute infusion (every 15 \pm 5] minutes), and 30 minutes after the infusion. For subsequent infusions, vital signs do not need to be obtained during the infusion if the prior infusion was tolerated without symptoms.
- f. Once the baseline physical exam has been conducted, a simple symptom-directed physical exam should be performed for all subsequent visits. Height and weight will be collected at Day 0 only.
- g. Imaging will be performed by CT scan as defined by RECIST/irRC at screening and every 6 weeks after first study injection for the first year, then every 12 weeks for tumor staging until disease progression and includes a confirmatory scan performed at least 4 weeks later. MRI, bone scans or PET/CT at baseline or subsequent visits will be performed only if clinically indicated.
- h. Blood for immunogenicity will be collected at clinical sites that are trained in peripheral blood mononuclear cells (PBMC) isolation. Baseline samples will be drawn twice to ensure a good yield. At least 55 mL should be collected in 8 Cell Preparation Tubes (CPT)TM tubes for T-cell response assays. See the Lab Manual for processing details.
- i. Initial safety labs are to be performed within 4 days before treatment initiation. On treatment days during the study dosing period, the hematology and clinical chemistry laboratories must also be performed and reviewed before dosing and may be performed up to 48 hours prior to the planned dosing.
- j. Thyroid function tests (triiodothyronine [T₃], thyroxine [T₄], and thyroid stimulating hormone [TSH]) should be taken at initial screening and at least every 3 months while being treated with atezolizumab. As thyroid disorders could occur at any time as a result of atezolizumab treatment, patients should be monitored for changes in thyroid function for clinical signs and symptoms of thyroid disorders (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation).
- k. Urine pregnancy test must be performed for women of childbearing potential within 72 hours before study drug administration and negative before study drug administration, including during the follow-up period if atezolizumab administration is continued. Serum pregnancy test may be performed if the site's standard operating procedures allow.
- l. Atezolizumab should be continued every 3 weeks for 2 years (from Day 0) or until disease progression unless toxicity occurs.
- m. The pre-treatment biopsy must be completed ≤ 6 months prior to screening; if not available, a fresh biopsy may be included in the screening process. The tissue biopsy taken on Day 98 can be performed ± 2 weeks from this study visit; however, the patient may opt out of the Day 98 biopsy after a discussion with a physician and documentation in the patient's chart. If a tumor biopsy is not feasible, a biopsy may be done at a subsequent visit with approval provided by the Sponsor.
- n. Once patients have progressed and study drugs are discontinued for more than 30 days, their physicians will be contacted by the sites every 3 months by telephone until the study is completed (last patient, last death in the study) to assess OS. The attending physician will be contacted quarterly until study completion for identification of subsequent treatments and survival status.

Figure 1 Dosing Schedule for Each Treatment Arm

A. Combination Treatment Arm



B. Control Arm



Abbreviations: PBMC = peripheral blood mononuclear cell; CPI = checkpoint inhibitor.

Red syringe = LV305 injections; Green arrows = G305 injections; blue antibodies indicate atezolizumab treatment days.

The combination treatment arm will consist of administration of CMB305 and atezolizumab (A). Dosing of CMB305 (LV305 and G305) will occur every 2 weeks beginning with the administration of 2 consecutive doses of LV305 followed by alternating administration of G305 and LV305 for 12 weeks (i.e. during the Treatment Phase). Atezolizumab will be administered every 3 weeks. The control arm (B) will receive atezolizumab alone every 3 weeks.

Note: For the combined treatment arm (A), the trial will be conducted in 4 phases: Treatment Phase (study Days 0 to 84), Booster Phase (post Day 84 to 1 year post Day 0), Maintenance Phase (from 1 year to 2 years post Day 0), and Survival Follow-up Phase (quarterly thereafter). For the control arm (B), the trial will be conducted in 3 phases: Treatment Phase (study Days 0 to 84), Maintenance Phase (post Day 84 to 2 years post Day 0), and Survival Follow-up Phase (quarterly thereafter). Dosing with atezolizumab may continue up to 2 years until confirmed progression in both treatment arms. G305 may be given every 6 weeks following the Day 84 dose for up to 1 year (from Day 0) as a booster injection during the restaging follow-up visits.

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1.0 GENERAL INFORMATION

1.1 Sponsor and Investigator Information

Trial Sponsor

Immune Design Corporation
1616 Eastlake Ave. E, Suite 310
Seattle, WA 98102

Sponsor's Medical Monitor

PPD
Immune Design Corporation
601 Gateway Blvd., Suite 250
South San Francisco, CA 94080

Lead Principal Investigator

Robert Maki, M.D, PhD, Mount Sinai Medical Center, New York, NY

1.2 Protocol Revision History

Version	Date	Comment
01	29 July 2015	Initial version
02	27 September 2015	Revised the atezolizumab risk profile and AE management guidelines and corrected internal inconsistencies, added toxicities attributed to atezolizumab in the DLT evaluation, updated timing of immunogenicity blood draws, added assessments for anti-therapeutic antibodies and thyroid function, updated and simplified justification of sample size and interim analysis, added MEOI

definitions to a new Appendix B, and clarified tumor interpretation guidelines.

03	08 March 2017	<p>Overall Survival was added to the primary objective and study endpoint. The evaluation of the immune response and histologic and molecular tissue changes in tumor tissue changes or peripheral blood, time to next treatment, and distant metastasis free survival were added as secondary objectives and study endpoints. The evaluation of best overall response rate and duration of response was updated to be exploratory objectives/endpoints, and the evaluation of clinical benefit rate and the quality of life were added as exploratory objectives and study endpoints. Comparison of overall survival and progression-free survival was also added as exploratory endpoints. Progression-free survival study endpoint was updated. Treatment phases (Treatment Phase, Booster Phase, Maintenance Phase, and Survival Follow-up Phase) were incorporated into the study design. Peripheral blood and tissue biopsy collection was updated to occur in all enrolled patients. For tissue biopsies, Day 98, at 6 months or longer (for patients with treatment response), and the time of progression were added as collection visits. In addition, for Study Day 98, peripheral blood and tissue biopsy collection was updated to occur \pm 2 weeks and that patients may opt out of this biopsy on this visit. Tumor biopsy collection procedures for patients with progressive disease was clarified and updated. The methodology for the statistical efficacy analysis was updated. The collection of blood for anti-therapeutic antibodies was removed. Study procedures were clarified to illustrate that 3 informed consent forms (including an agreement to obtain blood samples and biopsies if the patient progresses but wishes to remain on study) are to be collected. Vital signs measurement times were clarified. Survival follow-up contact methods were updated. The study rationale was updated. Details regarding the collection of archival tissue were added. Additional administrative changes were made throughout the document to ensure clarity and consistency throughout the protocol.</p>
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2.0 LIST OF ABBREVIATIONS

Abbreviation	Description
ADL	activities of daily living
AE	adverse event
AF	aqueous formulation
Ag	antigen
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
APC	antigen-presenting cell
AST	aspartate aminotransferase
ATA	anti-therapeutic antibodies
BCT	blood collection tube
BICR	blinded independent centralized review
BP	blood pressure
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
C _L	mean apparent clearance
CPI	checkpoint inhibitor
CPT	Cell Preparation Tubes
CRF	Case Report Form
CR	complete response
CRP	C-reactive protein
CSF	colony stimulating factor
CT	cancer/testis antigen or Computed Tomography
CTL	cytotoxic T-lymphocyte
DC	dendritic cell
DC-SIGN	DC-specific intercellular adhesion molecule-3-grabbing non-integrin receptor (CD209)
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DMFS	distant metastasis free survival
DMPC	1,2-dimyristoyl-sn-glycero-3-phosphocholine

Abbreviation	Description
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
EDC	electronic data capture
EOS	end-of-study visit
FCBP	female of child bearing potential
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GLA	glucopyranosyl lipid A
GLAAS	glucopyranosyl lipid A adjuvant system
GLA-SE	glucopyranosyl lipid A stable emulsion
GM-CSF	granulocyte-macrophage colony stimulating factor
Hb	hemoglobin
HBc	Hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HepB	Hepatitis B
HepC	Hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IMDZ	Immune Design Corporation
ID	intra-dermal
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin

Abbreviation	Description
IM	intramuscular
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irRC	immune-related response criteria
irSD	immune-related stable disease
IV	intravenous
IWRS	interactive web response system
LV	lentiviral vector
mAb	monoclonal antibody
MEOI	medical event of interest
MHC	major histocompatibility complex
MITT	modified intent-to-treat
MRI	magnetic resonance imaging
MRCL	myxoid/round cell liposarcoma
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NK	natural killer
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small-cell lung carcinoma
ORR	overall response rate
OS	overall survival
PAR	progression arrest rate
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1 receptor
PD-L1	PD-1 ligand
PET	positron emission tomography
PFR	progression-free rate

Abbreviation	Description
PFS	progression-free survival
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	stable disease
SE	stable oil in water emulsion/stable emulsion
SINV	Sindbis virus
SINVar1	DC-SIGN targeting Sindbis virus envelope glycoprotein
SIRS	systemic inflammatory response syndrome
SOP	standard operating procedures
SVGmu	Sindbis virus glycoprotein mutant
T ₃	triiodothyroxine
T ₄	thyroxine
TAA	tumor-associated antigen
TGR	tumor growth rate
TLR4	toll-like receptor 4
TNF	tumor necrosis factor
TRP1	tyrosine-related protein-1
TSH	thyroid stimulating hormone
TTNT	time to next treatment
ULN	upper limit of normal
US	United States
vg	vector genomes
V _{ss}	volume of distribution at steady state
WBC	white blood cell

3.0 INTRODUCTION AND RATIONALE

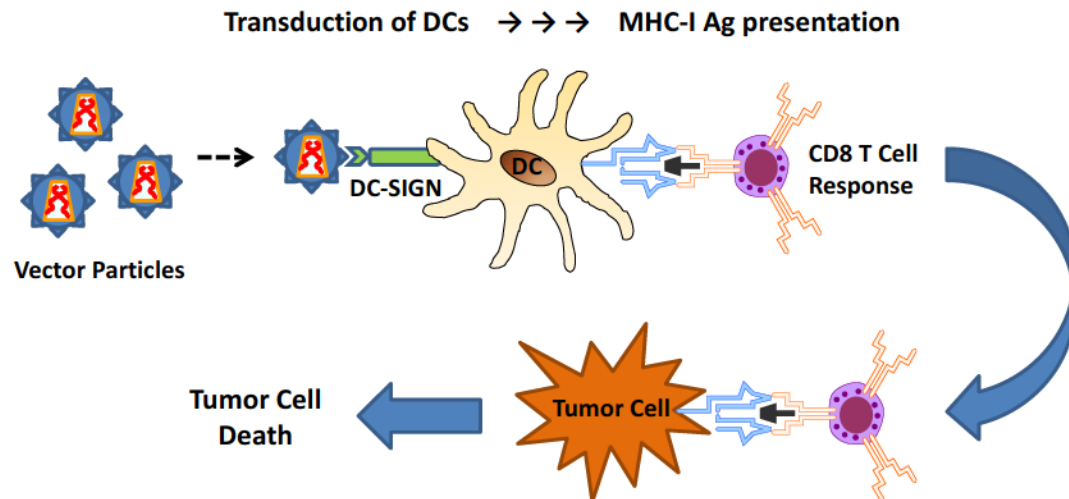
The development of immunotherapeutic products that target specific tumors and appropriately harness the immune system to kill tumor cells is a promising approach for the treatment of human malignancies. Effective therapeutic immunization strategies for cancer require the induction of potent, stable, and self-renewing CD8 T cell populations directed against defined tumor-associated targets (TAAs). Human tumor cells express a variety of TAAs that are not expressed, or are minimally expressed, in normal tissues, and can serve as targets for the host cellular immune system to induce tumor destruction. The development of effective cancer therapeutic products may require both the induction of appropriate cellular immune responses and a mechanism to overcome evasion mechanisms.

NY-ESO-1 is a TAA and was one of the first cancer-testis (CT) antigens (Ag) described.¹ It is considered one of the top ten cancer Ags on the list for all cancers.² Normally, its expression is restricted to germ cells and is not seen in normal somatic tissues. However, NY-ESO-1 expression is seen in approximately 1/4 to 1/3 of melanoma, lung, esophageal, liver, gastric, prostate, ovarian, and bladder cancers. Up to 45% of melanomas and $\geq 80\%$ of sarcomas reported NY-ESO-1 expression.^{3,4,5,6} Thus, immunotherapeutics targeting NY-ESO-1 have the potential to be broadly applicable to a variety of cancer indications.

Immune Design (IMDZ) has developed a lentiviral vector (LV)-based immunotherapeutic platform called ZVex™ engineered to deliver Ag-encoding nucleic acids to dendritic cells (DCs) *in vivo*⁷ enabling direct Ag presentation to generate effective anti-tumor CD8 T cell responses. LV305 is a lentiviral vector that encodes NY-ESO-1 and is designed to generate NY-ESO-1-specific CD8 T-cell populations in patients where no such populations can be detected; thereby priming a T-cell mediated response. LV305 can also expand pre-existing NY-ESO-1-specific CD8 T-cell populations.⁶

LV305 selectively enters DCs via the dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin receptor (DC-SIGN, also known as CD209; see [Figure 2](#)). Following cell entry and transduction, the encoded Ag (i.e., NY-ESO-1) is expressed by the cellular machinery and subsequently presented as peptides via the major histocompatibility complex (MHC) class I pathway, which, in animal models, has resulted in the generation of robust CD8 T-cell responses and protective anti-tumor immunity. The prototype vector utilizes an engineered Sindbis virus (SINV) glycoprotein as the pseudotyping envelope. This envelope, Sindbis virus glycoprotein mutant (SVGmu), was demonstrated to utilize the DC-SIGN receptor on DCs to enable DC transduction by vector particles and, as a result, induce high magnitude CD8 T-cell immune responses after a single immunization in mice.^{8,9}

Figure 2 LV305 Binding and Entry via DC-SIGN into DCs, Induction of CD8 T-Cell Responses and Subsequent Tumor Cell Killing

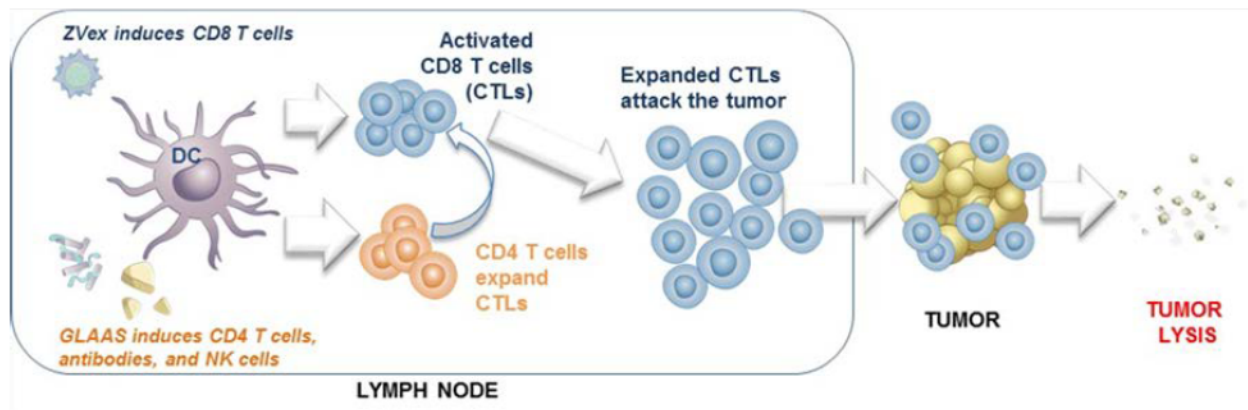


Ag = antigen; DC = dendritic cell; DC-SIGN = dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin receptor (CD209); MHC-1 = major histocompatibility complex-1.

G305 is composed of a full-length NY-ESO-1 recombinant protein and an adjuvant, glucopyranosyl lipid A-stable emulsion (GLA-SE).⁶ Glucopyranosyl lipid A (GLA) is a synthetic Toll-like receptor 4 (TLR4) agonist. TLR4 is a cell surface receptor found on the surface of many immune cells such as DCs, which activates the innate immune response when exposed to endotoxin lipid A. GLA improves the immunogenicity of a wide variety of Ags by increasing the magnitude of the Th1 immune response marked by a high Ag-specific immunoglobulin (Ig) ratio of IgG2:IgG1 and increased production of inflammatory cytokines (e.g., interferon [IFN] γ , tumor necrosis factor [TNF] α , and interleukin [IL]-12). Hence, GLA can activate Ag-specific CD4 T cells that are known to support and promote CD8 T-cell responses specific to the same Ag by prolonging the survival and enhancing the function of the CD8 T cells. As a TLR4 agonist, GLA-SE is aimed at activating Ag-presenting cells (APCs) like DCs to boost the immune response to the co-administered Ag, i.e., NY-ESO-1.⁶

CMB305 is an active immunotherapy approach that combines the 2 different study agents, LV305 and G305. It is designed to induce antitumor responses to the TAA NY-ESO-1. As illustrated in Figure 3, each agent can preferentially stimulate different portions of the immune system and, when given sequentially, complement each other, leading to additive, if not synergistic, effects. Further details can be found in the CMB305 IB.⁶

Figure 3 Interaction of Products and Cells in a ZVex™ Prime, GLAAS Boost that Generates a Synergistic Immune Response to Lyse Tumor Cells



CTLs = cytotoxic T-lymphocyte; DC = dendritic cells; GLAAS = Glucopyranosyl lipid A Adjuvant System.
Source: Figure 1 of the CMB305 IB⁶

Preclinical models, using either of the CMB305 components (LV305 or G305) alone have shown enhanced immune responses in CD4 and CD8 T-cell responses to a specific Ag. The sequential administration of the CMB305 components also further enhanced the response and demonstrated that the development or priming of CD8 T cells using an LV followed by the boosting of the immune response using a protein-adjuvant approach can lead to potent stimulation of anti-tumor immunity.⁶ This so-called heterologous prime-boost approach capitalizes on the ability of each agent to stimulate different components of the immune system (e.g., CD4 helper T cells, CD8 cytolytic T cells, natural killer [NK] cells, antibodies, and APCs) that are required to activate and generate potent and long-lasting immunity. Mice treated with this approach have demonstrated that LV305 primarily elicits CD8 T-cell responses and peak CD4 T-cell responses are observed following boost therapy with G305 administration. Using a B16F10 melanoma mouse model, the combination of an LV with sequential GLA-protein dosing resulted in greater CD4 and CD8 T-cell responses and reduced tumor growth than were seen with the use of either agent alone.⁶

Interim results from Phase 1 clinical studies with each component of CMB305 have also demonstrated favorable responses. The LV305 trial has demonstrated an increased T-cell response and decreased disease progression in patients treated with the vector. Approximately 67% of patients have achieved a response of stable disease (SD) with an average of ~288 days and progression-free rate (PFR) of 42%.¹⁰ Results from the G305 study have shown a significant humoral and CD4 T-cell responses against NY-ESO-1 and 67% of patients achieved SD with a mean duration of 245 days.¹¹ The first in-human trial with the CMB305 combination product is currently ongoing (Protocol IMDZ-C131). While no interim efficacy results are available, the

product is being well tolerated with no dose-limiting toxicities (DLTs) seen in the dose-escalation phase of the trial.

The programmed death (PD)-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control.¹² The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 binds two ligands, programmed-death receptor ligand-1 (PD-L1) and PD-L2. Although healthy organs express little (if any) programmed-death receptor-1 ligand (PD-L1), a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor^{13,14} which plays a critical role in immune evasion by tumors¹⁵. PD-L1 also binds to receptor B7.1 found on activate T cells, B cells and monocytes and downregulates immune responses in peripheral tissues.^{16,17} As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer.¹³

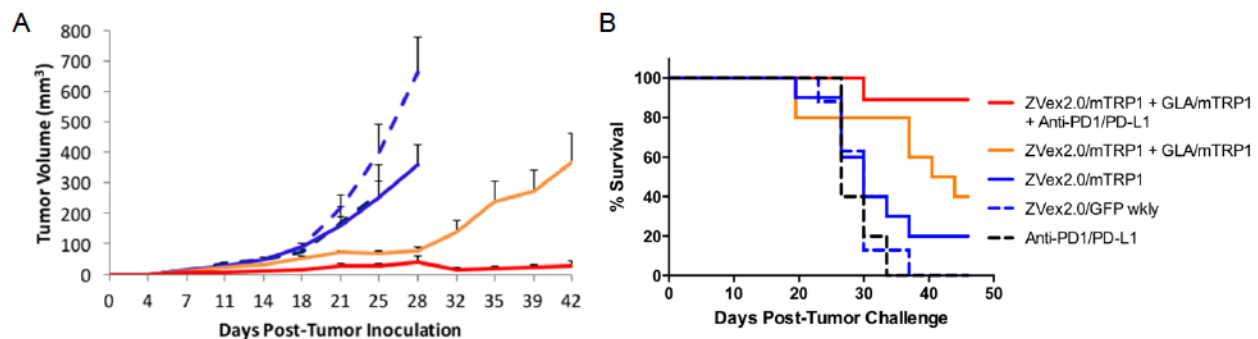
Consequently, the anti-tumor function of the newly expanded CD8 T cell population created by CMB305 is at risk of inhibition by immune checkpoints like PD-1/PD-L1 found on tumor cells. When activated, the PD-1/PD-L1 axis negatively affects the ability of T cells to proliferate, generate cytokines, and kill cancer cells.^{20,21} Blocking the interaction of PD-1 with its ligands, using a monoclonal antibody (mAb) against PD-L1 can restore immune function and enhance anti-tumor immune responses. The inhibition of PD-L1 and PD-1 interaction in mouse tumor models has resulted in anti-tumor effects.^{22,23} To remove this tumor-induced immune blockade with treatments such as CMB305 for enhanced anti-tumor activity, checkpoint inhibitors (CPI) such as atezolizumab (formerly MPDL3280A, Roche) could be used.

Atezolizumab is an anti-PD-L1 mAb being investigated as a treatment of solid tumors and hematological malignances. High levels of PD-L1 are expressed on a wide variety of cancer cells, histiocytes, and other cells within the tumor microenvironment. The binding of PD-1 on tumor-infiltrating T cells to its ligand PD-L1 leads to inhibition of anti-tumor immune activity. It has been investigated in a recent Phase 1a dose-escalation study of 140 patients including approximately 29% of patients with melanoma and 22% of patients with non-small cell lung carcinoma (NSCLC).²⁴ The effect of these inhibitors in treating sarcomas is currently unknown.

Clinically, anti-PD-1/PD-L1 blocking antibodies are active as a single agent, but are limited in their ability to induce objective responses (complete response [CR] and partial response [PR]). It is hypothesized that tumor-reactive T cells are present, but are being suppressed by this pathway and blocking this axis would restore anti-tumor immunity. Thus, in cancer patients the PD-1/PD-L1 pathway is hypothesized to block the immune response such that CD8 T cells generated by the immune response to CMB305 would be affected by this pathway. Therefore, CMB305 activity may be enhanced if used with a PD-L1 blocking antibody, especially in the presence of tumor expressing PD-L1.

A preclinical IMDZ study with melanoma (B16F10) tumor-bearing mice actively treated with an LV expressing a mouse homolog of a TAA associated with melanoma cells (tyrosine-related protein-1 [TRP1]) and in combination with anti-PD-1 and anti-PD-L1 therapy resulted in controlled tumor growth (unpublished IMDZ study data, 2015). As shown in Figure 4, results were significantly better with the combination treatment than with the LV product alone or empty-vector control.

Figure 4 Therapeutic Efficacy Against Subcutaneous Tumor Growth of a 7-dose Sequential Combinatorial Regimen of ZVex2.0/mTRP1 and recombinant mTRP1/GLA-SE in C57BL/6 Mice With or Without anti-PD-1/PD-L1 blockade



GFP = Green fluorescent protein (vector control); PD1 = anti-programmed death receptor -1 antibody (clone RMP1-14 was used); PD-L1 = programmed death receptor ligand-1; SC = subcutaneous; TRP1 = a TAA expressed in melanoma cells (expressed via ZVex2.0 lentiviral vector); wkly = weekly.

B16F10 tumors were implanted in the footpads of C57BL/6 mice. At 12 days post-implantation, tumors were palpable and on average approximately 4x4x3 mm in size. Starting at day 12, the therapy consisted of either weekly SC administration of ZVex2.0/mTRP1 (3×10^{10} vg; blue line) at the base of the tail or weekly administration of ZVex2.0/mTRP1 (L) and 3 μ g recombinant mTRP1/GLA-SE (5 μ g; P) using the regimen L-L-P-L-P-L-P. The latter group was further divided into mice receiving IP injections of anti-PD1/PD-L1 (red line) or isotype control (orange) antibodies. A negative control group was mock-treated with the irrelevant vector ZVex2.0/GFP (black hashed) or anti-PD1/PD-L1 (blue hashed). Tumor sizes were assessed every 3 or 4 days (A). Survival was monitored and recorded using a Kaplan-Meier plot for the three treatment groups (B). Source: Unpublished IMDZ study data, 2015

3.1 Summary of Known and Potential Risks to Human Subjects

Study patients exposed to gene transfer technology such as CMB305 are at risk of long latency adverse events (AEs) such as prolonged persistence, integration of genetic material into host genomes, prolonged expression of transgene, and altered expression of host genome, etc. Viral vector persistence could result in continued expression of the transgene or delayed effects of viral infection. LV305 has been highly engineered from the native lentiviral vector⁷ to minimize such safety risks to patients. Only essential viral genome components have been included such as those which: permit only a single round of infection, prohibit replication inside the cell, and the genome has been modified to be self-inactivating, so that no viral transcripts can be made after infection.⁶ Furthermore, the LV305 construct has a split genome and the homology between the separated components has been reduced to minimize the likelihood of recombination and

replication and has been rendered integration deficient. Aside from the modifications to the wild-type vector, the target cells (DCs expressing the DC-SIGN receptor) typically only survive for up to three weeks.⁶ All factors considered, the persistence of LV305 in humans is expected to be short-lived.

Due to the nature of the LV305 vector, there may be a concern that patients receiving LV305 may have a potential risk of contracting a SINV-like infection. SINV is widely and continuously found in insects (the main vectors are *Culex* and *Culiseta* mosquitoes) and vertebrates in Eurasia, Africa, and Oceania; however, clinical infections are rare and most exclusively reported in Northern Europe and no fatalities have been reported. SINV infection in humans is usually silent though it can manifest as a mild flu-like illness marked by fever, rash, arthritis, headache, myalgia, and joint manifestations which can persist for months or years.⁶ Based on the absence of SINV infections in the US, it is considered highly unlikely that any patients enrolled in the study will have pre-existing antibodies to SINV that would neutralize LV305. LV305 also lacks the necessary genes to replicate and produce SINV;⁶ therefore, it is highly unlikely that inoculation of LV305 will result in a SINV-like human infection.

There is substantial experience using viral vectors or recombinant peptides, with or without vaccine adjuvants, to immunize cancer patients with NY-ESO-1. Previously employed vectors have included vaccinia, fowlpox, and canarypox, none of which have been associated with serious adverse events (SAEs) that were considered possibly, probably or definitely related to the study target Ag.¹ NY-ESO-1 Ag or peptide fragments have been administered to more than 750 patients in at least 41 clinical trials as vaccines or hypersensitivity injections and were generally well tolerated.⁶

Despite the risks, preclinical and the current clinical safety profile of each of the CMB305 components, LV305 and G305, indicate that the sequential combination of these agents should be well tolerated with minimal risk (see the CMB305 IB). Preclinical studies in mice, rabbits, and non-human primates, have shown LV305, GLA-SE, NY-ESO-1, and CMB305 are well-tolerated. Safety and toxicology evaluations in a repeat-dose study with BALB/c mice showed only mild inflammation at the injection sites which was resolving in the recovery phase samples.⁶

GLA has been extensively evaluated in human subjects.^{6,25} Over 1000 human subjects have been injected with GLA adjuvant in either of its formulations (SE or the aqueous formulation [AF]) with or without Ag. Dosing has ranged from 0.5 to 10 µg with repeat dosing and >270 human subjects have had 1 year of systematic post-vaccination follow-up with no noteworthy long latency AEs or autoimmune or inflammatory AEs reported.⁶ The most commonly observed AEs, to date have been injection site reactions of mild to moderate severity (using the conservative “2007 FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in

Preventive Vaccine Clinical Trials”²⁶). The only noted laboratory abnormalities were transient increases in acute phase reactants (e.g., C-reactive protein [CRP] and fibrinogen) and peripheral blood neutrophils. Overall, fewer than 4% of AEs reported in association with GLA-containing vaccines have been Grade 3 in severity.⁶ Expected AEs are listed in the IB for CMB305 and include injection site reactions, fever, fatigue, chills, myalgia, and arthralgia.

LV305 and G305 have been administered in a limited number of subjects; however, the vaccine formulations containing recombinant NY-ESO-1 protein or synthetic peptides are generally safe and well-tolerated. Most reported AEs have been Grade 1-2 injection site reactions or flu-like symptoms⁶, (see the NY-ESO-1 IB, CMB305 IB, and ref to press release). No significant AEs or SAEs were noted. SAEs that were noted were unrelated to study treatment.

A number of risks and/or toxicities have been identified with the use of atezolizumab including dermatologic reactions (e.g., rash, pruritus, dry skin, etc.), hepatitis (as evidenced by elevations in aspartate amino transferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase), hypothyroidism, influenza-like illness (e.g., fever, fatigue, asthenia, chills, etc.), infusion-related reactions (e.g., fever, chills, dyspnea, flushing), and pneumonitis (frequently in patients with lung cancer). In addition, other potential risks identified with atezolizumab use include the following: colitis, endocrine disorders, hypersensitivity, neurologic disorders, and pericardial effusion. Furthermore, the development of anti-therapeutic antibodies (ATAs) against atezolizumab have been observed in patients in all dose cohorts and was associated with changes in PK for some patients in the lower dose cohorts of atezolizumab (0.3, 1, and 3 mg/kg) but has not had a significant impact on PK for doses from 10 to 20 mg/kg. To date, no clear relationship between the detection of ATAs and AEs or infusion reactions has been observed. Specific details regarding these toxicities are provided in [Appendix F](#).

The recent update to the Atezolizumab Investigator’s Brochure (IB) outlines more stringent approaches for the management of immune-mediated toxicity. Given this, the management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity and other immune mediated adverse events has been updated in this protocol and are referred to the IB. Systemic immune activation (SIA) has been identified as a potential risk of atezolizumab when given in combination with other immunomodulating agents. The management recommendations regarding early identification and management of SIA have been added.

Overall, it is not expected that the administration of atezolizumab will add safety concerns to CMB305, given their different routes of administration and non-overlapping mechanisms of action. Cancer immunotherapies have previously been combined with checkpoint inhibitors. A GVAX vaccine combined with the checkpoint inhibitor ipilimumab was tested in a Phase 1 study.¹⁷ In that study, immune-related adverse events (irAEs) were similar in incidence and

character as had been previously observed with single agent ipilimumab. Ipilimumab was also evaluated in combination with the cancer vaccine PROSTVAC in patients with metastatic castration-resistant prostate cancer. No dose-limiting toxicities were seen and only side effects typical of ipilimumab were observed.¹⁸ The reports from these clinical trials suggest that when used in combination, cancer immunotherapeutic approaches are not likely to enhance the toxicity of CPIs.

3.2 Study Rationale

The development of immunotherapies that harness the immune system to kill specific, targeted tumor cells is a promising approach for the treatment of human malignancies with a number of approved treatment options for various malignancies. The concept of enhancing the immune system to self and non-self Ags has shown that a combined prime-boost approach yields considerably higher responses than either approach alone.²⁰ Preclinical work has demonstrated that combining LV305 and G305 in a sequential manner (i.e., CMB305) results in an additive or synergistic effect in the development of antigen-specific CD8 and CD4 T cells, as well as antibody-producing B cells. The use of such approaches, along with immune CPIs, have been shown to enhance the anti-tumor response preclinically in a melanoma model (Figure 4). Immune therapy in oncology has demonstrated efficacy that does not occur within the first weeks of administration and may have a delayed response which warrants collection of efficacy assessments at later times during and after active therapy. This study will evaluate the safety, efficacy, and immunogenicity by clinical and biomarker assessments of CMB305 in combination with atezolizumab in patients with locally advanced, relapsed, or metastatic sarcoma.

4.0 OBJECTIVES

4.1 Objectives

4.1.1 Primary Objective

The primary objective is to evaluate overall survival (OS) and progression-free survival (PFS) with CMB305 (sequentially administered LV305 and G305) in combination with atezolizumab or with atezolizumab alone, in patients with locally advanced, relapsed, or metastatic sarcoma expressing NY-ESO-1.

4.1.2 Secondary Objectives

The secondary objectives are the following:

- To evaluate the safety of CMB305 in combination with atezolizumab and atezolizumab alone in patients with locally advanced, relapsed, or metastatic sarcoma expressing NY-ESO-1.
- To evaluate progression-free survival rates at 6 months after start of study treatment (Day 0)
- To evaluate the immune response and histologic and molecular tissue changes in the tumor tissue and peripheral blood
- To evaluate the time to next treatment (TTNT)
- To evaluate the distant metastasis free survival (DMFS)

4.1.3 Exploratory Objectives

The exploratory objectives are the following:

- To compare efficacy assessments, such as tumor growth rate (TGR), and progression arrest rate (PAR)
- To compare PFS and OS²⁸ between treatment arms
- To evaluate the immunogenicity of CMB305 in combination with atezolizumab compared to atezolizumab alone
- To evaluate available pre-, on-, and post-treatment tumor tissue and blood for histologic, immunohistologic, and genomic markers
- To evaluate the best overall response rate (ORR; by Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 modified to use immune-related Response Criteria [irRC]²⁷) and duration of response (DOR)
- To evaluate the clinical benefit rate (CBR)

- To evaluate the quality of life as a composite endpoint including but not limited to the following: while on study, the incidence of hospitalization, transfusions, and laboratory markers (eg. absolute neutrophil count, hemoglobin and platelets)

4.2 Endpoints

4.2.1 Primary Endpoints

The primary endpoints are the following:

- OS
- PFS

4.2.2 Secondary Endpoints

The secondary endpoints include the following:

- Safety
- PFR at 6 months
- TTNT
- Immune response and histologic and molecular tissue changes in tumor tissue or peripheral blood
- DMFS

4.2.3 Exploratory Endpoint

The exploratory endpoints are the following:

- TGR
- PAR
- To compare OS and PFS between treatment arms
- ORR as assessed by RECIST (v1.1) modified to use irRC
- DOR
- CBR
- Immune responses as measured by changes from baseline in anti-NY-ESO-1 immunity
- Biomarkers
- Quality of life

4.2.4 Safety Endpoints

The safety endpoints include the nature, frequency, and severity of AEs, medical events of interest (MEOI; see [Appendix B](#)), laboratory abnormalities, and other safety assessments

(including vital signs, LV305 persistence, physical examination findings, electrocardiograms [ECGs], etc.).

5.0 INVESTIGATIONAL PLAN

5.1 Overall Trial Design and Plan

This is a randomized, open-label, Phase 2 trial of CMB305, a treatment regimen of LV305 and G305, in combination with atezolizumab or with atezolizumab alone in patients with sarcoma who have had an inadequate response, relapse, and/or unacceptable toxicity with one or more prior systemic, surgical, or radiation cancer therapies. Approximately 80 patients at up to 20 sites in the United States (US) and Canada will be enrolled.

All patients will have tumor samples screened for expression of NY-ESO-1 to determine eligibility. Archival tumor specimens will be obtained from patients to determine PD-L1 molecular status. Patients will be randomized in a 1:1 allocation ratio to receive CMB305 in combination with atezolizumab or atezolizumab alone. Randomization will be 1:1 and stratified by disease type. For the combined treatment arm, the trial will be conducted in 4 phases: Treatment Phase (study Days 0 to 84), Booster Phase (post Day 84 to 1 year post Day 0), Maintenance Phase (from 1 year to 2 years post Day 0), and Survival Follow-up Phase (quarterly thereafter). For the control arm, the trial will be conducted in 3 phases: Treatment Phase (study Days 0 to 84), Maintenance Phase (post Day 84 to 2 years post Day 0), and Survival Follow-up Phase (quarterly thereafter).

CMB305 treatment will consist of 2 doses of LV305 administered on Days 0 and 14, followed every 2 weeks with alternating doses of G305 and LV305. In total, 4 doses of LV305 and 3 doses of G305 will be administered over a period of 3 months. Patients will receive CMB305 according to doses and treatment schedules determined in previous studies. LV305 will be administered intradermally (ID) at a dose of 1×10^{10} vector genomes (vg) and G305 will be administered intramuscularly (IM) at a dose of GLA-SE (5 µg) mixed with 250 µg of NY-ESO-1 protein. Atezolizumab will be given intravenously (IV) every 3 weeks and may be continued up to 2 years until toxicity develops or confirmed progression. A G305 booster dose will be given every 6 weeks in the first year until disease progression (to coincide with the staging follow-up visits). The control arm (atezolizumab treatment alone) will return to the clinic for dosing every 3 weeks until progression or toxicity develops.

Peripheral blood will be collected for immunogenicity assays at baseline, then on Days 42, 70, and 98 (\pm 2 weeks). Tissue biopsies will be taken in each treatment group from consenting subjects before treatment and on Day 42, on Day 98 (\pm 2 weeks), at 6 months or longer (for patients with treatment response), and at the time of progression to assess immune cell invasion, including changes in PD-L1, CD4, CD8/Ki-67 and/or CD3/perforin expression. If a patient undergoes a tumor biopsy at any time after disease progression, investigators are strongly encouraged to provide biopsy tissue to the sponsor for immune response and tumor changes analysis.

Imaging will be performed approximately every 6 weeks for 12 months, then every 12 weeks for tumor staging until progression. Tumor responses will be assessed at the sites by evaluating tumor images/scans using RECIST modified to use irRC-specified confirmation and unidimensional tumor measurements. Adjudication will be performed by blinded independent central review (BICR) following the same rules. The irRC modification requires a confirmation of CR/PR/progressive disease (PD) at least 4 weeks later with imaging; once confirmed, the date of progression is defined as the first date that the total tumor burden was shown to have increased by at least 20% compared with the nadir.

Patients will be followed until confirmed radiographic disease progression to determine ORR and PFS. In addition, OS status will be followed up until the end of the trial. If the patient dies, the date of death will be documented by the local physician and/or registries.

All SAEs, DLTs, and MEOIs deemed potentially related to the study agents will be reviewed by the Sponsor and an independent Data Monitoring Committee (DMC).

Following completion of CMB305 dosing, patients will continue with clinical assessment and imaging approximately every 6 weeks until disease progression, as defined by RECIST (v1.1) modified to use irRC. The expected duration of a patient's participation in the trial is up to 2.1 years, including Screening, Treatment Phase, Booster Phase (for patients in the combined treatment arm), and Maintenance Phase (with follow-up visits until disease progression). Patients will then enter the Survival Follow-up Phase and their physicians will be contacted every 3 months by telephone to assess OS.

For patients receiving CMB305, peripheral blood will be collected for an assay to test for LV305 persistence at baseline, at 24 weeks, and at 12 and 24 months following the first LV305 injection. Depending on the results through 12 months, annual assessments may continue until 2 consecutive samples show no evidence of LV305 persistence.

Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments at the same frequency as would have been followed if the patient had remained on study drug until the patient dies, experiences disease progression, withdraws consent, starts a new anti-cancer therapy, or until the study closes, whichever occurs first.

For patients who are on study and did not have tumor progression, a biopsy is required at Day 98 (approximately 3 months after start of treatment). The patient may opt out of the Day 98 biopsy after a discussion with a physician and documentation in the patient's chart. If a tumor biopsy is not feasible, a biopsy should be done at a subsequent visit with approval provided by the Sponsor.

For patients who have progressive disease or a tumor response for 6 months or longer, a biopsy will be obtained to document changes in intratumoral histology and intratumoral immune changes at the time of progression.

For patients who have had progressive disease while on study and are in a long-term follow-up, if a biopsy is obtained for any reason (i.e. for a nonstudy reason), a sample to assess long term tumor and immune system changes should be provided to the Sponsor.

On-study radiotherapy and surgeries should continue to be recorded until documented radiographic progression, even if progression occurs after study treatment discontinuation. Non-protocol systemic anti-cancer therapies administered before documented radiographic progression should be recorded as concomitant medications.

5.2 Dosing Regimen and Rationale

LV305 will be administered as 2 consecutive doses followed by alternate dosing of G305 and LV305 every 2 weeks. Atezolizumab will be given IV in combination with CMB305 every 3 weeks starting on Day 0 (Figure 1). The control arm (i.e., atezolizumab only) will be dosed with the atezolizumab every 3 weeks starting at Day 0. Note that dosing of atezolizumab will continue every 3 weeks up to 2 years until toxicity develops for patients in both study arms. Further details regarding treatment administration are provided in Section 7.2.

The dosing regimen was chosen based on preclinical data, Phase 1 clinical data, published literature, and discussions with Investigators. The dosing of CMB305 follows the same regimen that is being used in a Phase 1b study conducted by IMDZ (Protocol IMDZ-C131) and is designed to maximize the prime-boost development of NY-ESO-1-specific CD8 T cells. Timing of the first 2 doses was adjusted (from 3 to 2 weeks apart) to simplify the schedule, which is not expected to affect the immunogenicity. Given the findings from preclinical studies and the predicted mechanisms of action when given as a prime-boost, LV305 and G305 are expected to have synergistic effects and induce a strong anti-tumor T cell (CTL) response in cancer patients.⁶ In preclinical studies, this heterologous prime-boost approach can result in the induction of approximately 5x more CD8 T cells than immunization with the LV alone and can also facilitate the induction of Ag-specific CD4 T cells and antibody-generating B cells. In addition to increasing the magnitude of the CTL response, a memory CTL response is also enhanced, which supports long-term immune surveillance.⁶

5.3 Rationale for Dose Selection

The doses of the CMB305 components chosen for this study are the following: 1×10^{10} vg of LV305, 250 μ g NY-ESO-1, and 5 μ g GLA-SE. These doses were chosen based on separate Phase 1 studies of each agent (Protocols ID-LV305-2013-001 and IDC-G305-2013-001) and

available safety and immunogenicity data which demonstrated that the CMB305 components were safe and effective in boosting the immune response against NY-ESO-1 and achieving SD and/or PFS.^{10,11} Furthermore, the first in-human trial of CMB305 is currently being conducted (Protocol IMDZ-C131) using the same doses chosen for this study. The use of LV305 and CMB305 is also being investigated in combination with anti-PD-1 agents in these Phase 1 studies. At the time of this protocol, no DLTs or treatment-related SAEs have been reported in over 4 dozen patients treated in these clinical studies.

Atezolizumab will be dosed according to available PK data from previous clinical studies. Preliminary PK data of 0.03-20 mg/kg atezolizumab appeared to show linear PK at doses ≥ 1 mg/kg. For the 1 mg/kg and 20 mg/kg dose groups, the mean apparent clearance (C_L) and mean volume of distribution at steady state (V_{ss}) had a range of 3.11 to 4.14 mL/kg and 48.1 to 67.0 mL/kg, respectively, which was consistent with the expected profile of an IgG1 antibody in humans. The fixed dose of 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) was selected on the bases of both non-clinical studies and available clinical activity, safety, PK, and immunogenicity data developed by Roche. Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg administered every 3 weeks. The maximum tolerated dose (MTD) of atezolizumab was not reached and no DLTs have been observed at any dose in the PK study.

5.4 Safety Monitoring

5.4.1 Safety Run-in

The first 6 patients will be randomized 1:1 to receive the CMB305 in combination with atezolizumab or atezolizumab alone (using a block size of 6) to investigate the safety of the sequential combination. The 3 patients in the combination arm will be observed for treatment emergent DLTs in the first 42 days of therapy. During the safety observation period, all SAE and DLT safety events deemed potentially related to the study agents will be reviewed by the Sponsor and the independent DMC. If no DLTs are observed, enrollment of patients into the remainder of the study will commence.

If 1 of the 3 patients in the combination treatment arm experiences a DLT during the safety “run-in” evaluation, an additional 6 patients will be randomized (1:1). If 2 or more of the 6 patients in the combination treatment arm experience DLTs, dosing in the CMB305 plus atezolizumab combination treatment arm will stop, and the safety of the combination will be reviewed by the Sponsor and the independent DMC. Based on this review, the DMC may recommend, and the Sponsor may choose, to reduce the dose of one or more components of CMB305 (dose de-escalation) and treat an additional 3 to 6 patients with the combination treatment regimen following the same 3+3 design, or they may recommend stopping the combined treatment. Should a lower dose prove to be safe, patient’s enrollment in the randomized treatment arms will

commence using the lower dose of that component. Following evaluation by the DMC and the sponsor, a modification to the dose/treatment schedule could be recommended.

5.4.2 Dose-Limiting Toxicities

AE severity assessments will be performed using NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Unacceptable toxicity is defined when one third or more of the subjects treated with the combined regimen develop an AE considered Grade 3 or higher and considered at least possibly related to CMB305 or atezolizumab with the exceptions below. Hospitalizations primarily intended to expedite diagnostic evaluations or for elective surgery will not be considered as serious adverse events (SAEs) for the purpose of ascertaining DLT.

Any treatment emergent grade 3 or higher AE that occurs in the DLT assessment window, which is the first 42 days after initiation of study drug, that is deemed possibly, probably or definitely related to the combination of CMB305 and atezolizumab will be considered DLTs with the following exceptions:

- Alopecia or vomiting (unless not controlled by optimal anti-emetics)
- Hepatic enzyme elevations associated with the baseline Grade 2 abnormalities that are noted as exceptions above
- Grade 3 laboratory AEs that are asymptomatic and return to baseline or to Grade 1 within 3 days, unless identified specifically as DLT by the investigator or the Data Monitoring Committee (DMC)
- Grade 3 fatigue
- Grade 3 systemic reactions (such as fever, headache, influenza like symptoms, myalgia, malaise, or nausea) that return to baseline or Grade 1 within 3 days of study inoculation

Atezolizumab has a recognized safety profile. AEs in the combined treatment arm that are attributed to atezolizumab will be evaluated by the DMC and sponsor, but will not be immediately considered as DLTs except as noted ([Section 5.4.3](#)). All DLTs should be reported to the Sponsor in an expedited manner (within 24 hours) and will be reviewed by the DMC. Although these events will not contribute automatically to the DLT stopping criteria, these reviews may lead to modification or stopping of the treatment program if related, treatment-emergent AEs indicate a safety profile that is inconsistent or significantly worse than reported with the use of atezolizumab alone.

During the safety run-in, the following patients will not be considered evaluable for DLTs and will be replaced:

- Patients who withdraw or are withdrawn for either study treatment prior to completing the DLT assessment window for any reason other than a DLT
- Patients who do not receive the full assigned dose of either study treatment during the DLT assessment window for reaction other than a DLT.

Replaced patients will remain on study treatment if they otherwise meet criteria to continue dosing and continue assessments.

5.4.3 Toxicities Associated with Atezolizumab

Atezolizumab will be withheld until resolution (i.e., return to Grade 0-1) for the following event(s):

- Grade ≥ 2 pneumonitis
- Grade ≥ 3 symptomatic hepatic toxicities that do not resolve to Grade 2 within 48 hours or Grade ≥ 3 asymptomatic hepatic toxicities that do not resolve to Grade ≤ 1 within 3 weeks of onset with the following exceptions:
 - For patients with Grade 2 AST, ALT, alkaline phosphatase abnormality at baseline, an increase to $>8\times$ the upper limit of normal (ULN) that does not resolve to Grade 2 within 48 hours (if symptomatic) or Grade ≥ 3 asymptomatic hepatic toxicities that do not resolve to Grade ≤ 1 within 3 weeks of onset (if asymptomatic) will be considered a DLT.
- Grade ≥ 2 diarrhea or colitis
- Symptomatic hypothyroidism, hyperthyroidism, pan hypopituitarism, or any Grade ≥ 3 endocrine events
- Grade ≥ 3 ocular events
- Grade ≥ 3 dermatologic events
- Grade ≥ 2 neuropathy
- Grade ≥ 4 neutropenia (absolute neutrophil count [ANC] $<500/\mu\text{L}$) lasting ≥ 7 days, thrombocytopenia, anemia, or Grade ≥ 3 febrile neutropenia
- Grade ≥ 3 non-hematologic, non-hepatic organ toxicity, excluding the following:
 - Grade 3 immune related AE (irAE) that resolves to Grade ≤ 1 within 3 weeks of its onset (may include events that resolve after medical treatment, including immunosuppressant therapy)
 - Grade 3 nausea or vomiting that resolves to Grade ≤ 1 within 72 hours of appropriate supportive therapy
 - Grade ≥ 3 fatigue that resolves to Grade ≤ 2 within 7 days
 - Grade 3 arthralgia that can be adequately managed with supportive care or that resolves to Grade ≤ 2 within 7 days

- Grade 3 fever (in the absence of any clinically significant source of fever) that resolves to Grade ≤ 2 within 7 days with supportive care
- Grade ≥ 3 laboratory abnormality that is asymptomatic and deemed by the Investigator not to be clinically significant
- Grade 3 tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Grade 3 infusion reaction that resolves within 6 hours to Grade ≤ 1

These reactions, along with any DLTs, will be reviewed by the DMC on a case-by-case basis and may be considered DLTs if they meet the criteria outlined above. Atezolizumab treatment can be resumed in patients whose adverse reactions recover to Grade 0-1.

5.5 Study Stopping Rule

The preliminary safety of the individual components of CMB305 (LV305 and G305) have been studied in separate Phase 1 studies; however, the safety of the CMB305/atezolizumab combination will be investigated during the 6-12 patient Safety Run-in. The safety profile of CMB305 is discussed in the IB.⁶ Dosing will be suspended in this study if DLT is observed in one third or more patients on the combined regimen (assuming a minimum of 12 combined regimen patients were enrolled at that point and would represent the initial denominator), pending review and recommendation from the DMC.

The Sponsor may also choose to terminate this study at any time. Investigators will be notified if the study is placed on hold, completed, or closed.

5.6 Dosing Delays/Dose Modifications

There are no adjustments for dose delays for a given patient. Treatment delays of >14 days from the treatment plan for CMB305 components prior to Visit 12 are not permitted. If a patient experiences a DLT during the study, their treatment will be suspended. Further treatment of this patient with LV305, G305, or atezolizumab will be made on a case-by-case basis following evaluation of the risks/benefits by the Investigator and Medical Monitor in consultation with the DMC.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should resume study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for the interruption should be documented in the patient's study record. Further details regarding dosing delays and modifications are provided in [Section 7.2.2](#).

5.7 Overall Study Duration and Follow-Up

The expected duration of patient participation on study treatment is 2.1 years. The study period will consist of Screening (study Day -30 to -1), Treatment Phase (study Days 0 to 84), Booster Phase (in the combined treatment arm) with continuation of G305 boosters (post Day 84 to 1 year [post Day 0] or until disease progression), Maintenance Phase with continuation of atezolizumab treatment (for the combined treatment arm, 1 year to 2 years [post Day 0] and, for the control arm, post Day 84 to 2 years [post Day 0], or until disease progression), and Survival Follow-up Phase (quarterly thereafter). The overall study duration will depend on speed of enrollment and time to the number of events.

Following completion of CMB305 dosing, patients will continue with imaging and clinical assessment every 6-9 weeks until disease progression, as defined by the RECIST v1.1 criteria modified to use irRC ([Section 6.3](#)). Patients or their physicians will then be contacted by the sites every 3 months by telephone to assess OS.

For patients receiving CMB305, blood will be collected to test for LV305 persistence at baseline and then at 6, 12, and 24 months following the first study treatment administration. Depending on the results from the 12-month sample, annual assessments may continue until 2 consecutive yearly samples show no evidence of LV305 persistence.

Patients with confirmed radiographic disease progression by irRC will be followed thereafter by the site every 3 months by contacting their primary physician by telephone as long as they are able to engage in follow-up until date of death recorded. Follow-up telephone contact will ascertain vital status, as well as possible occurrence of second malignancies and any SAE that might be possibly related to CMB305 treatment.

5.8 Independent Data Monitoring Committee (DMC)

A DMC will be established to provide independent review of safety data and to assure that the risk to patients is minimized. The DMC will operate in accordance with a signed charter and will be composed of 2 oncologists familiar with clinical use of the study drugs and an ad hoc independent, knowledgeable biostatistician.

Safety data will be collected and monitored on an ongoing basis throughout the study. IMDZ will summarize all available safety and laboratory data on all patients at regular intervals (at least every 3 months) during the study, as specified in the DMC charter. IMDZ and the DMC will conduct separate reviews of these data for any safety trends that might impact the treatment of patients. Safety issues that arise out of such ongoing reviews could lead to modifications of the treatment program.

The unblinded DMC will review all cumulative safety information from the Safety Run-In prior to recommendations for further patient enrollment (Section 5.4.1). All related and unexpected (i.e., expedited) SAEs and DLTs will be reviewed as individual cases arise; related and unexpected SAE reports will be expedited to regulatory authorities, investigators, and DMC members. DLTs and SAEs considered at least possibly related to study regimen will be reviewed by the DMC and the Sponsor as they are reported and on an ongoing basis. These reviews may lead to modification or stopping of the treatment program if related, treatment-emergent adverse events indicate a safety profile that is inconsistent or significantly worse than reported with the use of either CMB305 or atezolizumab alone. The DMC will also perform periodic reviews of all AEs, laboratory results, and patient discontinuations.

The DMC may convene on an ad-hoc basis to evaluate any urgent safety issues. Upon request, the DMC will be granted access to any available data pertinent to the issues under evaluation. IMDZ will provide cumulative data, as specified in the DMC charter, to the DMC for review.

5.9 Archival Tissue

A representative formalin-fixed paraffin embedded (FFPE) archival tumor specimen collected at first diagnosis and/or subsequent tumor recurrence(s) consistent with the patient's diagnosis is required for NY-ESO-1 diagnosis and participation in this study. A minimum of 8 unstained serial sections are needed. Documentation of NY-ESO-1 expression in prior tumor samples may have been collected from any procedure performed before baseline activities. There is no time limit for use of the results from the IMDZ-approved central lab.

In addition, a pre-treatment tumor sample (FFPE block [preferred] or a minimum of 17 unstained serial sections, including 5 slides at 4 μm and 12 slides at 7 μm) should be derived from a fresh biopsy or a prior resection/biopsy performed ≤ 6 months prior to screening for immune analysis. This specimen must be accompanied by the associated pathology report. Fine-needle aspiration, brushing, cell pellet from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases is not evaluable for tumor PD-L1 expression and is therefore not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation.

For samples not meeting minimum requirements for size/slide number, contact the Medical Monitor via your site contact with information on tissue size and tumor content/number of slides to determine eligibility.

Alternatively, or if the archival tumor sample does not meet minimum requirements, the patient may be offered the option of undergoing a pretreatment procedure (excisional or core tumor biopsy) to obtain an adequate tumor sample. Acceptable samples include core needle biopsies for deep tumor tissue (minimum 3 cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous (SC), or mucosal lesions. A similar biopsy will be taken for specimens on Day 42, on Day 98 (± 2 weeks), at 6 months or longer (for patients with treatment response), and at the time of progression.

6.0 SELECTION AND WITHDRAWAL OF PATIENTS

This study plans to enroll patients with locally advanced, relapsed, or metastatic sarcoma whose tumor expresses the NY-ESO-1.

Patient eligibility criteria in the proposed trial have been designed to ensure that the enrolled patients are adequately healthy to tolerate investigational therapy, ill enough to be appropriate for investigational therapy, and have sufficiently low tumor burden or indolent disease to be appropriate for a vaccine therapy. Potential risks include injection site reactions and systemic AEs, which could include immunologically-related AEs. Safety monitoring will be intensive and comprehensive with careful monitoring for acute adverse reactions and includes regular reviews by an independent DMC.

6.1 Inclusion Criteria

Patients must meet ALL of the following criteria to be enrolled in the study:

1. Locally advanced, relapsed, or metastatic sarcoma with measurable tumor burden following therapy, as defined by RECIST v1.1; the total of all lesions must be ≤ 12 cm (for synovial sarcoma) or ≤ 15 cm (for myxoid/round cell liposarcoma [MRCL])
2. Tumor histology consistent with synovial sarcoma or MRCL
3. Tumor specimen positive for NY-ESO-1 expression by IHC
4. Inadequate response, relapse, and/or unacceptable toxicity with one or more prior systemic, surgical, or radiation cancer therapies
5. Have resolution of toxic effect(s) of the most recent prior therapy to Grade 1 or less (except Grade 2 or less neuropathy or alopecia). If subject received major surgery or radiation therapy, they must have recovered from the toxicity and/or complications from the intervention.
6. ≥ 18 years of age before the first scheduled dose
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
8. Electrocardiogram (ECG) without evidence of clinically significant abnormality
9. If female of childbearing potential (FCBP), willing to undergo pregnancy testing and agrees to use at least 2 adequate barrier contraceptive methods during the dosing period and for 90 days after the last injection of CMB305 or atezolizumab
10. If male and sexually active with a FCBP, must agree to use highly effective contraception such as latex condom during the dosing period and for three months after last CMB305 injection
Note: Abstinence is acceptable for either gender if this is the established and preferred contraception for the subject.

6.2 Exclusion Criteria

Patients meeting any of the following criteria will not be eligible for participation in the study:

1. Investigational therapy within 4 weeks prior to CMB305 dosing
2. Prior administration of other NY-ESO-1-targeting immunotherapeutics
3. Prior treatment with immune checkpoint therapies, including anti-CTLA-4, anti PD-1, and anti PD-L1 therapeutic antibodies, or any other antibody or drug targeting T cell costimulation
4. Treatment with systemic immunostimulatory agents (including but not limited to IL-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to first dose
5. Significant immunosuppression from:
 - a. Concurrent, recent (≤ 3 weeks prior to the first schedule dosing) or anticipated need for treatment with systemic corticosteroids (the use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor). The use of topical or inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.
 - b. Other immunosuppressive medications (≤ 3 weeks prior to the first scheduled dosing) including but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor (anti-TNF) agents or conditions such as common variable hypogammaglobulinemia.
6. Other cancer therapies, including chemotherapy, radiation, biologics or kinase inhibitors within 3 weeks prior to the first scheduled dosing
7. Has received colony stimulating factors (CSFs; including granulocyte [G]-CSF, granulocyte-macrophage [GM]-CSF, or recombinant erythropoietin) within 4 weeks prior to the first scheduled dosing
8. Psychiatric, other medical illness, or other condition that in the opinion of the Investigator prevents compliance with study procedures or ability to provide valid informed consent
9. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see [Appendix E](#) for a more comprehensive list of autoimmune diseases)
 - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
 - Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.
10. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), risk of pulmonary toxicity, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

11. Significant cardiovascular disease, such as New York Heart Association cardiac disease (\geq Class II), myocardial infarction within the previous 3 months prior to study treatment, unstable arrhythmias, or unstable angina
12. Inadequate organ function, including the following:
 - a. Marrow: ANC \leq 1500/mm³, platelets $<$ 75,000/mm³, or hemoglobin (Hb) $<$ 10 g/dL
 - b. Hepatic: ALT, and AST $>$ 2.5 \times ULN (OR \geq 5 \times ULN for subjects with liver metastases), total serum bilirubin $>$ 1.5 \times ULN (OR direct bilirubin \geq ULN for patients with total bilirubin levels $<$ 1.5 \times ULN; patients with Gilbert's Disease may be included if their total bilirubin is $<$ 3.0 mg/dL)
 - c. Renal: creatinine $>$ 1.5 \times ULN
 - d. Other: prothrombin time (PT), international normalized ratio (INR), or partial thromboplastin time (PTT) $>$ 1.5 \times ULN
13. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently). Patients with indwelling catheters (e.g., PleurX[®]) are allowed.
14. Uncontrolled tumor-related pain. Patients requiring pain medication must be on a stable regimen at study entry. Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment. Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
15. Uncontrolled hypercalcemia ($>$ 1.5 mmol/L ionized calcium (Ca) or Ca $>$ 12 mg/dL or corrected serum calcium $>$ ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab. Patients who are receiving these agents specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible. Patients who are receiving denosumab prior to enrollment must be willing and eligible to discontinue its use while on study and receive a bisphosphonate instead.
16. History of other cancer within 3 years (except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, localized prostate cancer treated with curative intent, ductal carcinoma in situ treated surgically with curative intent, or other cancers with a similar outcome)
17. Evidence of active tuberculosis or recent ($<$ 1 week prior to first scheduled dosing) clinically significant infection requiring systemic therapy (prophylactic antibiotics [e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease] are permitted)
18. Evidence of active hepatitis B (HepB), hepatitis C (HepC), or Human Immunodeficiency Virus (HIV) infection. Active HepB is defined as having a positive HepB surface antigen (HBsAg) test at screening. Patients with past/resolved HepB viral infection (defined as having a negative HBsAg test and a positive antibody to HepB core antigen [anti-HBc] antibody test) are eligible. HepB viral DNA must be negative in these patients prior to the

first scheduled dosing. Patients positive for HepC antibody are only eligible if polymerase chain reaction (PCR) is negative for HepC viral RNA.

19. Administration of a live, attenuated vaccine within 4 weeks prior to the first scheduled dosing or anticipation that such a live attenuated vaccine will be required during the study. Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist[®]) within 4 weeks prior to the first scheduled dosing or at any time during the study.
20. Known active or untreated central nervous system (CNS) metastases. Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:
 - a. No metastases to cerebellum, brain stem, midbrain, pons, medulla, or within 10 mm of the optic apparatus (optic nerves and chiasm)
 - b. No evidence of interim progression ≥ 4 weeks between the completion of CNS-directed therapy and the screening radiographic study and ≥ 2 weeks since discontinuation of corticosteroids
 - c. No ongoing requirement for dexamethasone as therapy for CNS disease; anticonvulsants at a stable dose allowed
21. Pregnant, planning to become pregnant within 6 months of treatment, or nursing
22. Known allergy(ies) to any component of CMB305, atezolizumab, or severe allergic reactions to monoclonal antibodies, fusion proteins, or CHO cell products

6.3 Study Discontinuation and Patient Withdrawal Criteria

While patients will be encouraged to continue on study for safety follow-up, patients **MUST** be discontinued from receiving further study agent for the following reasons:

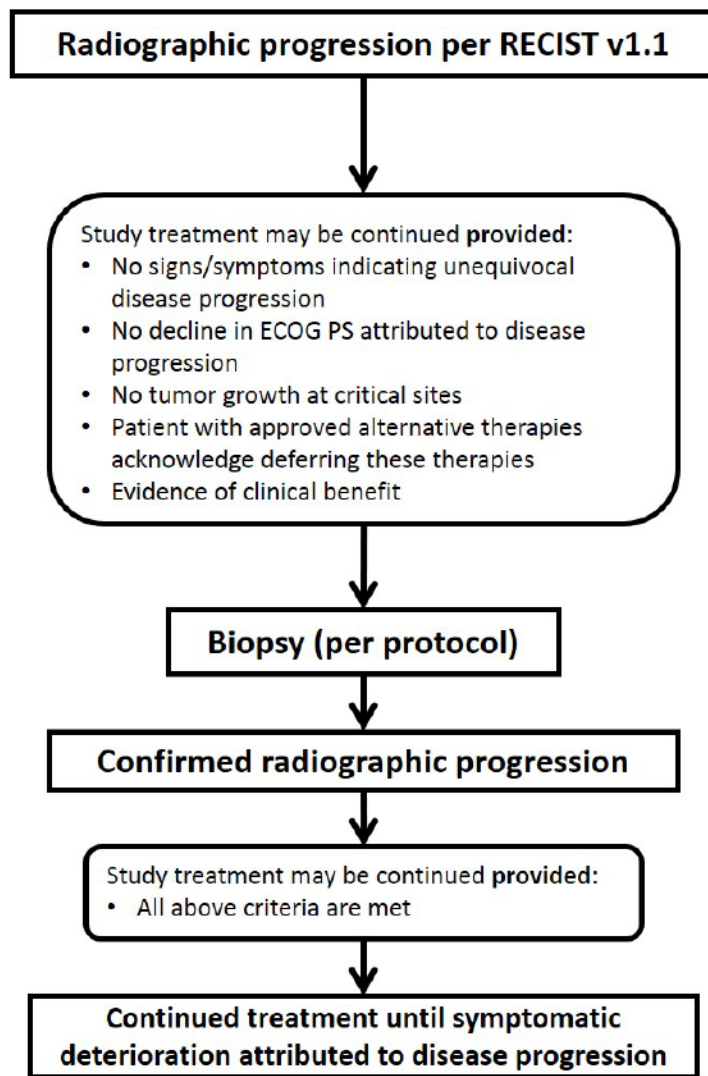
- Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status (see Figure 5)
- Intolerable toxicity related to study treatment, including development of an irAE determined by the investigator and Medical Monitor to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment
- Use of another non-protocol anti-cancer therapy
- Withdrawal of informed consent (patient's decision to withdraw for any reason).
- Pregnancy (**NOTE:** All FCBPs should be instructed to contact the Investigator immediately if they suspect they might be pregnant at any time during study participation.)

- Termination of the study by Sponsor for safety or other reasons.
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical illness (e.g., infectious disease).
- Any clinical AE, laboratory abnormality or intercurrent illness that, in the opinion of the Investigator, indicates that continued dosing on the study is not in the best interest of the patient.
- Patients who cannot tolerate CMB305, atezolizumab, or outpatient study procedures.
- PD by irRC criteria.²⁷

As long as they are receiving atezolizumab and/or combination treatment, patients will be permitted to continue study treatment if the RECIST v1.1 criteria for PD are met provided they meet all of the following criteria (Figure 5):

- Evidence of clinical benefit as assessed by the Investigator
- Absence of symptoms and signs (including worsening of laboratory values; e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor growth at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial apparent progression.

Figure 5 Conditions for Continuing Atezolizumab Alone or in Combination in the Presence of Increased Radiographic Tumor Size



ECOG PS=Eastern Cooperative Oncology Group performance status; ICF=Informed Consent Form; RECIST=Response Evaluation Criteria in Solid Tumors v1.1.

Unless consent is withdrawn and the patient is unwilling to continue with safety follow-up, the patient is lost to follow-up, or the study is terminated, all efforts should be made to continue safety monitoring of all patients who received CMB305 and/or atezolizumab. A safety evaluation should always be done at the last site visit if feasible.

Patients who withdraw from the study prior to the EOS should be followed for new AEs for at least 30 days after their last dose of CMB305 and/or atezolizumab. If the patient withdraws

prematurely and is unwilling to continue safety follow-up, any subsequent SAE that may be causally related to CMB305 or atezolizumab that comes to the attention of the site staff should be reported to IMDZ.

Patients in whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the Investigator provided they meet the criteria above.

Patients who have permanently discontinued atezolizumab must discontinue study treatment if they meet criteria for disease progression per RECIST/irRC. The primary reason for study treatment discontinuation should be documented on the appropriate electronic Case Report Form (eCRF). Patients who prematurely discontinue study treatment will not be replaced.

Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments at the same frequency as would have been followed if the patient had remained on study drug until the patient dies, experiences disease progression, withdraws consent, starts a new anti-cancer therapy, or until the study closes, whichever occurs first.

On-study radiotherapy and surgeries should continue to be recorded until documented radiographic progression, even if progression occurs after study treatment discontinuation. Non-protocol systemic anti-cancer therapies administered before documented radiographic progression should be recorded as concomitant medications.

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

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

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

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

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

- Excessively slow recruitment
- Poor protocol adherence

- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP) No study activity (i.e., all patients have completed and all obligations have been fulfilled)

7.0 STUDY TREATMENTS

7.1 Investigational Drugs

The investigational drug is CMB305, a prime-boost combinatorial regimen comprised of 2 different active immunotherapy agents, LV305 and G305 administered sequentially to prime and boost the immune system in order to induce a strong CD8 T cell response against tumor cells resulting in tumor regression. The prime-boost therapy is being tested in combination with investigational anti-PD-L1 CPI atezolizumab.

7.1.1 LV305

LV305 is the product name for ZVex2.0 encoding the NY-ESO-1 CT antigen. It is a modified LV-based on IMDZ's ZVex™ platform designed to target production of NY-ESO-1 in DCs via a modified Sindbis virus glycoprotein (SINVar1). It has been engineered to enhance safety such that it is dendritic cell-tropic, replication-incompetent, and integration-deficient.⁷ LV305 contains 1×10^{10} vg/mL in Tris buffer (pH 7.5) containing 5% sucrose and L-arginine as outlined in Table 3.

Table 3 LV305 Drug Product Components

Component	Amount per mL	Amount per vial	Function
LV305	1×10^{10} vg/mL	1.4×10^{10} vg/mL	Active component
L-arginine	8.71 mg/mL	12.2 mg/vial	Excipient
Tris buffer	6.06 mg/mL	8.48 mg/vial	Excipient
Sucrose	50 mg/mL	70 mg/vial	Excipient

vg = viral genomes.

Source: CMB305 Investigator Brochure⁶

For further details regarding LV305, its properties, and formulation, please consult the CMB305 IB.⁶

7.1.1.1 Investigational Drug Packaging and Labeling

The LV305 investigational Drug Product will be supplied in a one-vial configuration where a 1 mL injection volume will correspond to the total dose. Each vial contains 1.4 mL of formulated LV305 (1×10^{10} vg/mL) packaged in a 2 mL vial.

7.1.1.2 Storage and Disposition of the Investigational Drug Products

LV305 must be stored at -60°C (or colder). Upon completion of the study, all remaining materials must be returned to IMDZ unless otherwise instructed.

7.1.1.3 Dose Preparation for Administration to the Patient

The Drug Product will be used as provided in the vial. Instructions detailing thawing of the vial and preparation of dosing syringes will be provided in the Pharmacy Manual.

One (1) mL of the thawed product will be administered as 8×125 μL ID injections (2 injections over each deltoid and 2 over each of the quadriceps) on Days 0, 14, 42, and 70 as outlined in the Schedule of Events (Table 1) and the Pharmacy Manual. Each ID injection should be at least 3 cm from the neighboring injection.

7.1.2 G305

G305 is comprised of recombinant NY-ESO-1 full-length protein with a His-tag that is cleaved prior to final purification (182 amino acids and ~ 18 kDa), which is mixed with GLA-SE to form a 2% oil/water emulsion. GLA is a synthetic Lipid A analog that can bind to the TLR4 receptor activating the innate immune response in a number of different immune cells including DCs.⁶ G305 can induce the activation of a potent adaptive immune response against NY-ESO-1 involving antibodies, CD4⁺ T cells, and other effector immune cells. For further information regarding G305, its components, properties, and formulation, please consult the CMB305 IB.⁶

7.1.2.1 Investigational Drug Packaging and Labeling

The Investigational Drug Product G305 will be supplied in a 2-vial configuration. One vial will contain the formulated protein antigen NY-ESO-1 and the second vial will contain the adjuvant GLA-SE.

Along with GLA, the GLA-SE formulation contains squalene (oil), glycerol, tocopherol (vitamin E), 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), surfactant (polaxamer), and ammonium phosphate buffer.

NY-ESO-1 protein will be packaged as 500 µg of protein/mL in 2 mL vials, each containing 0.65 mL of formulated protein. GLA-SE will be packaged in 3 mL clear glass vials each containing 0.8 mL of formulated adjuvant.

Detailed instructions for admixing the protein with adjuvant will be provided in the Pharmacy Manual.

7.1.2.2 Storage and Disposition of the Investigational Drug Products

The NY-ESO-1 protein must be stored at **-60°C (or colder)**. GLA-SE is an emulsion that must be stored at **2 to 8°C**. **GLA-SE MUST NOT BE FROZEN**. Upon completion of the study, all remaining materials must be returned to IMDZ unless otherwise instructed.

7.1.2.3 Dose Preparation for Administration to the Patient

Dose preparation instructions will be provided in the Pharmacy Manual. One (1) mL of the mixed product will be administered via IM injection in the deltoid or femoral region (anterior upper thigh) using alternating limb inject sites on Days 28, 56, and 84 as outlined in the Schedule of Events ([Table 1](#) and [Table 2](#)) and the Pharmacy Manual.

7.1.3 Atezolizumab

Atezolizumab (formerly MPDL3280A) is an anti-PD-L1 human IgG1 mAb consisting of 2 heavy chains (448 amino acids) and 2 light chains (214 amino acids) produced in Chinese hamster ovary (CHO) cell. It was engineered with a single amino acid substitution (asparagine to alanine) at position 298 of the heavy chain resulting in non-glycosylated antibody minimizing its ability to bind to Fc-receptors. This loss of binding eliminates Fc-effector function and depletion of PD-L1 expressing cells. Atezolizumab is being investigated as a potential therapy in humans against solid tumors and hematologic malignancies. Atezolizumab is contraindicated for patients with a history of severe allergic anaphylactic reactions to chimeric, human or humanized antibodies, or fusion proteins, as well as for patients with known hypersensitivity to CHO cell products or any component of the atezolizumab formulation.

7.1.3.1 Investigational Drug Packaging and Labeling

The atezolizumab drug product is provided in a single-use, 20-mL glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. 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.

For further details, see the atezolizumab Pharmacy Manual and IB.

7.1.3.2 Storage and Disposition of the Drug Product

Atezolizumab must be refrigerated at 2°C to 8°C (36°F to 46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in atezolizumab drug product; therefore, the 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. Upon completion of the study, all remaining materials must be returned to IMDZ.

7.1.3.3 Dose Preparation for Administration to the Patient

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. A dose of 1200 mg atezolizumab will be administered by IV infusion every 3 weeks. The investigational products will be delivered in infusion bags with IV infusion lines with product contacting surfaces of polyvinylchloride (PVC) and polyolefin and 0.2 µm in-line filters (filter membrane of polyethersulfone). No incompatibilities have been observed between atezolizumab and PVC or polyolefin infusion materials (bags and infusion lines).

Specific instructions for the preparation and administration of the atezolizumab infusion solution are contained within the Pharmacy Manual.

7.2 Treatment Administration

For patients randomized to the combination treatment arm, the dosing regimens for LV305 and G305 will mimic those used in previous Phase 1 studies. The dose of each agent will be given according to the schedules outlined in [Table 1](#) (combination dosing arm with atezolizumab) or [Table 2](#) (control arm).

Two doses of LV305 will be administered 2 weeks apart on Weeks 0 and 2, which will be followed every 2 weeks with G305 alternating with LV305 ([Figure 1A](#)). The alternating regimen that will be used was designed primarily to maximize the induction of CD8 T-effector/memory cells by LV305 and then expand or boost them with the G305. Nonclinical studies suggest that injections every 2–4 weeks generate the most durable and highest magnitude immune responses^{6,20} and that the responses continue to be boosted with additional treatments.

Patients will be given an IV infusion of 1200 mg atezolizumab over 30 to 60 minutes every 3 weeks starting on Day 0 until disease progression or unacceptable toxicity ([Figure 1A&B](#)). The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is

tolerated without infusion-associated AEs, the second infusion may be delivered over 30 (\pm 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (\pm 10) minutes. For the first infusion, the patient's vital signs (HR, respiratory rate, BP, and temperature) should be measured within 15 minutes of the infusion, during the 60-minute infusions (every 15 [\pm 5] minutes), and 30 minutes after the infusion. For subsequent infusions, vital signs do not need to be obtained during the infusion if the prior infusion was tolerated without symptoms. The management of any infusion-related reactions are outlined in [Section 7.4.4.1](#).

Patients in both study arms will be treated with atezolizumab therapy alone every 3 weeks starting at from Day 0 until disease progression or unacceptable toxicity. Due to administrative reasons, atezolizumab treatment may be administered up to 3 days before or after the scheduled dosing day.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. Further details are provided in [Section 9.4.1](#).

7.2.1 Randomization

Patients will be randomized 1:1 to the combination dosing arm or control arm of the study no more than 4 days prior to dosing (Day 0). Randomization will be stratified by type of disease.³⁰ An automated interactive web response system (IWRS) will be used to manage the randomization and treatment assignment. Patients who withdraw from the study will not be replaced. Refer to the Study Reference Manual for details on randomization and registration.

7.2.2 Dose Modification Guidelines

Dosing interruptions are permitted in case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of scheduled interruption, unless otherwise discussed with Sponsor. The reason for interruption should be documented in the patient's study records.

There are no adjustments for dose delay for a given patient, and treatment delays for the CMB305 components that are >14 days from the treatment plan before Visit 12 will not be allowed. During the study, if a patient experiences a DLT, treatment of that patient will be suspended. A patient may be considered for receiving further injections of the LV305, G305, or atezolizumab investigational drug product on a case-by-case basis following evaluation of the benefit/risk ratio to the patient by the Investigator and Medical Monitor, in consultation with the

independent DMC (e.g., for patients who have experienced a tumor response and had a non-life- and non-organ-threatening DLT, continuation of treatment as per protocol may be considered).

No reduction or modification of the atezolizumab dose will be allowed. Any 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. As a result, study treatment must be withheld for AEs or infusions reactions associated with atezolizumab treatment as outlined in [Appendix F](#).

While most 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. The primary approach to Grade 1-2 irAEs is supportive and symptomatic care; for higher grade irAEs, steroids by mouth or parenterally are given, and either skipping a dose or stopping therapy is appropriate. Recurrent Grade 2 irAEs may also mandate skipping a dose of atezolizumab or the use of steroids as outlined in [Appendix F](#).

Discontinuation of atezolizumab may not have immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or TNF α inhibitors as outlined in [Appendix F](#).

7.3 Drug Accountability

Under no circumstances is it permitted to use study supplies for any purposes other than those specified in this Protocol.

The Investigator or medically qualified, authorized delegate will be provided with forms to enable accurate recording of all study doses at the study facility at all times. The Investigator, or designee, must sign a statement that he/she has received study injections intended for the study. At any given time, the figures of supplied, used, and remaining doses of study drug must match. At the end of the study, it must be possible to reconcile delivery records with those of used and unused stocks. Account must be given of any discrepancies.

7.4 Prior and Concomitant Therapy

7.4.1 Prior Therapy

Any investigational agent or cancer therapy is prohibited during the 21 days prior to Day 0, including chemotherapy, radiation, kinase inhibitors, immunotherapy, G-CSF, GM-CSF, or other biologics. Systemic corticosteroid use is not permitted within four weeks prior to dosing. Patients who have previously received NY-ESO-1 directed immunotherapies or any antibody or drug targeting T-cell costimulation will not be eligible.

7.4.2 Prohibited Concomitant Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority–approved or experimental, is prohibited. The following treatments are prohibited during study until the end of the study or tumor progression:

- Any chemotherapy, hormonal therapy, immunotherapy, radiotherapy, herbal therapy, or investigational drug other than LV305, G305, or atezolizumab.
- Any corticosteroid (>10 mg/day prednisone or equivalent dose) within 3 weeks of first study treatment and during the study period. However, systemic glucocorticoids are permitted to modulate symptoms for an MEOI of suspected immunologic etiology.
- Other concurrent immunosuppressive medications such as methotrexate, cyclosporine, and azathioprine.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, are not allowed.

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for subsequent infusions at the discretion of the treating physician after consultation with the Medical Monitor.

After Day 84, certain forms of radiotherapy may be considered for pain palliation if patients are deriving benefit (e.g., treatment of known bony metastases).

Patients experiencing a mixed response requiring local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, and radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue study treatment. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression. Such cases must be discussed with and approved by the Medical Monitor.

There are no known procedure-related risks with use of atezolizumab. The following therapies are excluded while patients are receiving study drug:

- Patients who are receiving a receptor activator of nuclear factor kappa B ligand (RANKL) inhibitor (denosumab) prior to enrollment must be willing and eligible to receive a bisphosphonate instead; denosumab could potentially alter the activity and the safety of atezolizumab.

- Immunostimulatory agents not part of study treatment, including but not limited to IFN- γ or IL-2; these agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab. Systemic corticosteroids, TNF- α inhibitors, mycophenolate and other immune suppressants may be administered for the treatment of immune-related toxicities at the discretion of the treating physician after consultation with the Medical Monitor.

In addition, all patients should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab. Atezolizumab is not metabolized via cytochrome P450 enzymes or conjugation/glucuronidation reactions. No drug interaction studies for atezolizumab have been conducted or are planned. There are no known interactions with other medicinal products or other form of interactions.

7.4.3 Permitted Concomitant Therapy

The following medications will be permitted during the study:

- Antihistamines
- Antiemetics
- Antidiarrheals
- Aspirin
- Nonsteroidal anti-inflammatory drugs (NSAIDs)

7.4.4 Supportive Care Guidelines for Atezolizumab Treatment

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator related to atezolizumab treatment. Guidance regarding the identification, evaluation, and supportive care measure for the management of these events with potential immunologic etiology, including infusion-related reactions, are outlined in [Appendix F](#). Where appropriate, these guidelines include the use of corticosteroids, additional anti-inflammatory agents, or other concomitant medications if symptoms do not improve with administration of corticosteroids. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. These treatment guidelines are intended to be applied when the Investigator determines the events to be related to atezolizumab. Note, if after the evaluation the event is determined to be not related, the Investigator is instructed to follow the reporting guidance but does not need to

follow the treatment guidance (summarized in [Appendix F](#) along with dose modification guidelines).

7.4.4.1 Infusion-related Reactions

Symptoms that occur during or within 24 hours after an infusion of atezolizumab may be part of an acute infusion reaction. The non-serious symptoms should be recorded as separate AEs on the AE eCRF. Serious symptoms should be reported as one SAE with the most medically significant sign or symptom as the primary event term. Additional signs and symptoms should be reported in the 'Additional Case Details' section of the AE eCRF page.

Infusion-related reactions will be managed according to severity according to the following procedures:

- In the event that a patient experiences a mild infusion-related event (National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI CTCAE] Grade 1), 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 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 infusion-related event (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the patient should have his or her infusion immediately interrupted and 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 the infusion rate that was in progress at the time of the onset of the infusion-related event.
- For severe or life-threatening infusion-related events (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 infusion-related events will not receive further infusion and will be further managed as clinically indicated until the event resolves.

Further details regarding the management of Infusion-related reactions are provided in [Appendix F](#).

7.5 Diet/Activity/Other Considerations

7.5.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

7.5.2 Contraception

Animal reproduction studies have not been conducted with CMB305 to evaluate the effect of the components on reproduction or fetal development. Atezolizumab may have adverse effects on a fetus *in utero* and it is not known if atezolizumab therapy has any adverse effects on the composition of sperm. Furthermore, human IgGs are known to cross the placental barrier and the PD-1/PD-L1 pathway has been linked with pregnancy maintenance.³¹

Currently, there is no human data demonstrating the effects of this line of CPI therapy in pregnancy, lactation, or reproductive potential. Therefore, non-pregnant, non-breast-feeding women may only be enrolled into the trial if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as:

1. Surgically sterilized,
2. Postmenopausal (a woman who is ≥ 45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or
3. Not heterosexually active for the duration of the study.

The 2 birth control methods can be either 2 barrier methods, or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from Study Visit 1 throughout the study period up to 90 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide as per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, SC, intrauterine, or IM agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

It is unknown whether atezolizumab or any components of CMB305 are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

8.0 STUDY PROCEDURES

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB), and according to GCP standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB, except where it may be necessary to eliminate an immediate hazard to a research patient. In such case, the deviation will be reported to the IRB as soon as possible (also see [Section 16.2](#)).

8.1 Visit Windows

Visits from Day 0 to 105 will have a window of ± 3 days from the specified study day. Follow-up phase visits (after Day 105) will have a window of ± 4 days. Refer to the Schedule of Events ([Table 1](#) and [Table 2](#)) for the timing of visits and the specific procedures that will be performed at each visit.

8.2 Study Visits

8.2.1 Screening Visit(s): Weeks -4 to 0 (Days -30 to -1)

Patients will undergo screening and enrollment procedures up to 30 days prior to Study Day 0. Assessments may occur at multiple visits. Screening procedures/assessments include the following:

1. Consent for assessment of tumor biopsy surgical specimen

No trial-specific staging or biopsy procedures will be undertaken prior to completion of the consenting process. However, if a patient has had tests performed prior to providing informed consent as part of standard of care (considered standard for the patient and routine medical practice, based upon their presentation at the time), and ALL of the following conditions are met, then these data may be allowed as part of the study data:

- The tests fulfill all requirements of the study, i.e., are complete and follow the procedures outlined in the study;
- The tests have been completed within the specified number of days to perform pre-treatment assessments; and
- It is medically unwise to repeat a test/procedure or it poses undue additional risk to the patient.

NY-ESO-1 expression will be determined for pre-study tumor samples by IHC. Tumor tissue specimens from any prior surgical resection or biopsy may be examined for NY-ESO-1 expression, and the analysis will be performed by a central lab. A separate screening consent form will be available and may be used to screen patient tumor samples for NY-ESO-1 expression prior to signing the primary consent form for participation on this clinical study. However, pre- and on-study biopsies may also be required for immune testing if lesions are accessible.

NY-ESO-1 testing results of tumor tissue obtained in conjunction with a different IMDZ study may also be used to qualify for this trial if the testing was performed by an IMDZ-approved central lab. For this study, there is no time limit on when the test was performed and the use of its results to qualify for this study. Confirmation of NY-ESO-1 expression should be made before beginning other screening procedures. Tumor histology including an evaluation of immune cell invasion and composition will also be examined.

2. Informed consent/Human Insurance Portability and Accountability Act (HIPAA) authorization
Prior to study enrollment, each patient will receive complete information, both verbally and in writing, about the nature of the study, the anticipated risks, discomfort associated with the study, and about the right to interrupt participation in the study at any time. Prior to participation in the study, each patient (or representative) will have signed the written, IRB-approved Informed Consent Form (ICF) and HIPAA form. This should be done within 30 days prior to their anticipated dosing start date (Day 0). An agreement to continue in the study and obtain tumor biopsy if the patient meets the criteria for progressive disease but wishes to remain on study should also be obtained.
3. Review of inclusion/exclusion criteria and determination of patient eligibility ([Section 6.0](#)).
4. Demographics
5. Medical history – includes a review of systems, general medical and surgical history, concomitant illnesses, current medications, and tumor-specific therapy history. Oncologic baseline disease characteristics/history will be recorded (diagnosis, disease stage, ECOG status [[Appendix A](#)], and RECIST lesions [[Appendix C](#)]). (Any changes to Medical History from initial collection of data to Day -1 should be updated to the records.)
6. Full Physical examination, including height, weight, vital signs (including temperature, respiratory rate, HR, and resting BP), and 12-lead ECG.
7. Assessment of diagnosis and stage of disease (tumor staging), including Computed Tomography (CT) of chest, abdomen, pelvis. Other assessments such as magnetic resonance imaging (MRI), bone scan or positron emission tomography (PET)/CT should be performed only if indicated for the cancer indication.
8. Blood sample collection. Up to 78 mL of blood will be collected for the following evaluations:
 - HIV/HepB/HepC testing (5 mL) – As part of study eligibility, patients must have a negative HIV test at screening. LV305 is an engineered LV that contains genes originally derived from HIV and it is not known if treatment with LV305 will result in seroconversion of patients to positive upon HIV screening. Secondary confirmatory assays such as Western Blot can be used to demonstrate that the normal complement of HIV proteins is not present (unless the patient has developed a true HIV infection). Patients in the combined treatment arm will be provided with a card from the study Sponsor describing the possibility of a screening test becoming positive and the importance of confirmatory testing. In the event a study patient should have a positive

screening HIV test, the site should inform and consult IMDZ for recommendations on the most appropriate confirmatory test to use.

- Cellular immunity (approximately 55 mL) – collected in 8 CPT™ Heparin tubes for T-Cell response assays and performed at sites where staff are trained in peripheral blood mononuclear cell (PBMC) isolation.
- Safety laboratory evaluations (10 mL) – includes hematology and clinical chemistry.
- LV305 persistence testing (8 mL) – Only for those subjects randomized to the combination treatment arm.

9. Urinalysis

10. Urine pregnancy test for FCBPs

11. Thyroid function tests (triiodothyronine [T₃], thyroxine [T₄], and thyroid stimulating hormone [TSH])

12. Tumor biopsy (for patients who provide consent for the biopsy procedure). The pre-treatment biopsy must be completed ≤ 6 months prior to screening. If unavailable, a new biopsy may be performed.

13. Randomization and enrollment into the study

Once patients have been properly consented, and all inclusion/exclusion and screening criteria have been documented as being met, patients will be enrolled into the study. Randomization must occur no more than 4 days before Day 0.

8.2.2 Treatment Phase (Weeks 0-12 Treatment Visits, Study Days 0 to 84)

The following procedures will be performed at all study visits for subjects in both treatment arms:

1. AEs and SAEs (including MEOIs)
2. Concomitant Medications
3. Vital Signs (temperature, HR, resting BP) obtained pre-dose and 30 minutes, post-dose. For the first atezolizumab infusion, the patient's vital signs (HR, respiratory rate, BP, and temperature) should be measured within 15 minute of the infusion, during the 60-minute infusion (every 15 [± 5] minutes), and 30 minutes after the infusion. For subsequent infusions, vital signs do not need to be obtained during the infusion if the prior infusion was tolerated without symptoms.
4. Physical examination: simple targeted physical examination
5. ECOG status
6. Urine pregnancy test for FCBP on treatment days. Note: pregnancy test must be performed within 72 hours before study drug administration and negative before study drug administration.
7. Blood samples (10 mL) for safety laboratory evaluations within 4 days before treatment initiation and up to 48 hours before each subsequent dose.

The following procedures will occur at select study visits according to the study visit schedule provided in [Table 1](#) and [Table 2](#):

- Blood samples will be collected at selected sites on Study Days 0, 42, and 70 for immunological assessments including cellular immunity (55 mL).
- A blood sample will be collected at Study Day 84 for thyroid function tests.
- Tumor Staging: includes CT scans to evaluate progression per RECIST/irRC will be performed every 6 weeks. MRI, bone scans or PET/CT will only be performed if clinically necessary.
- Tumor biopsy on Days 0 and 42
- Patients in the combination treatment arm will receive study drug LV305 at Study Day 0, Week 2, 6, and 10; G305 will be administered at Weeks 4, 8, and 12.
- Atezolizumab will be administered every 3 weeks (Weeks 0, 3, 6, 9, and 12).

8.2.3 Post-CMB305 Long-term Treatment Study Visits

Following the Treatment Phase, patients in the combined treatment arm will enter the Booster Phase (post Day 84 to 1 year post Day 0); patients who complete the Booster Phase will then enter the Maintenance phase (1 year to 2 years post Day 0). Patients in the control arm will enter the Maintenance Phase (post Day 84 to 2 years post Day 0).

8.2.3.1 Booster Phase (Combined Treatment Arm Only: post Day 84 to 1 year post Day 0)

The following procedures will be performed in the combined treatment arm during these visits:

1. AEs and SAEs (including MEOIs)
2. Concomitant Medications
3. Vital Signs
4. Physical examination: simple targeted examination
5. ECOG status
6. A G305 booster will be given in the combined treatment arm 6 weeks following the Day 84 dose and every 6 weeks thereafter for 1 year (from Day 0) or until disease progression.
7. Atezolizumab administration will be administered on Day 105 and every 3 weeks thereafter for 1 year (from Day 0) or until toxicity develops or progression. After Day 105, one of three atezolizumab doses may be delayed by 1 week (28 days instead of 21 days for one cycle) to allow for vacations.
8. Urine pregnancy test must be performed for FCBP within 72 hours before study drug administration and negative before study drug administration, if patients are still receiving booster doses of G305 and/or atezolizumab.

Blood samples for cellular immunity (55 mL) and a tumor biopsy will occur on Day 98 (\pm 2 weeks) and the following procedures will occur on Day 105:

- 12-lead ECG
- Blood for safety laboratory evaluations (10 mL)
- Urine pregnancy test for FCBPs
- Administration of atezolizumab

All subjects will return to the clinic every 3 weeks for 1 year (from Day 0) or until disease progression (whichever is later) for the following assessments:

1. AEs and SAEs (including MEOIs; only those possibly related to study drug will be reported)
2. Concomitant Medications (only those related will be reported)
3. Vital Signs
4. Physical Examination (symptom-specific)
5. ECOG status
6. Blood for safety laboratory evaluations (10 mL)
7. Thyroid function tests should be monitored at least every 3 months
8. Tumor staging by CT every 6 weeks for the first year, then every 12 weeks

The following procedures will occur at select study visits according to the study visit schedule provided in [Table 1](#):

- A tumor biopsy should be performed at 6 months or longer (for patients with treatment response) and at the time of progression
- A blood sample will be collected at Day 168 for HIV testing (5 mL).
- Blood samples will be collected at Day 168

8.2.3.2 Maintenance Phase (Combined Treatment Arm: From 1 Year to 2 Years Post Day 0; Control Arm: Post Day 84 to 2 Years Post Day 0)

The following procedures will be performed these visits:

1. AEs and SAEs (including MEOIs)
2. Concomitant Medications
3. Vital Signs
4. Physical examination: simple targeted examination
5. ECOG status
6. For patients in the control arm, atezolizumab administration will be administered on Day 105 and every 3 weeks thereafter for 1 year (from Day 0) or until toxicity develops or progression. After Day 105, one of three atezolizumab doses may be delayed by 1 week (28

days instead of 21 days for one cycle) to allow for vacations. For patients in the combined treatment arm, atezolizumab administration will continue to be administered every 3 weeks for 1 year (from 1 year to 2 year post Day 0) or until toxicity develops or progression.

7. Urine pregnancy test must be performed for FCBP within 72 hours before study drug administration and negative before study drug administration, if patients are still receiving booster doses of G305 and/or atezolizumab.

For patients in the control arm, blood samples for cellular immunity (55 mL) and a tumor biopsy will occur on Day 98 (\pm 2 weeks) and the following procedures will occur on Day 105:

- 12-lead ECG
- Blood for safety laboratory evaluations (10 mL)
- Urine pregnancy test for FCBPs
- Administration of atezolizumab

All subjects will return to the clinic every 3 weeks for the following assessments:

1. AEs and SAEs (including MEOIs; only those possibly related to study drug will be reported)
2. Concomitant Medications (only those related will be reported)
3. Vital Signs
4. Physical Examination (symptom-specific)
5. ECOG status
6. Blood for safety laboratory evaluations (10 mL)
7. Thyroid function tests should be monitored at least every 3 months
8. Tumor staging by CT every 6 weeks for the first year, then every 12 weeks

The following procedures will occur at select study visits according to the study visit schedule provided in [Table 1](#):

- A tumor biopsy should be performed at 6 months or longer (for patients in the control arm with treatment response) and at the time of progression
- For patients in the control arm, a blood sample will be collected at Day 168 for HIV testing (5 mL).
- Blood samples will be collected at Day 168 (controlled arm), then again at 12 and 24 months (post Day 0) for LV305 persistence testing (8 mL).

8.2.4 Survival Follow-up Phase (Post-Maintenance Phase Long-Term Quarterly Follow-up)

Following radiographic disease progression and discontinuation of study drugs for more than 30 days, patients will be followed-up by quarterly telephone calls to the attending physician or database search until study completion for survival status and subsequent treatment.

9.0 ASSESSMENTS OF EFFICACY AND SAFETY

9.1 Timing of Assessments

The timing of study assessments is summarized in the Schedules of Events for each treatment arm ([Table 1](#) and [Table 2](#)) and detailed in [Section 8.2](#) (Study Conduct). After five cycles of atezolizumab administration, one of three cycles may be delayed by 1 week (28 days instead of 21 days for one cycle) to allow for vacations.

9.2 Demographics, Medical History, and Baseline Characteristics

Medical history includes previous clinically significant diseases, surgeries, cancer history and therapies, responses to prior therapies and medications used by the patient within 28 days prior to screening. Demographic information will include age, sex, race, ethnicity, etc. ECOG Performance status will be assessed using standard methodologies and criteria outlined in [Appendix A](#).

9.3 Efficacy Assessments

9.3.1 Tumor Response Based upon RECIST and irRC

Tumor staging by CT will be performed every 6 to 9 weeks and images/scans will be evaluated by the sites for treatment decisions and later by BICR for tumor responses. The RECIST v1.1 criteria modified to use irRC³⁷ will be used to determine disease progression as defined in [Appendix C](#). The irRC also require a confirmation of CR/PR/PD at least 4 weeks later with imaging. Once confirmed, the date of progression will be defined as the first date that the total tumor burden was shown to have increased by at least 20% compared with nadir. For this study, the modified irRC using unidimensional measurements of the tumor will be implemented (see [Appendix C](#) and [Appendix D](#)). Evaluations will be used for determination of PFR, PFS, ORR, DOR, and time to response. OS will also be evaluated.

9.3.2 Immune Response

The following exploratory immune monitoring will be conducted:

- Cellular immunogenicity as measured by changes from baseline and over the course of the trial period in peripheral blood levels of T cells, T-cell effector and memory populations, and T-cell associated cytokine production.
- Humoral immunogenicity as measured by changes from baseline and over the course of the trial period with anti-NY-ESO-1 antibodies or TAAs.
- Evaluation of dosing response by RNA profiling of PBMCs as measured by the changes from baseline.

Details for sample handling and assay performance will be provided in the Immune Monitoring Manual.

9.3.3 Exploratory Biomarkers

Pre-, on-, and post-treatment blood or tumor samples may be collected for exploratory analyses of potential biomarkers of CMB305 or atezolizumab immunogenicity and clinical tumor response. A number of exploratory analyses are being investigated, but the predictive value of such tests is not yet known. The data collected from these exploratory tests will help to define a set of biomarkers that might be used in future studies to help define the ability of CMB305 to stimulate antitumor immune responses, to help stratify patients who might respond to these treatments, and/or to determine a minimum therapeutic dose. Exploratory blood tests may include functional assays of cytolytic T cells or other immune cells directed against autologous tumor cells or surrogate target cells, modifications of current assays to detect antitumor cellular immunity, detection or analyses of circulating tumor cells, and/or analyses of other (as of yet undefined) tumor markers and immune function.

Pre- and on-study cancer biopsy tissue will be examined for evidence of antitumor cellular immunity (e.g., CD8 T cell or NK cell infiltration, tumor necrosis, etc.) and for evidence of immune suppression within the tumor microenvironment. Blood or tumor samples will only be used to examine the patient's immune response, their cancer, or to help evaluate any potential toxicity arising in the study. The samples will not be examined for unrelated research or diseases.

9.4 Safety Assessments

Safety will be evaluated for all treated patients using NCI CTCAE v4.03.²⁹ Safety assessments will be based on medical review of both solicited and spontaneously reported AEs, SAEs, and MEOIs including symptoms, physical examination findings, vital signs, laboratory findings, ECGs, and discontinuations for AEs. After initiation of study drug, all AEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or until initiation of another anti-cancer therapy, whichever occurs first.

9.4.1 Definitions

Adverse Event (AE) - Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, medical treatment, or procedure and which does not necessarily have to have a causal relationship with this regimen. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, medical treatment, or procedure whether or not considered possibly, probably, or definitely related to the medicinal product.

Unexpected Adverse Event – An AE is “unexpected” when its nature (specificity), severity, or frequency are not consistent with the known or foreseeable risk of AE associated with the research procedures described in the protocol, informed consent form, or the Investigator Brochure.

Serious Adverse Event (SAE) – Any adverse event occurring that results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
Note: Hospitalizations not to be reported as SAEs include admissions for a planned medical/surgical procedure (such as scheduled tumor excision or debulking surgery) or routine health assessment requiring admission for baseline/trending of health status documentation (e.g., routine colonoscopy) or admission for social purposes such as lack of housing, economic inadequacy, care-giver respite, or family circumstances.
- A persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is a medically important condition which is judged by a health care professional as serious

The term “life-threatening” refers to an event in which the patient was at risk of death at the time of the event, and it does not refer to an event that hypothetically might have caused death if it were more severe.

Disability refers to a substantial disruption of a person’s ability to conduct normal life function.

Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. These may also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; or blood dyscrasias or convulsions that do not result in hospitalization.

When there is doubt regarding an AE meeting the criteria for an SAE, the Investigator should default to reporting the AE as an SAE.

Pregnancy – Although pregnancy is not considered an SAE, and is instead a normal human experience, all pregnancies reported in the month before or after the last investigational injection

must be reported to the Sponsor using the Pregnancy Report Form as outlined in the Site Safety Manual.

Overdose– An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. In this trial, an overdose will be defined as ≥ 1000 mg (5x the dose) of atezolizumab. For reporting purposes, an overdose will be considered, regardless of adverse outcome, as an important medical event. All cases of overdose must be reported immediately to the Sponsor.

Medical Events of Interest – Select non-serious AEs and SAEs identified by the Sponsor will be considered MEOIs. All MEOIs outlined in [Section 9.4.8](#) must be reported to the Sponsor using the MEOI Report Form as outline in the Site Safety Manual.

9.4.2 Adverse Event Severity

All AEs will be evaluated according to the NCI CTCAE v4.03 (2010).²⁹

For AEs not listed in this reference scale, severity will be assessed by the Investigator according to the criteria in Table 4.

Table 4 Adverse Event Severity Assessment

Grade 1 (Mild)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 (Moderate)	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4 (Life threatening)	Life-threatening consequences; urgent intervention indicated.
Grade 5 (Death)	Death related to AE.

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Changes in the severity of an AE should be documented to enable an assessment of the duration of the event at each level of intensity. AEs characterized as intermittent require documentation of onset and duration of each episode.

9.4.3 Relationship to Investigational Drug

The Investigator will report his or her interpretation of the relationship between an AE and the study treatment on the basis of their clinical judgment and the definitions in [Table 5](#).

Table 5 Assessment of Relationship

Definitely related	AEs clearly attributable to study regimen administration.
Probably related	AEs for which there is a reasonable possibility of causal association to study regimen.
Possibly related	AEs for which there is confounding by comorbidities, medications or other considerations but for which it is not unreasonable that the AE may have been caused by study regimen. Note that it is not appropriate to invoke “you can’t rule it out.”
Not related	AEs that are considered clearly not causally related to study regimen, or for which there is a clear alternative explanation

AE = adverse event

If there is any question whether or not an AE is possibly, probably or definitely related, the Investigator should default to conservatism in categorization. Similarly, if an event meets one of the definitions described above and there is any doubt regarding the serious nature of an AE, the Investigator should default to conservatism by calling an AE an SAE.

9.4.4 Adverse Event Collection Period

AEs include any untoward signs (including abnormal laboratory findings) or symptoms experienced by the patient and will be collected from the time of enrollment until 30 days after the last dose of study drug. All enrolled patients will have periodic assessment of clinical and laboratory AEs. All AEs and SAEs will be collected at each Study Visit following completion of all scheduled procedures. Thereafter, new malignancies and SAEs that come to the attention of the site staff that are considered at least possibly related to CMB305 or atezolizumab will be collected until the last patient contact.

9.4.5 Adverse Event Reporting

At each study visit (including unscheduled visits), the Investigator, or designee, will determine whether any AEs have occurred. AEs will be reported in the patient’s medical record and on the AE CRF page and each will be classified according to the criteria in [Section 9.4.2](#) and [Section 9.4.3](#). If known, the diagnosis should be recorded, in preference to the listing of

individual signs and symptoms. Any pre-existing conditions that are detected as part of the initial screening procedures will need to be reported in the medical history and not as an AE. However, pre-existing conditions that worsen following enrollment should be reported as an AE.

AEs that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the AE eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction).

For all patients, progression of the cancer under study is not considered an AE unless it assessed by the Investigator as drug-related.

All AEs and SAEs that are unexpected and considered possibly, probably, or definitely related to study regimen will be reported to the US Food and Drug Administration (FDA) by IMDZ, or designee, in accordance with the requirements outlined in the Code of Federal Regulations (CFR), 21 CFR §312.32. Deaths due to cancer progression will not be reported as expedited events but must be reported to the Sponsor as SAEs within the 24 hour time period. The Investigator will continue to monitor the patient until any new, changed, or worsened AE resolves, returns to baseline, or until the Investigator and IMDZ agree that follow-up is no longer necessary. AEs must be followed until resolution whenever possible.

The Investigator is responsible for the appropriate medical care and safety of patients who have entered this study. The Investigator must notify the Sponsor within 24 hours if either of the following events occurs:

- Any event considered an MEOI (see [Section 9.4.8](#))
- Any event meeting the criteria for an SAE

The nature, severity, and frequency of AEs will be monitored on an ongoing basis for risk assessment and to determine if risk management interventions are warranted (i.e., expedited notification of safety findings to investigators, IRBs, or regulators; update of IB and ICF risks and re-consenting study patients; revision of safety monitoring procedures; revision of eligibility criteria or other study procedures).

9.4.6 Serious Adverse Event Reporting

If an SAE occurs, the Investigator must notify IMDZ within 24 hours of awareness of the event (see contact information below). If the SAE is fatal or life-threatening, IMDZ must be notified immediately, irrespective of the extent of available SAE information. In the rare event that the Investigator or designee does not become aware of the occurrence of a SAE immediately, the Investigator or designee must report the event within 24 hours of their awareness and document

the time of when his/her first awareness occurred. For all SAEs, the Investigator or designee is obligated to pursue and provide information to IMDZ in accordance with the timeframes for reporting specified above. In addition, the Investigator may be requested to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE case report form. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of causality.

During the screening period, any new SAEs experienced by patients (pre-study treatment) will be reported to IMDZ if the events are considered related to study procedures. For the period after signing the ICF until Day 0, any new SAEs determined to be related to study tests or procedures (not including cancer-related events) and any hospitalizations that are experienced by patients will be reported on the SAE form and in the eCRF. From the start of study treatment (Day 0) until 30 days following cessation of study drug (or if the patient initiates new anticancer therapy, whichever is earlier), SAEs will be reported on the SAE form and in the eCRF. After that point, any SAE that comes to the attention of the site staff that may be causally related to study drug (i.e., there is a reasonable possibility that the event may have been caused by the drug) will be reported to IMDZ.

SAEs will be monitored until they have resolved, returned to baseline, or until they are no longer clinically significant, stable, or do not require additional follow-up, as judged by the Investigator and IMDZ.

STUDY CONTACT FOR REPORTING SERIOUS ADVERSE EVENTS	
Everest Clinical Research Inc.	
Telephone:	PPD [redacted] (office) or PPD [redacted] (mobile)
Fax:	See the SAE Report Completion Guidelines
Email:	SAE forms to PPD [redacted] Supplemental information to PPD [redacted]

9.4.7 Adverse Event Follow-up

Patients with radiographic disease progression will be followed every 3 months by telephone until the study is completed (last patient, last death in the study). Follow-up telephone calls will ascertain vital status, possible occurrence of second malignancies, and subsequent treatment as outlined in [Section 5.7](#). In the event of death, attempts will be made to establish the date and cause of death, as applicable.

9.4.8 Medical Events of Interest

Selected non-serious AEs are classified as MEOIs (see below) and must be recorded as such on the AE Case Report Forms and reported the Sponsor either by electronic media or paper on a MEOI Report Form. Sponsor Contact information can be found in [Section 9.4.6](#).

MEOIs for this trial include the following:

- DLTs
- An overdose of Sponsor's product that is not associated with clinical symptoms or abnormal laboratory results.
- An elevated AST or ALT lab value that is $\geq 3x$ ULN and an elevated total bilirubin lab value $\geq 2x$ ULN and, at the same time, an alkaline phosphatase laboratory value that is $< 2x$ ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

***Note:** These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

- The following confirmed treatment-emergent autoimmune conditions:
 - Pneumonitis
 - Hypoxia or dyspnea \geq Grade 3
 - Colitis
 - Endocrinopathies: diabetes mellitus, pancreatitis, or adrenal insufficiency
 - Vasculitis
 - Hepatitis
 - Transaminitis: \geq Grade 2 (AST or ALT $> 3x$ ULN and bilirubin $> 2x$ ULN) OR AST/ALT $> 10x$ ULN
 - Systemic lupus erythematosus
 - Guillain-Barre syndrome
 - Skin reactions: vitiligo, pemphigoid
 - Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome (SIRS), or infusion reaction syndrome.

Subjects should be assessed for possible MEOIs prior to each dose of study treatment. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an MEOI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate

possible immune-related MEOIs, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

MEOIs identified from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported to the Sponsor within 24 hours of the event in the same manner as outlined for SAEs (Section 9.4.6).

9.4.9 Pregnancy

Several nonclinical studies have already demonstrated that the PD-L1/PD-1 signaling pathway is essential in establishing maternal/fetal tolerance, which is necessary for embryo-fetal survival during gestation.³¹ As a result, no developmental or reproductive toxicity studies have been conducted with atezolizumab. The effects of atezolizumab on human reproduction or on the fetus or the developing infant are unknown but it is expected to have an adverse effect. Furthermore, it is not known whether atezolizumab is excreted in human milk; however, antibodies are known to cross the placenta and are excreted in breast milk during lactation.

Based on the critical role that PD-L1/PD-1 pathway plays in the maintenance of maternal-fetal tolerance and the excretion of antibodies during lactation, atezolizumab should not be administered to pregnant women or nursing mothers. The effects of atezolizumab on human reproduction or on the fetus or the developing infant are unknown but it is expected to have an adverse effect.

Absence of pregnancy must be confirmed prior to initiation of atezolizumab. Female patients of childbearing potential should utilize contraception and take active measures to avoid pregnancy while undergoing atezolizumab treatment and for at least 90 days after the last dose of atezolizumab.

If a female patient inadvertently becomes pregnant while on treatment with CMB305 or atezolizumab, they will be immediately removed from the study. The site will contact the patient at least monthly to document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is an SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator should make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male patient impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor.

Sexually active men and FCBPs must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Before enrolling FCBP in this clinical trial, all FCBPs must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. All patients (men and women) must sign an informed consent form documenting this discussion.

All FCBPs must have a negative pregnancy test within 2 weeks prior to the study regimen initiation. If the pregnancy test is positive, the patient must not be enrolled in the study.

In addition, all FCBPs should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If, following initiation of study dosing, it is subsequently discovered that a trial patient is pregnant or may have been pregnant within one month before or 4 months after study regimens, the patient will be permanently discontinued. The patient will be followed for as long as possible by the Investigator or designated health care professional to determine pregnancy outcomes for both mother and child. If the female partner of a male patient enrolled in the study becomes pregnant, the Investigator (or designated health professional) should request permission to approach the partner regarding follow-up in order to determine pregnancy outcomes of the mother and baby.

9.4.10 Laboratory Safety Assessments

Blood will be collected a specific study visits as outlined in [Section 8.2](#) and the schedules of events for each treatment arm. Laboratory assessments to be performed include, but are not limited to, the following:

- Hematology: white blood cell (WBC) count with differential, ANC, red blood cell (RBC) count, Hb, hematocrit, platelet count, PT/PTT, and INR;
- Clinical chemistry (or local panel if inclusive of the following): sodium, chloride, potassium, glucose, blood urea nitrogen (BUN), creatinine, calcium, AST, ALT, total bilirubin, alkaline phosphatase, lactic acid dehydrogenase, total protein, and albumin; and
- Urinalysis (at baseline): protein, glucose, blood, leukocytes, nitrites, urobilinogen, bilirubin, pH, specific gravity, and ketones.

Screening safety laboratory safety assessments should be performed within 4 days of treatment initial. On dosing days, hematology and clinical chemistry assessments should be performed and reviewed prior to study drug administrations. These assessments may be done up to 48 hours prior to dosing.

Results will be documented in the patient CRFs. Clinically significant findings may be recorded as AEs.

9.4.10.1 Thyroid Function Tests

Assessments for thyroid function including triiodothyronine [T_3], thyroxine [T_4], and thyroid stimulating hormone [TSH] will be performed at screening and at least every 3 months while being treated with atezolizumab. Patients will be monitored for changes in thyroid function during treatment with atezolizumab for clinical signs and symptoms of thyroid disorders. Assessments will be performed at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. Results will be documented in the patient CRFs. Clinically significant findings may be recorded as AEs.

9.4.11 Other Laboratory Tests

Blood samples will also be obtained for immunological testing and serology for atezolizumab concentration. Testing for HIV, HepB, and HepC will be performed at screening and must be negative for entry into the study. Blood for immunological testing will be drawn twice at baseline to ensure a good yield. Results will be documented in the patient CRFs. Clinically significant findings may be recorded as AEs.

LV305 was originally derived from HIV, but most of the genome has been replaced to enhance safety and specificity. The product utilizes 3rd generation lentiviral vector technology, which means that it is devoid of all HIV-derived accessory genes.⁷ However, some proteins are included in the particle that may cause screening tests for HIV to become positive as a result of the treatments, although confirmatory testing would likely be considered indeterminate. The conventional screening test for HIV infection is the repeatedly reactive immunoassay (IA), followed by a confirmatory test. If a patient is tested for HIV and screened positive, the CDC recommends further testing with an FDA-approved 2nd generation antibody immunoassay to detect HIV-1 and/or HIV-2 antibodies.³² This test would usually be interpreted as positive if bands appear at the site of two or more of the following HIV antigens: p24, gp41, or gp120/160. If only one band is positive, the test would be considered indeterminate. Specimens that are reactive on the initial assay and negative or indeterminate on the HIV-1/HIV-2 antibody differentiation IA are then to be tested with an FDA-approved nucleic acid test (NAT) for HIV-1 RNA. Under normal circumstances, a reactive NAT result indicates the presence of acute HIV-1 infection and a negative result indicates the absence of HIV-1 infection. However, at least one NAT (the Roche COBAS AmpliPrep/COBAS Taq-Man HIV-1 Test, v2.0) was reported to have been falsely positive in two patients who had been treated with a different lentivirus.³³ An extensive search failed to detect wild-type infectious HIV-1 or vector-derived replication-competent virus and a PCR assay for HIV proviral DNA (Roche COBAS AMPLICOR HIV-1

MONITOR Test, v1.5), as well as a p24 enzyme-linked immunosorbent assay (ELISA), were both negative. Unfortunately, there is no simple path to a definitive diagnosis. While there is a chance of seroconversion, it is predicted to be low because the lentiviral vector used in this program is replication-incompetent and integration-deficient. Even if seroconversion occurs in some assays, it does not mean that the patient has HIV (unless they had become truly infected from some other exposure); careful follow-up testing needs to be done to evaluate that potential. Testing will be done at study entry and on Day 168 to evaluate the chance of seroconversion with LV305; any positives will be further evaluated to determine the true status of infection. Patients are also given a 'Dear Doctor' letter at study entry in case they have HIV testing done at an external lab.

9.4.12 Vital Signs

Vital sign assessments performed at specified study visits will include temperature, HR, and resting BP. These assessments should be performed prior to dosing and 30 minutes postdose administration on drug dosing days. For the first atezolizumab infusion, the patient's vital signs (HR, respiratory rate, BP, and temperature) should be measured within 15 minute of the infusion, during the 60-minute infusion (every 15 [\pm 5] minutes), and 30 minutes after the infusion. For subsequent infusions, vital signs do not need to be obtained during the infusion if the prior infusion was tolerated without symptoms.

9.4.13 Physical Examination

A complete physical examination including height and weight will be performed during screening. Subsequent physical examinations will be simple symptom-directed examinations. Clinically significant deteriorations will be recorded as AEs.

9.4.14 12-Lead Electrocardiogram (ECG)

A 12-lead ECG will be done at screening and at the final post-treatment Visit (Day 105). Clinically significant findings may be recorded as AEs.

9.4.15 LV305 Persistence

For subjects treated with CMB305, peripheral blood will be collected to assay for the persistence of LV305 at baseline, and 6, 12, and 24 months by PCR. Depending on the results through 12 months, annual assessments may continue until 2 consecutive samples show no evidence of LV305 persistence.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

The study endpoints ([Section 4.2](#)) include both clinical efficacy and safety. Where possible, parameters will be quantified for direct comparisons between the treatment groups.

10.2 Data Analysis

The final analysis will be conducted when at least 72 deaths have been observed, or sooner if the Sponsor so decides. Details of all analyses, populations, and data handling rules will be provided in a Statistical Analysis Plan (SAP) and finalized prior to database lock.

10.2.1 Analysis Populations

For the purpose of statistical analysis, there are 2 analysis populations: Intent-to-Treat population (ITT), and Safety population.

The ITT population consists of all randomized subjects. All analyses of this population will be based on the treatment arm to which the subjects are randomized.

The Safety Population will consist of all patients who received at least one injection/dose of study treatment. The Safety Population is the primary population for safety analyses including AEs and clinical laboratory data. Trial product exposure will also be summarized using the Safety Population.

10.2.2 Analyses

In general, categorical variables will be summarized by number and percentages and continuous variables will be summarized with descriptive statistics. All study data will be provided in listings.

10.2.2.1 Patient Disposition

Summaries will include patients who completed the study and for those who did not complete the study, reasons for early discontinuation.

10.2.2.2 Baseline Characteristics

Patient age, race, gender, weight, height, and other demographic information including medical history, disease history, and medication history will be summarized by treatment group.

10.2.2.3 Treatment Administration/Compliance

Treatment administration, exposure, and compliance with study treatments/procedures will be documented and summarized. Exposure and compliance data will be summarized for all patients in each treatment group/arm.

10.2.2.4 Efficacy Analyses

10.2.2.4.1 Primary Efficacy Analysis

The primary efficacy analysis will be the evaluation of OS and PFS based on the ITT Population.

Overall survival is defined as the time interval from randomization to death of any cause. Patients who are alive will be censored at the last known date alive or data analysis cutoff date, whichever is earlier. PFS is defined as the time interval from randomization to tumor progression or death. Accordingly, the precise definition of progression and the timing of imaging scans to progression are very important. Every effort must be made to assure that timeframes for follow-up imaging scans are achieved, so that both treatment groups can be usefully compared. Assessments must be adequate to evaluate target lesions, non-target lesions, and to search for new lesions.

PFS will be based on RECIST 1.1 response guidelines modified to use irRC-specific confirmation. PFS will be defined as the time from randomization to disease progression or death (any cause), whichever occurs first. The irRC modification requires a confirmation of progressive disease (PD) at least 4 weeks later with imaging; once confirmed, the date of progression is defined as the first date that the total tumor burden was shown to have increased by at least 20% compared with the nadir. Patients who do not have disease progression or have not died will be censored at the date when the last tumor assessment determines a lack of progression. If a patient begins a new anti-cancer therapy or has radiotherapy or surgery at a lesion site prior to confirmed progression (or death), the patient will be censored at the last assessment where the patient was documented as progression free prior to the intervention. Patients with two or more missing response assessments prior to a visit with progression (or death) will be censored at the last visit where the patient is documented to be progression free.

The primary efficacy analysis will be the evaluation of OS and PFS using Kaplan-Meier methodology and will be performed on the ITT Population for each treatment arm. Kaplan-Meier plots and 95% confidence intervals (CIs) for 75%, 50% and 25% survival, if reached, will be provided for each treatment group.

10.2.2.4.2 Secondary Efficacy Analysis

A secondary efficacy analysis will be based on the proportion of patients that are progression-free at 6 months after start of study drug treatment (Day 0). Each treatment group will be evaluated with a Simon 2-stage design (Section 10.3.1). Time-to-next-treatment and DMFS will be compared between treatment arms based on a stratified log-rank test. The Kaplan-Meier curve will summarize TTNT graphically by treatment arm. Tabular summaries of the Kaplan-Meier curves will be provided by treatment arm.

Immune response and histologic and molecular tissue changes in tumor tissue or peripheral blood will be summarized by treatment arm.

10.2.2.5 Safety

Descriptive statistics will be performed for all safety information including AEs, SAEs, laboratory findings and discontinuations of patients at all data collection timepoints. No formal statistical hypothesis will be tested.

The highest toxicity grades per patient will be tabulated for AEs and laboratory measurements, and the number and percent of patients reporting AEs (all, severe or worse, serious and related) will be quantified. Listings will be required for all on-study deaths, SAEs and AEs that lead to withdrawal from study. New SAEs experienced by patients during the Screening Period (pre-study treatment) will be reported to IMDZ if the events are considered related to study procedures and will be tabulated separately.

10.2.2.6 Exploratory

10.2.2.6.1 Overall Survival and Progression-Free Survival

Exploratory comparisons between treatment arms of OS and PFS will be based on stratified log-rank tests. Weighted log-rank tests will be explored if delayed treatment effect is observed.

Exploratory analyses of OS at 6, 12, 18, and 24 months, and PFS at 3 and 12 months will also be assessed.

10.2.2.6.2 Overall Response Rate and Duration of Response

Overall response rate is defined as the number of patients with best overall response of CR or PR divided by the number of evaluable patients.

Duration of response is defined as the time from CR or PR to progression or death, among patients with CR or PR. The DOR event and censoring rules are the same as that described

under PFS. Exploratory comparisons of the DOR will be based on stratified log-rank tests. ORR will be compared between treatment arms using a stratified logistic regression model. TGR, PAR, CBR, and quality of life will be evaluated for each group.

10.2.2.6.3 Immunogenicity

Descriptive statistics will be performed comparing the baseline and treatment administration peripheral blood NY-ESO-1-responsive T cells between the 2 treatment arms. Analyses will be performed to determine if there are any statistically significant changes from baseline values. Changes from baseline in serial anti-NY-ESO-1 antibodies will be expressed as geometric mean titers.

10.2.2.6.4 Biomarkers

Descriptive statistics will be provided for biomarkers and treatments will be compared using analysis of variance (ANOVA), or non-parametric method when appropriate, of specific genes (e.g., T-cell receptors) and/or gene-networks (e.g., signaling of immune cells) and gene modules (e.g., sets of genes [typically 100-200]) that are up- or down-regulated in concert in certain conditions or disease states (e.g., infection, autoimmunity, etc.) will be performed. Data will be used to compare the baseline with responses post-treatment. Additionally, joint models of overall survival and longitudinal biomarkers may be explored.

10.2.2.6.5 Tumor Growth Rate, Progression Arrest Rate, Clinical Benefit Rate, and Quality of Life

Tumor growth rate and PAR will be explored between treatment arms. Additionally, the relationship between TGR and OS, and PAR and OS, may be explored.

Clinical benefit rate will be explored using methods similar to that described for ORR.

Quality of life as a composite endpoint (including but not limited to the following: while on study, the incidence of hospitalization, transfusions, and laboratory markers [eg. absolute neutrophil count, hemoglobin, and platelets]) will be explored.

10.3 Interim Analysis

An exploratory analysis of the PFR at 6 months after treatment initiation will be used as a non-binding futility analysis for each treatment arm. Upon obtaining the progression status after 6 months on study from the first 36 (18 per arm) and subsequently from all enrolled patients, interim analyses will be performed and presented to the DMC, which will include estimates of PFS and assessment of PFR. Based on the assumptions in Section 10.3.1, futility guidelines at Stage 1 will be based on 18 patients and will require at least 6 patients to be progression free to

continue on to Stage 2. With an additional 22 patients at the end of Stage 2, at least 14 of the total of 40 patients should be progression free at 6 months after initial dosing to recommend further study in this setting. No formal interim analysis will be performed for efficacy. For the purposes of safety monitoring, key safety analysis will also be performed quarterly. The DMC will evaluate the available data and make necessary recommendations to the study. Details will be outlined in the DMC charter.

A final analysis will be conducted when at least 72 deaths have been observed, or sooner if the Sponsor so decides.

10.3.1 Sample Size

The median PFS for first-line chemotherapy for patients with metastatic synovial sarcoma has been reported to be 2.5 to 8.3 months; 34 PFS with atezolizumab in the post-chemotherapy setting is unknown. Thus, no power calculations based on comparisons of PFS were made. However, based on an unacceptable and desirable median PFS of 3 months and 5.2 months, respectively, corresponding PFRs at 6 months were derived. With an unacceptable PFR of 25% and an acceptable PFR of 45% at 6 months, a Simon 2-stage design will be used to examine the PFR in 40 patients in each arm ($\alpha=0.1$, $\beta=0.15$). For this study, two groups of approximately 40 patients each (approximately 80 patients total) will be dosed with CMB305 with atezolizumab or with atezolizumab alone to assess the quartiles (25%, 50%, and 75%) of PFS with 95% confidence intervals (CIs) and the PFR at 6 months. If favorable results are observed, the study may be expanded to improve the estimates of PFS.

10.4 Multiplicity

The primary analyses for this study will be the evaluation of OS and PFS using Kaplan-Meier methodology. Kaplan-Meier plots and 95% confidence intervals (CIs) for 75%, 50% and 25% survival, if reached, will be provided for each treatment arm. There will be no adjustment to multiplicity. All p values are considered nominal.

11.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Information on the CRFs will be verifiable to source documents. Other records that will be considered source documents include, but are not limited to, hospital records, clinic charts, radiographic data, laboratory reports and pathology reports. Copies of source documents that should be sent to IMDZ or its authorized representative, if requested, include hospital or clinic records, radiographic data, laboratory reports, pathology reports, operative summaries and discharge reports. Other source documentation may include hospital discharge summaries, if available, or information in lieu of a discharge summary, such as discharge orders or progress notes; any relevant notes pertaining to AEs, additional surgical procedures, or deaths and autopsy reports. Any documentation sent from the site should be redacted to exclude patient identifying information.

12.0 DATA QUALITY CONTROL AND QUALITY ASSURANCE

IMDZ performs quality assurance checks on all clinical studies that it sponsors. Prior to enrollment of any patients in this study, IMDZ or its authorized representative and the Investigator will review the Protocol, the IB, the CRFs and completion instructions, the procedure for obtaining informed consent, and AE/SAE reporting procedures. Site monitoring visits will be performed by IMDZ or its authorized representative on a regular basis pursuant to its Monitoring Plan. During these visits, information recorded on the CRFs will be verified against source documents. After the CRFs are received by IMDZ or its authorized representative, they will be reviewed for safety information, legibility, completeness, accuracy and logical consistency. The data will be entered into a database. Additional computer programs that identify selected protocol deviations, out-of-range data, and other data errors may be used to help monitor the study. As necessary, requests for clarification or correction will be sent to the Investigator.

Independent auditors from IMDZ or its authorized representative will be allowed by the Investigator to audit previously monitored data. In addition, audits may be conducted by appropriate regulatory authorities.

Data entered in the CRF will be source verified for accuracy and completeness. In addition, protocol compliance and compliance with FDA regulations and the International Conference on Harmonisation (ICH) GCP guidelines will be verified.

13.0 ETHICAL CONSIDERATIONS

13.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The Protocol and the ICFs must have the approval of a properly constituted IRB responsible for approving clinical studies. The signed IRB approval letter must specify the date of Protocol and ICF approval, and identify the approved documents including the Investigator's name and the Protocol version, date, and title. Any patient materials or advertisements used to recruit volunteers should also be reviewed and approved by the IRB. Patients should not be solicited for participation in the study and clinical supplies will not be shipped until a signed approval letter from the IRB has been received and a contractual agreement has been signed by IMDZ or its authorized representative and the clinical site.

13.2 Ethical Conduct of the Study

All investigators must have received formal training in the ethical conduct of human research. The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. All CRFs, compliance with the protocol, compliance with GCP, and compliance with the FDA's 21 CFR, as applicable, will be monitored by an independent monitor routinely at each institution participating in this trial. This process, as well as the process for the documentation of the monitoring, will be documented in detail in the Clinical Monitoring Plan Document.

13.3 Patient Information and Consent

Written informed consent must be obtained from the patient prior to performing any study-related procedures, including screening assessments. The Investigator or Investigator's designee will provide background information on the study, including the benefits and risks of the investigative regimen. The Investigator or Investigator's designee will also encourage the prospective patient to ask questions about the study and will provide the prospective patient with sufficient opportunity to consider whether or not to participate.

Original signed ICFs must be filed in the patient records at the site. A copy of the signed consent must also be provided to the patient.

The patient ICF template that has been provided for this study may be revised by the Investigator or an IRB based on the institution's requirements. However, all changes requested by the Investigator or an IRB, even those that are not substantial and/or do not affect the rights, safety or welfare of a patient, must be approved by IMDZ. If IMDZ determines that the revisions are substantial and/or affect the rights, safety or welfare of a patient, the ICF must be reviewed and approved by both IMDZ and local IRB before the ICF can be utilized.

13.4 Patient Confidentiality

Patient names shall not be revealed to IMDZ or its authorized representative. Only the patient identifier will be recorded in the CRF, and if the patient's name appears on any other document, it must be redacted and replaced with the patient identifier before a copy of the document will be supplied to IMDZ or its authorized representatives. Study findings stored on a computer will be stored in accordance with local data protection laws. In the event of accidental communication of such information, immediate steps to redact the information from all study files will be implemented, with appropriate documentation in the patient study file.

14.0 DATA HANDLING AND RECORD KEEPING

14.1 Case Report Forms

The Investigator is responsible for maintaining adequate and accurate medical records from which information will be transferred into the study database. Information on the CRF should be verifiable to source documents. The CRFs should be completed by the Investigator or delegated personnel. In the context of this protocol CRF will refer to electronic CRFs.

An eCRF will be created for each patient in the electronic data capture system. Investigator personnel will receive training pertaining to use of the database and procedures for entering patient data. Trained personnel will then complete the forms for each patient according to the provided instructions. Queries in the electronic data capture (EDC) system will be used for corrections that become necessary after data verification procedures. Completed eCRFs will be reviewed and electronically signed by the Investigator indicating his/her assurance of the accuracy of all recorded data. It is expected that the Investigator and his/her staff will cooperate with the monitoring team and provide missing data or respond to queries in a timely manner.

Only complete CRFs, reviewed and signed by the Investigator indicating his/her assurance of the accuracy of all recorded data, will be accepted. It is expected that the Investigator and his/her staff will cooperate with the monitoring team and provide any missing data or data clarifications in a timely manner. Data Clarification Forms may be used for corrections that become necessary after in-house data verification procedures.

14.2 Record Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, if required by the applicable regulatory requirements or by an agreement with

IMDZ. It is the responsibility of IMDZ to inform the Investigator/institution as to when these documents no longer need to be retained.

Essential documents are those documents, which individually and collectively, permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator, Sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.

Any or all of the documents should be available for audit by the Sponsor's auditor and inspection by the regulatory authorities.

IMDZ or its authorized representative will maintain all records related to this investigational study, according to 21 CFR §312.32 and any other local regulatory requirements. In addition, paragraph 4.9.5 of the ICH E6 guidelines applies.

15.0 FINANCING AND COMPENSATION

The financial aspects of the trial are documented in an agreement between the Sponsor and the Investigator/institution. Details regarding Sponsor-provided insurance/indemnity, patient compensation and costs to patients are documented in an agreement between the Sponsor and the Investigator/the institution. A summary of this information for the patient is also provided in the informed consent.

16.0 CHANGES IN STUDY CONDUCT

16.1 Protocol Amendments

Any amendment to the study protocol must be approved by IMDZ. A protocol amendment may not be implemented until after it has been submitted to the FDA and approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the protocol change must be documented in an amendment and reported to the IRB within 5 working days. Once a protocol amendment has received approval from IMDZ, the Investigator will submit it to the IRB for written approval. The approval letter, signed by the IRB Chair, must refer specifically to the Investigator, the protocol title, the protocol amendment number, and the date of the protocol amendment. IMDZ is responsible for submitting all protocol amendments to the FDA.

16.2 Protocol Deviation Reporting

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol, such as the accidental destruction of a tissue biopsy sample intended for immune assessment to characterize the patient's type of tumor in order to determine study

eligibility, or an accidental misread of a laboratory value as being within the reference range when it actually is sufficiently abnormal to preclude study participation by the patient.

Important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a patient's rights, safety or wellbeing such as the Investigator prescribing or administering the wrong dose, or the study patient being scheduled to return for follow-up intervention outside the protocol-dictated window as a convenience to the patient or study staff. While interpretation of inclusion/exclusion criteria can be discussed with the medical monitor, exceptions generally will not be approved without IRB approval.

There will be unforeseen circumstances that are beyond the Investigator's control (e.g., a patient not attending a scheduled follow-up visit). Prior approval will not be granted in these situations, but the Investigator should report these events upon determining that a deviation has occurred.

The Investigator is responsible for complying with and adhering to IRB procedures for reporting protocol deviations and violations. All protocol deviations should be documented and forwarded to IMDZ or its authorized representative.

Protocol deviations will be collected during the study, and reported by IMDZ or its authorized representative to the FDA and IRBs yearly in the annual report. Participating investigators will receive regular updates regarding their site's deviations.

17.0 PUBLICATION POLICY

It is expected that the results of this study will be published in a peer-reviewed journal. A publication plan for the primary results will be discussed with the PIs and established before the start of the trial. Any manuscripts reporting the results of this clinical trial must be provided to the Sponsor by the Principal Investigator for review and comment prior to submission for publication. IMDZ will have 30 days from the date of receipt for review, and shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that the Sponsor's confidential and proprietary data, in addition to the Sponsor's intellectual property rights, are protected. Abstracts, press releases, and other media presentations must also be forwarded to the Sponsor prior to release. No publication, manuscript, or other form of public disclosure shall contain any of the Sponsor's confidential/proprietary information. Co-authorship of subsequent publications with IMDZ personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

18.0 REFERENCES

1. Gnjatic S, Nishikawa H, Jungbluth AA, Gure AO, Ritter G, Jager E, et al. NY-ESO-1: review of an immunogenic tumor antigen. *Adv Cancer Res.* 2006; 95: 1-30.
2. Cheever MA, Allison JP, Ferris AS, Finn OJ, Hastings BM, Hecht TT, et al. The prioritization of cancer antigens: a national cancer institute pilot project for the acceleration of translational research. *Clin Cancer Res.* 2009; 15(17):5323-5337.
3. Jungbluth AA, Antonescu CR, Busam KJ, Iversen K, Kolb D, Coplan K, et al. Monophasic and biphasic synovial sarcomas abundantly express cancer/testis antigen NY-ESO-1 but not MAGE-A1 or CT7. *Int J Cancer.* 2001; 94(2):252-256.
4. Jungbluth AA, Chen YT, Stockert E, Busam KJ, Kolb D, Iversen K, et al. Immunohistochemical analysis of NY-ESO-1 antigen expression in normal and malignant human tissues. *Int J Cancer.* 2001; 92(6):856-860. Erratum in: *Int J Cancer.* 202; 97(6):878.
5. Nicholaou T, Ebert L, Davis ID, Robson N, Klein O, Maraskovsky E, et al. Directions in the immune targeting of cancer: lessons learned from the cancer-testis Ag NY-ESO-1. *Immunol Cell Biol.* 2006; 84(3):303-317.
6. Investigator's Brochure for CMB305: LV305 and G305 Sequential Regimen. Immune Design Corp. Version 01. 27 September 2014.
7. Taren SU, Kelley-Clarke B, Nicolai CJ, Cassiano LA, Nelson LT, Slough MM, et al. Design of a novel integration-deficient lentivector technology that incorporates genetic and posttranslational elements to target human dendritic cells. *Mol Ther.* 2014; 22(3):575-587.
8. Fratta E, Coral S, Covre A, Parisi G, Colizzi F, Danielli R, et al. The biology of cancer testis antigens: putative function, regulation and therapeutic potential. *Mol Oncol.* 2011; 5(2):164-182.
9. Dai B, Yang L, Yang H, Hu B, Baltimore D, Wang P. HIV-1 Gag-specific immunity induced by a lentivector-based vaccine directed to dendritic cells. *Proc Natl Acad Sci USA.* 2009; 106(48):20382-20387.
10. Somaiah N, Block MS, Kim JW, Shapiro G, Hwu P, Eder JP, et al. Phase 1 First-in-Human Trial of LV305 in Patients With Advanced or Metastatic Cancer Expressing NY-ESO-1. Poster session presented at: The American Society of Clinical Oncology (ASCO) Annual Meeting; 2015 May 29 – 2015 Jun 02; Chicago, IL.

11. Mahipal, A, Odunsi K, Gnjatic S, Kim-Schulze S, Kenney R, Ejadi S. A First-in-Human Phase 1 Dose-escalating Trial of G305 in Patients with Solid Tumors Expressing NY-ESO-1. Poster session presented at: The American Society of Clinical Oncology (ASCO) Annual Meeting; 2015 May 29 – 2015 Jun 02; Chicago, IL.
12. Pedoeem A, Azoulay-Alfaguter I, Strazza M, Silverman GJ, Mor A. Programmed death-1 pathway in cancer and autoimmunity. *Clin Immunol.* 2014; 153(1):145-152.
13. Karim R, Jordanova ES, Piersma SJ, Kenter GG, Chen L, Boer JM, et al. Tumor-expressed B7-H1 and B7-DC in relation to PD-1+ T-cell infiltration and survival of patients with cervical carcinoma. *Clin Cancer Res.* 2009; 15(2):6341-6347.
14. Taube JM, Anders RA, Young GD, Xu H, Sharma R, McMiller TL, et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med.* 2012;4(127):127ra37.
15. Sanmamed MF and Chen L. Inducible expression of B7-H1 (PD-L1) and its selective role in tumor site immune modulation. *Cancer J.* 2014; 20(4):256-261.
16. Butte MJ, Keir ME, Phamduy TB, Sharpe AH, Freeman GJ. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. *Immunity.* 2007; 27(1):111-122.
17. Yang J, Riella LV, Chock S, Liu T, Zhao X, Yuan X, et al. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. *J Immunol.* 2011; 187(3):1113-1119.
18. van den Eertwegh AJ, Versluis J, van den Berg HP, et al. Combined immunotherapy with granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells and ipilimumab in patients with metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. *Lancet Oncol* 2012;13:509-17.
19. Madan RA, Mohebtash M, Arlen PM, Vergati M, Rauckhorst M, Steinberg SM, et al. (2012). Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. *Lancet Oncol* 13(5):501–810.
20. Pham NL, Badovinac VP, and Harty JT. A default pathway of memory CD8 T cell differentiation after dendritic cell immunization is deflected by encounter with inflammatory cytokines during antigen-driven proliferation. *J Immunol.* 2009; 183(4):2337-2348.
21. Mellman I, Coukos G, and Dranoff G. Cancer immunotherapy comes of age. *Nature.* 2011; 480(7378):480-489.

22. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci USA*. 2002; 99(19):12293-12297.
23. Strome SE, Dong H, Tamura H, Voss SG, Flies DB, Tamada K, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. *Cancer Res*. 2003; 63(19):6501-6505.
24. Herbst RS, Gordon MS, Fine GD, Sosman JA, Soria JC, Hamid O, *et al*. A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors. Presented at: The American Society of Clinical Oncology (ASCO) Annual Meeting 2013; Abstract 3000.
25. Coler RN, Bertholet S, Moutaftsi M, Guderian JA, Windish HP, Baldwin SL, et al. Development and characterization of synthetic glucopyranosyl lipid adjuvant system as a vaccine adjuvant. *PLoS ONE*. 2011; 6(1):e16333.
26. US Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research. Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials. September 2007.
27. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009; 15(23):7412-7420.
28. Verweij J. Other endpoints in screening studies for soft tissue sarcomas. *Oncologist* 2008;13 Suppl 2:27-31.
29. US Department of Health and Human Sciences. National Institutes of Health. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. June 14, 2010.
30. Salah S, Yaser S, Salem A, Al Mousa A, Abu Sheikha A, Sultan I. Factors influencing survival in metastatic synovial sarcoma: importance of patterns of metastases and the first-line chemotherapy regimen. *Med Oncol*. 2013; 30(3):639.
31. Tripathi S, Guleria I. Role of PD1/PDL1 pathway, and TH17 and treg cells in maternal tolerance to the fetus. *Biomed J* 2015;38:25-31.
32. Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. Published June 27, 2014. Available from <http://stacks.cdc.gov/view/cdc/23447>.

33. De Ravin S, Gray JT, Throm RE, et al. False-Positive HIV PCR Test Following Ex Vivo Lentiviral Gene Transfer Treatment of X-linked Severe Combined Immunodeficiency Vector, *MolTher* 2014; 22:244.
34. Salah S, Yaser S, Salem A, Al Mousa A, Abu Sheikha A, Sultan I. Factors influencing survival in metastatic synovial sarcoma: importance of patterns of metastases and the first-line chemotherapy regimen. *Medical oncology* 2013;30:639.
35. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*. 1989; 10(1):1-10.
36. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982; 5(6): 649-655.
37. Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. *Clin Cancer Res*. 2013; 19(14): 3936-3943.
38. Nishino M, Gargano M, Suda M, Ramaiya NH, Hodi FS. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab. *J Immunother Cancer* 2014;2:17.
39. Di Giacomo AM, Biagioli M, Maio M. The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. *Seminars in oncology* 2010;37:499-507.
40. Hejblum G, Lambotte O, Galicier L, et al. A web-based delphi study for eliciting helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients. *PloS one* 2014;9:e94024.
41. Teachey DT, Rheingold SR, Maude SL, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. *Blood* 2013;121:5154-7.
42. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;124:188-95.
43. Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer J* 2014;20:119-22.

APPENDICES

Appendix A ECOG Performance Status

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

*As published in Oken et al.³⁶

Appendix B Medical Events of Interest

MEOIs, also known as AEs of special interest (AESIs), for therapeutic oncology vaccines are largely inflammatory and autoimmune syndromes, including:

Neurologic

- Demyelinating conditions
 - Optic Neuritis
 - MS
 - Myelitis
 - Uveitis
- Encephalitis
- Guillan Barre Syndrome
- Bell's palsy
- Narcolepsy
- Myasthenia Gravis

Connective Tissue Disorders

- Inflammatory monoarthritis or polyarthritis
- Systemic lupus erythematosus
- Polymyositis or Dermatomyositis
- Sjogren's syndrome

Gastrointestinal Disorders

- Crohn's Disease
- Ulcerative colitis
- Other inflammatory bowel disease

Immune System Disorders

- Immune Thrombocytopenic Purpura
- Coomb's positive hemolytic anemia
- Psoriasis
- Erythema nodosum
- Alopecia
- Steven's Johnson Syndrome
- Vitiligo

Thyroid Disorders

Grave's Disease
Hashimoto's thyroiditis

Renal and Urinary Disorders

Nephritis
Hematuria

Vascular

Cutaneous vasculitis
Temporal arteritis
ANCA-Associated granulomatous polyangiitis
Coronary arteritis

Cardiac

Carditis
Pericarditis

Appendix C RECIST and Immune-Related Response Criteria

For this study, both RECIST v1.1 and RECIST-based irRC data will be collected but only irRC will be used to determine disease progression. Full RECIST definitions are included in the Study Reference Manual.

The irRC was originally developed using the World Health Organization (WHO) tumor response measurement criteria where bidimensional measurements were used to define tumor burden.²⁷ In solid cancers, RECIST is now more commonly used. RECIST uses the sum of the longest unidimensional measurement of tumor lesions as the basis of its criteria. Many have now adopted a modified RECIST-based irRC as the criteria used to measure the effect of immunotherapeutic approaches in solid cancers (see comparisons below). Nishino, *et al* prospectively examined the impact of using bidimensional vs. unidimensional measurements.³⁷ They concluded that irRC using the unidimensional measurements provided highly concordant response assessment compared with the bidimensional irRC, with less measurement variability and recommended the use of unidimensional irRC to assess response to immunotherapy in solid tumors.

Appendix Table 1 Summary of Measurement and Response Assessment Approaches for Bidimensional and Unidimensional Assessment Based on irRC

	Bidimensional assessment (the original irRC)	Unidimensional assessment
Measurable lesions	≥5 x 5 mm ² by bidimensional measurements	≥10 mm in the longest diameter
Measurement of each lesion	The longest diameter x the longest perpendicular diameter (cm ²)	The longest diameter (cm)
The sum of the measurements	The sum of the bidimensional measurements of all target lesions and new lesions if any	The sum of the longest diameters of all target lesions and new lesions if any
Response assessment	PD: ≥25% increase from the nadir PR: ≥50% decrease from baseline CR: Disappearance of all lesions	PD: ≥20% increase from the nadir PR: ≥30% decrease from baseline CR: Disappearance of all lesions
New lesions	The presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements.	

Confirmation Confirmation by 2 consecutive observations not less than 4 weeks apart was required for CR, PR, PD

As published in Nishino et al.³⁷

Nishino *et al.* went on to study the impact of reducing the number of target lesions to optimize the approach and found this did not significantly affect immune-related response assessment or measurement variability.³⁸ Their results show that using up to 2 target lesions per organ and up to 5 target lesions in total may be sufficient for immune-related response assessment, as long as the important features of irRC such as confirmation of progression and inclusion of new lesion measurements are kept. Decreasing the number of target lesions may also help to increase the practicality of immune-related response assessment. For this trial, the RECIST v1.1-based irRC will be used according to this optimized strategy.

Appendix Table 2 Summary of measurement approaches for two assessments

	irRC simulating RECIST 1.0	irRC simulating RECIST 1.1
Number of target lesions	Up to 5 per organ, up to 10 in total	Up to 2 per organ, up to 5 in total
Measurable lesions	≥10 mm in the longest diameter for all lesions	≥10 mm in the longest diameter for all lesions except for lymph nodes ≥15 mm in short axis for nodes
Measurement of each lesion	The longest diameter for all target lesions	The longest diameter for non-nodal lesions, short axis for lymph nodes
New lesions	The presence of new lesion does not define progression The measurements of the new lesion (s) are included in the sum of the measurements Up to 5 new lesions per organ, up to 10 new lesions in total can be added to measurements	Same as irRC simulating RECIST 1.0 except: A lymph node has to be ≥15 mm in the short axis to be a measurable new lesion and its short axis measurement is included in the sum Up to 2 new lesions per organ, up to 5 new lesions

As published in Nishino et al.³⁸

Appendix D Comparison of RECIST v1.1 vs. RECIST-based irRC

	RECIST v1.1	RECIST-based irRC
New, Measurable lesions (≥ 10 mm)	Recorded as PD	Incorporated into tumor burden (see Appendix C)
New, non-measurable lesions (< 10 mm)	Recorded as PD	Do not define progression (but preclude irCR)
Non-Target Lesions	Contributes to best overall response (CR, PR, SD, PD)	Contribute to irCR (complete disappearance required)
CR	Disappearance of all lesion in 2 consecutive observations ≥ 4 weeks apart	Disappearance of all lesions in 2 consecutive observations ≥ 4 weeks apart
PR	$\geq 30\%$ decrease in sum of the longest diameter of all index lesions compared with baseline in 2 observations ≥ 4 weeks apart, in the absence of new lesions or unequivocal progression of non-index lesions	$\geq 30\%$ decrease in tumor burden compared with baseline in 2 observations ≥ 4 weeks apart
SD	Neither sufficient shrinkage to qualify for PR or increase to qualify for PD when compared to the smallest sum of diameters while on study	30% decrease in tumor burden compared with baseline cannot be established nor 20% increase when compared with nadir
PD	$\geq 20\%$ increase in the sum of the diameters of the target lesions when compared to the smallest sum while on study. The sum must also demonstrate an absolute increase of ≥ 5 mm. The appearance of ≥ 1 new lesion is considered PD	$\geq 20\%$ increase in tumor burden compared with nadir (at any single timepoint) in 2 consecutive measurements ≥ 4 weeks apart.

CR = complete response; irRC = immune-related response criteria; irCR = immune-related complete response; PD = progressive disease; PR = partial response; RECIST = response evaluation criteria in solid tumors; SD = stable disease.

Overall Response Using the irRC

The overall response according to the irRC is derived from timepoint response assessments (based on tumor burden) as follows:

- Immune-related complete response (irCR): complete disappearance of all lesions (whether measurable or not, and no new lesions) and confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented
- Immune-related partial response (irPR): decrease in tumor burden $\geq 30\%$ relative to baseline and confirmed by a consecutive assessment at least 4 weeks after first documentation
- Immune-related Stable Disease (irSD): not meeting criteria for irCR or irPR, in absence of irPD
- Immune-related Progressive Disease (irPD): increase in tumor burden $\geq 20\%$ relative to nadir (minimum recorded tumor burden) and confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

Appendix E Preexisting Autoimmune Diseases

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Acute disseminated encephalomyelitis	Dermatomyositis	Neuromyotonia
Addison's disease	Dysautonomia	Opsoclonus myoclonus syndrome
Ankylosing spondylitis	Epidermolysis bullosa acqvista	Optic neuritis
Antiphospholipid antibody syndrome	Gestational pemphigoid	Ord's thyroiditis
Aplastic anemia	Giant cell arteritis	Pemphigus
Autoimmune hemolytic anemia	Goodpasture's syndrome	Pernicious anemia
Autoimmune hepatitis	Graves' disease	Polyarteritis nodosa
Autoimmune hypoparathyroidism	Guillain-Barré syndrome	Polyarthritis
Autoimmune hypophysitis	Hashimoto's disease	Polyglandular autoimmune syndrome
Autoimmune myocarditis	IgA nephropathy	Primary biliary cirrhosis
Autoimmune oophoritis	Inflammatory bowel disease	Psoriasis
Autoimmune orchitis	Interstitial cystitis	Reiter's syndrome
Autoimmune thrombocytopenic purpura	Kawasaki's disease	Rheumatoid arthritis
Behcet's disease	Lambert-Eaton myasthenia syndrome	Sarcoidosis
Bullous pemphigoid	Lupus erythematosus	Scleroderma
Chronic inflammatory demyelinating polyneuropathy	Lyme disease - chronic	Sjögren's syndrome
Chung-Strauss syndrome	Meniere's syndrome	Stiff-Person syndrome
Crohn's disease	Mooren's ulcer	Takayasu's arteritis
	Morphea	Ulcerative colitis
	Multiple sclerosis	Vogt-Kovanagi-Harada disease
	Myasthenia gravis	Wegener's granulomatosis

Appendix F Dose Modification and Supportive Care Guidelines for Atezolizumab

As of May 2015, atezolizumab has been administered to approximately 3200 patients with solid tumors and hematologic malignancies. In addition to studies presented in the previous sections, safety information for atezolizumab is also gleaned from studies in the entire development program, including those where atezolizumab is investigated in combination with other unapproved agents.

Study PCD4989g, in which atezolizumab is being used as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies, provides the majority of data (with 558 safety evaluable patients as of the data extraction date of 11 May 2015) for the safety profile of atezolizumab as monotherapy. Currently, no maximum tolerated dose, no dose-limiting toxicities and no clear dose-related trends in the incidence of AEs have been determined.

In trials investigating the combinations of atezolizumab with bevacizumab and/or chemotherapies, cobimetinib, or vemurafenib, the incidence of AEs in the treatment arms with combined use was consistent with the known safety profiles of the individual study drugs. Fatigue, decreased appetite, nausea and cough were commonly reported adverse events in single and combination therapy. The overall immune mediated adverse events reported for atezolizumab were considered moderate in severity and majority of patients were able to continue on atezolizumab therapy.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications.³⁹ A summary of identified risks for atezolizumab is presented in Appendix Table 3.

Appendix Table 3 Summary of Identified Risks of Atezolizumab

Identified Risk	Description of Risk
Colitis	Serious reports of biopsy confirmed colitis have been reported in less than 0.5% of patients who received single agent atezolizumab. The events were of Grade 2 or 3 in severity and the majority of reported colitis resolved following treatment. Patients continued to receive atezolizumab despite the event. Diarrhea (19.7%) has been reported with single agent atezolizumab. These events were considered mild to moderate and resolved without treatment.
Dermatologic reactions	Dermatologic reactions have been reported in 42% of patients receiving single agent atezolizumab. Reactions have been mild to moderate (<1% reported as severe). Commonly reported events in PCD4989g include rash (15%), pruritus (13%), dry skin (7%), maculopapular rash (6%), night sweats (6%) and erythema (3%). Alopecia, dermatitis acneiform, dermatitis psoriaiform, vitiligo, seborrheic dermatitis, lichen planus, bullous dermatitis and skin pigmentation changes have also been reported less commonly.
Endocrine disorders	Adrenal insufficiency has been observed in 0.2% of patients receiving single agent atezolizumab, and in <2% of patients receiving atezolizumab in combination with other chemotherapy. Associated laboratory parameters such as hyponatremia and hypokalemia were observed in <1 % of patients receiving single agent atezolizumab, and hyponatremia was observed in 1.6% of patients receiving atezolizumab in combination with chemotherapy. Hypothyroidism events have been reported in up to 6% of patients receiving atezolizumab across the clinical program. The majority of events were reported in patients receiving single agent atezolizumab. Events have generally been mild and patients who received treatment with thyroid replacement were able to continue on study treatment. Hyperthyroidism events have occurred in 0.7% of patients receiving single agent atezolizumab. The majority of patients with hyperthyroidism appear to be asymptomatic. Patients received treatment with anti-thyroid agents and were continued on study treatment.
Hepatitis	In patients receiving atezolizumab as a single agent, hepatitis and elevations of alkaline phosphatase, AST and ALT have been reported in 0.5%, 4.1%, 6.1% and 5.6% of patients, respectively. In the clinical program, <1% of patients experienced serious adverse events of hepatobiliary disorders including autoimmune hepatitis (5), hepatitis (3), and the following (1 patient each): drug induced liver injury, hepatic failure, abnormal hepatic function, hepatocellular injury, and liver disorder.
Hypersensitivity	Hypersensitivity reactions including allergic and anaphylactic reactions have been reported in <1% of patients receiving single agent. Outcomes for these events were considered resolved. Patients may present with complaints such as flushing, fever, chills, blood pressure change, tachycardia or shortness of breath
Influenza-like illness	Influenza like illness has been reported in patients receiving atezolizumab as a single agent in PCD4989g (7.3%). Events associated with influenza like illness were primarily observed one to two weeks after receiving the first cycle. Reactions have included fever, fatigue, asthenia, chills, myalgia, arthralgia and headache. The events have been mild to moderate in severity.

Identified Risk	Description of Risk
Infusion-related reactions	Symptoms may present within 30 minutes to 24 hours after infusion, are generally mild and manageable, and wane with subsequent infusions. With single agent atezolizumab, IRRs have been reported in 0.4% of patients. The most common symptoms reported with single agent use within 24 hours of the first cycle were pyrexia, fatigue, nausea, hypertension, headache and diarrhea.
Neurologic disorders	Myasthenia gravis and Guillain-Barré syndrome have been observed in less than 1% of patients taking atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Meningitis (non-infectious) has also been reported in <1% of patients. Patients with meningitis may present with altered mental status, confusion, headache, or fever. Diagnostic work-up is essential for an accurate characterization to differentiate between alternate etiologies.
Pneumonitis	Pneumonitis has been reported in 1.4% of patients receiving single agent atezolizumab. These events have been primarily observed in patients with lung cancer. Four fatal reports of pneumonitis have been reported. Patients may present with dyspnea, hypoxia or other respiratory complication. Diagnostic work-up is essential for an accurate characterization to differentiate between alternate etiologies such as infection, pulmonary embolism or underlying disease.

ALT=alanine transaminase; AST=aspartate transaminase; IRR=infusion-related reactions.

Note: This table is based on single agent data from Study PCD4989g as of the data extraction date of 11 May 2015 in 558 treated patients. The information is also based on a review of safety information across the atezolizumab development program as of the cutoff date for this version of the IB. Single-agent studies include GO28753, GO28754, GO28625, GO28915 and GO29293. Combination studies include WO29074, GO29322, and GP28328.

When the IB is used as the Reference Safety Information, the Appendix Table 4 provides a list of the adverse drug reactions (ADRs), which are considered “expected” for regulatory reporting purposes by the Sponsor. Descriptions of the risks associated with each of the listed ADRs are summarized in Appendix Table 3, including population exposed to the IMP, and intensity and frequency of the risk (where available).

The classification of an AE as an ADR is based on data available at the time of assessment. Data obtained at later dates may refute the connection between an AE and atezolizumab, and lead to an ADR being subsequently reclassified as an AE. Guidelines for management of these events are provided above.

Appendix Table 4 Expected Adverse Drug Reactions for Atezolizumab in All Indications for Regulatory Reporting Purposes Only

Risk	Notes/Exclusions
Gastrointestinal Disorders	Includes colitis, diarrhea, dysphagia, nausea, vomiting, abdominal pain and decreased appetite
Dermatologic reactions	Includes rash and pruritus
Endocrine disorders	Includes hyperthyroidism, hypothyroidism and adrenal insufficiency
Hepatitis^a	Includes ALT increased, AST increased, and hepatic enzymes abnormal
Hypersensitivity reactions/ Infusion-related Reactions	
Influenza-like illness	Includes arthralgia, musculoskeletal pain, asthenia, chills, fever, fatigue, and nasal congestion
Nervous system disorders	Includes meningitis, Guillain-Barré syndrome, myasthenic syndrome
Pneumonitis^a	Includes dyspnea and hypoxia
General and Metabolic disorders	Includes hyponatremia , hypokalemia, and insomnia
Vascular disorders	Includes hypertension and hypotension

^a Includes fatal events.

Note: Any term covered by the medical concepts presented in this list is considered “expected” for both non-serious and serious reports of suspected unexpected ADRs to Health Authorities, excluding events with fatal outcome unless detailed otherwise in the table.

The classification of an AE as a potential risk is based on the mechanism of action of atezolizumab, pre-clinical findings, as well as other agents with similar mechanisms of action. As of the cutoff date for the data included below, the safety profile remains consistent based on the known mechanism of action of atezolizumab. The potential risks associated with atezolizumab are summarized in Appendix Table 5, followed by guidelines for the management of these atezolizumab-specific AEs.

Appendix Table 5 Summary of Important Potential Risks of Atezolizumab

Potential Risk	Description of Risk
Anti-therapeutic Antibodies	ATAs have been observed in patients in the ongoing clinical program in multiple tumor types. The number of patients in the single arm study, PCD4989g, with a sample that showed positive ATA at baseline was consistent across dose groups with a prevalence rate ranging from 2.2-3.4%. The post-baseline ATA incidence ranged from 9.1-39.5% across different dosing groups, each with varied sample size. No consistent relationship has been observed between the ATA responses and PK, adverse events, or therapeutic activity. Monitoring and characterization of ATAs is ongoing for all clinical studies of atezolizumab.
Myopathies	Myositis (1 patient), myopathy (1 patient), and rhabdomyolysis (2 patients) have been reported across the clinical development program of atezolizumab. Patients who present with signs or symptoms of muscular pain should be assessed for inflammatory causes for muscle pains. Management of these patients should be along institutional guidelines.
Nephritis	Nephritis is a concern given the mechanism of action of atezolizumab and findings from other immune modulating agents. A single report of Grade 2 nephritis was observed in a patient treated with vemurafenib and atezolizumab, which was treated with prednisone with resolution. The patient had a history of hypertension, and concomitant medication included hydrochlorothiazide/losartan.
Other Endocrinopathies	Diabetes and pancreatitis are concerns given the mechanism of action of atezolizumab. Diabetes mellitus or hyperglycemia has been observed in 0.7% of patients in the PCD4989g study. In some cases, diabetes mellitus was a pre-existing condition. Pancreatitis has been observed in less than 1% of patients receiving atezolizumab in the PCD4989g study.
Systemic Immune Activation	Excessive activation of the immune system is a potential risk associated with atezolizumab, and has been observed when atezolizumab is used in combination with other immune modulating agents. One patient participating in Study BP29392 (atezolizumab in combination with RO7009789 [CD40 agonist]) developed SIA after the first cycle. In this study, CD40 agonist was administered first, followed by atezolizumab 6 weeks later. The patient developed autoimmune hemolytic anemia and pneumonitis 12 days after the first dose of atezolizumab with subsequent development of acute renal failure during hospitalization. Treatment with high dose steroids and supportive care was administered with resolution of events.

ATA=anti-therapeutic antibodies; SIA=systemic immune activation.

Note: This table is based on single agent data from Study PCD4989g as of 10 May 2015 in 558 treated patients. The information is also based on a review of serious adverse events and non-serious adverse events of special interest across the atezolizumab development program as of 10 May 2015. Single-agent studies include GO28753, GO28754, GO28625, GO28915 and GO29293. Combination studies include WO29074, GO29322, and GP28328.

Management of Atezolizumab-Specific Adverse Events

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

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

The investigator should consider the benefit-risk balance a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening immune-mediated adverse events. For the management of other adverse events associated with atezolizumab not provided in the following discussion, refer to the Atezolizumab IB.

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, or chronic obstructive pulmonary disease, or pulmonary hypertension:

- 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 (diffusion capacity of the lung for carbon monoxide [DL_{CO}])
- Pulmonary function testing with a pulmonary embolism protocol

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.

Appendix Table 6 Guidelines for Management of Atezolizumab-Associated Pulmonary Toxicity

Pulmonary Events/ Pneumonitis	Severity	Management
	Grade 1	<ul style="list-style-type: none"> • May continue atezolizumab with close monitoring • Re-evaluate on serial imaging • Consider pulmonary consultation
	Grade 2	<ul style="list-style-type: none"> • Withhold atezolizumab • Pulmonary and ID consultation with consideration for bronchoscopy/BAL • Start 60 mg prednisone or equivalent per day • When improves to Grade 0 or Grade 1, then taper steroids over ≥ 1 month • Atezolizumab may be resumed if the event improves to Grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less. • Treat as Grades 3-4 if recurrent episode of pneumonitis
	Grade 3 and 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab • Bronchoscopy/BAL is recommended • Start 60 mg prednisone or equivalent per day. • Taper steroids over ≥ 1 month once symptoms improve to Grade 0 or 1. • If not improving after 48 hours or worsening: add additional immunosuppression (e.g., infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil) • Contact Medical Monitor if atezolizumab is discontinued

BAL=bronchoscopic alveolar lavage; ID=infectious diseases; IVIG=intravenous immunoglobulin

Hepatic Events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment.

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

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

antibodies, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered.

Appendix Table 7 Management Guidelines for Hepatic Events

Hepatic events	Severity	Management
	Grade 1	<ul style="list-style-type: none"> • Continue therapy • Continue LFT monitoring
	Grade 2	<ul style="list-style-type: none"> • Monitor LFTs more frequently until return to baseline values • If persists $\geq 5-7$ days: withhold therapy and start 60 mg prednisone or equivalent per day; when LFTs are \leq Grade 1, taper steroids over ≥ 1 month, resume therapy if the event improves to Grade 0 or Grade 1 within 12 weeks and systemic steroid dose is ≤ 10mg oral prednisone equivalent per day
	Grade 3 and 4	<ul style="list-style-type: none"> • Discontinue therapy • Consider GI consult and liver biopsy to establish etiology of hepatic injury if necessary • Start 60 mg prednisone or equivalent per day • If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) may be considered. • Taper steroids over ≥ 1 month, when symptoms improve to Grade 0 or 1 • Contact Medical Monitor if atezolizumab is discontinued

GI=gastrointestinal; LFT=liver function test; TNF- α =tumor necrosis factor alpha.

Gastrointestinal Events

Immune-mediated colitis has been associated with the administration of atezolizumab.

If the event is of significant duration or magnitude or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia), the following are recommended:

- Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with 3 to 5 specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates for confirmation of the diagnosis of colitis. If possible, one or two biopsy specimens should be snap-frozen and stored.
- Perform laboratory tests to rule out alternate etiology (i.e., WBCs and stool calprotectin).

Appendix Table 8 Management Guidelines for GI Events (Diarrhea/ Colitis)

GI Events (Diarrhea/Colitis)	Severity	Management
	Grade 1 diarrhea or colitis	<ul style="list-style-type: none"> • Continue therapy • Symptomatic treatment • Endoscopy is recommended if symptoms persist for greater than 7 days. • Close monitoring
	Grade 2 diarrhea or Grade 2 colitis	<ul style="list-style-type: none"> • Withhold atezolizumab • Symptomatic therapy • GI consultation recommended • If persists <input type="checkbox"/> 5 days or recurs: Prednisone 60 mg/day or equivalent • Taper steroids over <input type="checkbox"/> 1 month when symptoms improve to Grade 0 or 1 • Treatment may be resumed if the event improves to Grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of prednisone 10 mg PO daily or less.
	Grade 3 diarrhea or colitis	<ul style="list-style-type: none"> • Withhold atezolizumab • GI referral and confirmation biopsy • Treat with IV steroids (1-2 mg/kg/day methylprednisolone or equivalent) and convert to oral steroids (prednisone 60 mg/day or equivalent) after improvement • When improves to Grade 0 or 1, then taper steroids over \geq 1 month • Treatment may be resumed if the event improves to Grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less.
	Grade 4 diarrhea or colitis	<ul style="list-style-type: none"> • Discontinue atezolizumab • GI referral and confirmation biopsy • Treat with IV steroids (1-2 mg/kg/day methylprednisolone or equivalent) and convert to oral steroids (prednisone 60 mg/day or equivalent) once improvement • When patient's diarrhea or colitis improves to Grade 0 or 1, then taper steroids over \geq 1 month • If not improving after 48h of initiating steroids or worsening, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) may be considered. • Contact medical monitor if atezolizumab is discontinued.

GI=gastrointestinal; PO=per oral; TNF- α =tumor necrosis factor alpha.

Endocrine Events

Thyroid disorders or adrenal insufficiency 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. TSH and free thyroxine (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.

Appendix Table 9 Management Guidelines for Endocrine Events

Endocrine Events	Severity	Management
	Asymptomatic hypothyroidism	<ul style="list-style-type: none"> Continue atezolizumab Start thyroid replacement hormone Monitor TSH weekly
	Symptomatic hypothyroidism	<ul style="list-style-type: none"> Withhold atezolizumab Start thyroid replacement hormone Consider referral to an endocrinologist Restart atezolizumab when symptoms are controlled by thyroid replacement and TSH levels are decreasing
	Asymptomatic hyperthyroidism	<ul style="list-style-type: none"> If serum TSH \square 0.5mU/L, repeat with free T4 and T3 to diagnose asymptomatic hyperthyroidism If confirmed, and in the absence of symptoms, continue atezolizumab and repeat tests in 4 weeks If thyroid values remain stable and patient is asymptomatic, follow lab results monthly Hold atezolizumab if TSH \square \leq 0.1mU/L or if patient develops symptomatic hyperthyroidism Consider referral to an endocrinologist and treat according to symptomatic hyperthyroidism guidelines
	Symptomatic hyperthyroidism	<ul style="list-style-type: none"> Withhold atezolizumab Start methimazole as needed Consider referral to an endocrinologist Restart atezolizumab when symptoms are controlled by thyroid replacement Permanently discontinue atezolizumab for life threatening immune-mediated hyperthyroidism.

Endocrine Events (cont.)	Severity	Management
	Symptomatic pan-hypopituitarism and any Grade 3-4 events	<ul style="list-style-type: none"> • Discontinue atezolizumab. • Endocrinologist consultation • Perform appropriate imaging. • Treat with an initial dose of methylprednisolone 1–2 mg/kg per day IV followed by oral prednisone 1–2 mg/kg per day. • Start steroid taper when symptoms improve to Grade 0 or Grade 1. Taper over > 1 month. • Patients with unexplained symptoms such as fatigue, myalgia, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathy as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if a symptomatic endocrinopathy is suspected. 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. • Contact the Medical Monitor if atezolizumab is discontinued.

T4=thyroxine; TSH=thyroid stimulating hormone.

Ocular Events

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.

Appendix Table 10 Management Guidelines for Ocular Events

Eye Events	Severity	Management
	Grades 1-2	<ul style="list-style-type: none"> • Evaluation by an ophthalmologist is strongly recommended • Treat with topical corticosteroid eye drops • Discontinue atezolizumab if symptoms persist despite treatment with topical immunosuppressive therapy • Topical immunosuppressive therapy. • Contact the Medical Monitor if atezolizumab is discontinued
	Grade 3-4	<ul style="list-style-type: none"> • Discontinue treatment • Start 60 mg prednisone or equivalent per day. • Taper steroids over □1 month once symptoms improve to Grade 0 or 1 • Contact the Medical Monitor if atezolizumab is discontinued

Infusion-Related Reactions

No premedication is indicated for the administration of atezolizumab in Cycle 1. Patients who experience an infusion-related reaction (IRR) with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions.

Appendix Table 11 Management Guidelines for Infusion-Related Reactions

Infusion Reactions	Severity	Management
	Grade 1	<ul style="list-style-type: none"> • Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate • If tolerated, the infusion rate may then be increased to original rate
	Grade 2	<ul style="list-style-type: none"> • Interrupt atezolizumab infusion • Administer aggressive symptomatic treatment. • Restart 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 • At next cycle, administer oral premedication with antihistamine and anti-pyretic and monitor closely for infusion reaction
	Grades 3 - 4	<ul style="list-style-type: none"> • Stop infusion • Proper medical management which may include oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen • Discontinue atezolizumab • Contact the Medical Monitor, if atezolizumab is discontinued.

IRR = infusion-related reactions.

Pancreatic Events

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

Appendix Table 12 Management Guidelines for Pancreatitis

Pancreatic events	Severity	Management
	Grade 1 amylase/lipase elevation	<ul style="list-style-type: none"> • Continue atezolizumab • Monitor amylase/lipase levels prior to dosing
	Grade 2 amylase/lipase elevation	<ul style="list-style-type: none"> • Continue atezolizumab • Monitor amylase/lipase weekly • Consider prednisone 10 mg PO daily or equivalent for prolonged elevation (e.g., more than 3 weeks)
	Grade 3 and 4 amylase/lipase elevation	<ul style="list-style-type: none"> • Withhold atezolizumab • Consult a gastroenterologist • Monitor amylase/lipase every other day and consider oral prednisone 60 mg daily or equivalent if no improvement • When lab abnormalities return to Grade 0 or 1, then taper steroids over \geq 1 month • Atezolizumab may be resumed if the event resolves to Grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less • Permanently discontinue atezolizumab for recurrent Grade 3 or 4 amylase/lipase elevations
	Autoimmune pancreatitis (abdominal pain and raised amylase/lipase levels)	<ul style="list-style-type: none"> • Withhold atezolizumab • Consult a gastroenterologist. • Administer IV steroids (prednisone equivalent of 60 mg/day) and convert to oral steroids when symptoms improve • When symptoms and lab abnormalities improve to Grade 0 or 1, then taper steroids over \square1 month • Atezolizumab may be resumed if the event improves to Grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of prednisone 10 mg PO daily or less • Permanently discontinue atezolizumab for life threatening immune-mediated pancreatitis or recurrent pancreatitis

Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Appendix Table 13 Management Guidelines for Dermatologic Events

Dermatologic events	Severity	Management
	Grade 1	<ul style="list-style-type: none"> • Continue atezolizumab • Symptomatic therapy with antihistamine as needed. • Consider topical steroids and/or other symptomatic therapy (e.g., antihistamines)
	Grade 2	<ul style="list-style-type: none"> • Continue atezolizumab • Consider dermatologist referral. • Administer topical steroids. • Consider higher potency topical steroids if rash unresolved.
	Grade 3	<ul style="list-style-type: none"> • Withhold atezolizumab • Consult a dermatologist • Administer oral prednisone 10 mg or equivalent. If rash unresolved after 48-72 hours, administer oral prednisone 60 mg or equivalent. • Restart atezolizumab if rash resolved and systemic dose is \leq 10 mg oral prednisone or equivalent per day
	Grade 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab for life-threatening immune-mediated dermatologic toxicities • Contact the Medical Monitor if atezolizumab is discontinued

Neurologic Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternate etiologies.

Appendix Table 14 Management Guidelines for Neurologic Disorders

Autoimmune Neuropathy	Severity	Management
	Grade 1	<ul style="list-style-type: none"> • Continue atezolizumab • Evaluate for alternate causes
	Grade 2	<ul style="list-style-type: none"> • Withhold atezolizumab • Evaluate for alternate causes • Treatment should be as per institutional guidelines
	Grade 3-4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab for life-threatening immune-mediated neuropathy • Permanently discontinue atezolizumab for myasthenia gravis or Guillain-Barré (all grades) • Treatment should be as per institutional guidelines • Contact the Medical Monitor if atezolizumab is discontinued.
Myasthenia gravis and Guillain-Barré	All Grades	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab for myasthenia gravis or Guillain-Barré (all grades) • Treatment should be as per institutional guidelines

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 alternate etiology, develop a sepsis-like syndrome after administration of atezolizumab.

Recommendations regarding early identification and management of SIA are provided below. In the event of suspected SIA, the Medical Monitor should be contacted immediately for additional guidance.

Early disease recognition is critical, and the clinician should consider SIA if, in the absence of alternate etiologies, the presence of ≥ 2 of the following are present:

- Hypotension refractory to aggressive IV fluid challenge
 May/can require vasopressor support
- Respiratory distress requiring aggressive supportive care
 Supplemental oxygen, possible intubation
- Fever greater than 38.5°C
- Acute renal or hepatic failure
- Bleeding from coagulopathy

- Unexplained laboratory abnormalities (change from baseline):
Cytopenias (\geq Grade 2 in two or more lineages), significant transaminitis, coagulopathy, elevated creatinine

Initial evaluation should include CBC with peripheral smear, PT, PTT, fibrinogen, D-dimer, ferritin, triglyceride, AST/ALT, total bilirubin, LDH, and a complete neurologic and abdominal examination (assess for hepatosplenomegaly).

If cytopenias (≥ 2 lineages and change from baseline) are present or ferritin is ≥ 3000 ng/mL, the following evaluations should also be performed:

- Bone marrow biopsy/aspirate (assess for evidence of hemophagocytosis)
- sCD25 (soluble IL-2 receptor)
- Natural killer cell activity
- Cytomegalovirus, Epstein-Barr virus and herpes-simplex virus evaluation (evaluate for reactivated or active disease)

SIA is a clinical syndrome characterized by the following:

- Onset greater than 24 hours after exposure to drug AND
- Progressive clinical deterioration in an acutely ill patient (in the absence of an alternate etiology) AND
- Involving multiple organs (≥ 2) AND
- Demonstrating specific lab abnormalities

Diagnosis of SIA should only be made in patients who present with a constellation of clinical findings as outlined above and who fulfill the following established diagnostic criteria in the absence of an alternate etiology. The diagnostic criteria and recommended management for systemic immune activation are provided in [Appendix Table 15](#).

Appendix Table 15 Diagnostic Criteria and Management for Systemic Immune Activation

SIA Criteria apply only when alternate etiologies have been excluded		
Major criteria		Minor criteria
<ul style="list-style-type: none"> • Fever $\geq 38.5^{\circ}\text{C}$ (on more than one occasion) • Ferritin >3000 ng/mL • Cytopenias \geqGrade 2 in two or more lineages • ≥ 2 age-adjusted SD elevation soluble IL-2 receptor • Severe multi-organ dysfunction • Decreased fibrinogen 		<ul style="list-style-type: none"> • Splenomegaly • Hemophagocytosis BM, spleen or LN • Elevated GGT or LFTs (AST/ALT/tBili) • Elevated triglycerides • Elevated LDH • Decreased natural killer-cell activity
Status	# of Criteria	Management
Consistent with SIA	4 major criteria	Consider tocilizumab (4 mg/kg IV) and Solumedrol [®] (1g IV QD). Contact the Medical Monitor for additional recommendations. Consider HLH-94 protocol if no clinical improvement.
Probable SIA	3 major criteria OR 2 major criteria AND 3 minor criteria	Depending on clinical severity, patient can be treated as per “Consistent with SIA” or “Possible SIA” case definition. Contact medical monitor for additional recommendations
Possible SIA	1 major criteria AND 4 minor criteria	Consider Solumedrol [®] (1g IV QD) Contact the Medical Monitor for additional recommendations. As per “Consistent with SIA” recommendations if no improvement or clinically worsening

BM=bone marrow; GGT=gamma-glutamyl transpeptidase; IL-2=interleukin-2; LFT=liver function test; LN=lymph node; SIA=systemic immune activation; IV=intravenous; QD=once a day. tBili=total bilirubin.

The criteria were adapted from a Delphi Survey of 26 experts regarding helpful criteria in the positive diagnosis of Hemophagocytic Syndrome in adult patients.⁴⁰ Standard of care for SIA has not been established. Case reports and recommendations have been published for cytokine release syndrome^{41, 42, 43} based on etiologic similarities, these practices have been incorporated into the above treatment recommendations. However, these recommendations do not replace clinical judgment and are intended as suggested guidance only.