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:	14-March-2019

Statistical Analysis Plan

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
Protocol Number:	IMDZ-C232
Study Drug:	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 × 1010 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). 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.
Sponsor:	Immune Design Corp. (IMDZ) 1616 Eastlake Ave. E, Suite 310 Seattle, WA 98102 USA
Version:	Final
Date:	2019-03-14

Statistical Analysis Plan Approvals

Protocol: IMDZ-C232

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LIST OF ABBREVIATIONS

Abbreviation	Description
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CI	confidence interval
CBR	clinical benefit rate
CRF	Case Report Form
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
GLA	glucopyranosyl lipid A
GLA-SE	glucopyranosyl lipid A stable emulsion
IMDZ	Immune Design Corp.
IHC	immunohistochemistry
INR	international normalized ratio
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
MEOI	medical event of interest
MRCL	myxoid/round cell liposarcoma
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
ORR	overall response rate

Abbreviation	Description
OS	overall survival
PAR	progression arrest rate
PD	progressive disease
PD-L1	Programmed cell death-1 ligand
PFR	progression-free rate
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
SI	International system
SLD	sum of longest diameters
T_3	triiodothyroxine
T_4	thyroxine
TEAE	Treatment-emergent adverse event
TGR	tumor growth rate
TSH	thyroid stimulating hormone
ULN	upper limit of normal
vg	vector genomes
WBC	white blood cell

1 INTRODUCTION

This Statistical Analysis Plan (SAP) documents the planned statistical methods for the analysis and display of data collected within the scope of Immune Design Corp. Protocol IMDZ-C232, version 03 dated 08 March 2017. The analysis of the data should allow changes in the plan to the extent that deviations from the original plan would provide a more reliable and valid analysis of the data. As such, deviations from this SAP must be substantiated by a sound statistical rationale and documented in the clinical study report (CSR).

This SAP details the analysis of the data collected in the study and the presentation of the results of the analyses. The table, listing, and figure (TLFs) shells are displayed in a companion document which provides information on the layout and format of the data displays. All TLFs will be generated based on Analysis Data Model (ADaM) datasets. ADaM dataset specifications will be developed to detail the programming specifications and mapping rules necessary to create the analysis datasets and the TLFs based on Study Data Tabulation Model (SDTM) datasets.

All statistical analyses will be performed using SAS® version 9.4.

2 STUDY OBJECTIVE

2.1 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.

2.2 Secondary Objective

The secondary objectives are:

- 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 (PFR) at 6 months after start of study treatment
- To evaluate the immune response and histologic and molecular tissue changes in tumor tissue and peripheral blood
- To evaluate the time to next treatment (TTNT)
- To evaluate the distant metastasis free survival (DMFS)

2.3 Exploratory Objective

The exploratory objectives are:

- To evaluate exploratory efficacy assessments, such as tumor growth rate and progression arrest rate
- To compare PFS and OS 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]) 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)

3 STUDY DESIGN

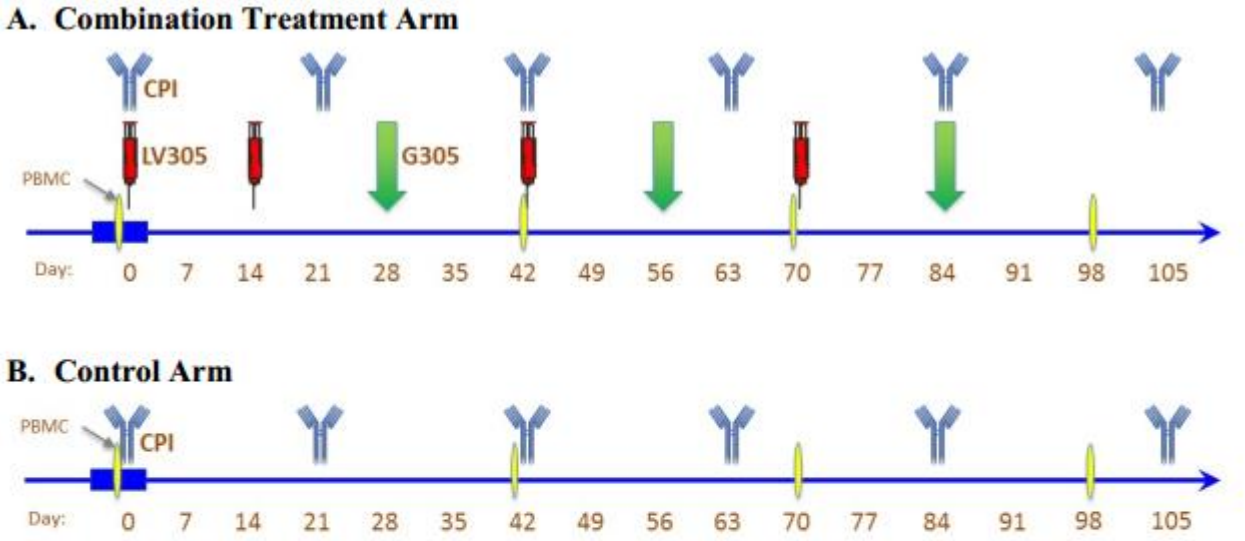
3.1 Overall Plan

This is a randomized, open-label, Phase 2 trial of CMB305, a regimen of LV305 and G305, in combination with atezolizumab (combination treatment arm) or with atezolizumab alone (control arm) 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.

CMB305 is composed of LV305, a modified third generation lentiviral vector expressing NY-ESO-1 gene and G305, NY-ESO-1 recombinant protein plus glucopyranosyl lipid A formulated in a stable emulsion (GLA-SE), that will be administered sequentially. 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 (via atezolizumab) in the treatment of patients with locally advanced, relapsed, or metastatic sarcoma.

The treatment dosing schema used is as follows (Figure 1).

Figure 1: Dosing Schedule for Each Treatment 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 received 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.

Up to 12 patients will be randomized 1:1 to receive CMB305 with atezolizumab or atezolizumab alone in a Safety Run-in, then up to a total of 80 patients at up to 20 sites in the United States and Canada will be enrolled and randomized. Randomization will be stratified by disease type. Archival tumor specimens will be obtained from patients where feasible to determine PD-L1 molecular status.

Part 1: 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 serious adverse event (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.

Study Stopping Rule

The safety of the CMB305/atezolizumab combination will be investigated during the 6-12 patient Safety Run-in. 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.

Part 2: Main Study

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 × 1010 vector genomes (vg) and G305 will 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 (± 2weeks). Tissue biopsies will be taken in each treatment group from consenting subjects before treatment and on Day 42, on Day 98 (± 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 (v1.1) 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 a patient dies, the date of death will be documented by the local physician and/or registries.

All SAEs, DLTs, 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).

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 non-study 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.

3.2 Study 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).

3.3 Randomization

In this study up to 12 Safety Run-in patients are randomized 1:1 to the CMB305 in combination with atezolizumab or control arms no more than 4 days prior to dosing. After the Safety Run-in, up to 80 patients will be randomized stratified by type of disease, synovial sarcoma versus myxoid round cell liposarcoma. Patients who withdraw from the study will not be replaced.

3.4 Study Assessments

Study procedures and schedule of assessments are specified in **Table 1** and **Table 2** below, for combination treatment and control arms, respectively.

Table 1 Schedule of Events – Combination Treatment Arm

Table 1 Schedule of Events – Combination Treatment Arm

	Screening	Treatment Phase									Booster Phase			Maintenance Phase	Survival Follow-up[q]
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	
Physical exam[f]	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	
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	143	153	163	173	238	248	258	323	333	388	398			

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 [± 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)™ 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 [T_3], thyroxine [T_4], 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

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[a]
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.

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 [± 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)™ 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 [T_3], thyroxine [T_4], 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.

4 SAMPLE SIZE DETERMINATION

Sample size was calculated using a Simon 2-stage design, assuming an unacceptable progression-free survival rate (PFR) of 25% and an acceptable PFR of 45% at 6 months, corresponding to an unacceptable and desirable median PFS of 3 months and 5.2 months, respectively and an exponential survival distribution, 40 patients in each arm (alpha=0.1, beta=0.15) were required. For this study, two groups of up to 40 patients each (up to 80 patients) were to be dosed with CMB305 with atezolizumab or with atezolizumab alone to assess PFS at 6 months and median of PFS with 95% CIs. If favorable results are observed, the study may be expanded to improve the estimates of PFS.

5 STUDY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint

5.1.1.1 Progression free Survival (PFS)

PFS will be based on RECIST 1.1 response guidelines modified to use irRC-specific confirmation. Progression-free survival (PFS) in months is calculated as: (date of first progression or death (any reason) – date of randomization +1)/30.4375. 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 the total tumor burden was shown to have increased by at least 20% compared with nadir. Patients without progression or death are censored at the date of the last disease assessment. 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. Patients without disease assessment post-baseline will be censored at the randomization date. As needed, we will use **Table 3** to specify how dates of progression events and dates for censoring of progression data are assigned. **Table 3** represents an analysis that only includes well-documented and verifiable progression events. In **Table 3**, the progression dates are:

- Based only on radiological assessments verified by an IRC and symptomatic deterioration date assessed by study investigator.
- Assigned to the first time when tumor progression was noted.
- The date of death when the patient is closely followed. However, deaths occurring after two or more missed tumor assessments (> 91 days after last tumor assessment) are censored at the last visit.

Progressive disease will be assessed by the unidimensional measurements approach of the Immune-related Response Criteria.

Table 3 – Progression-Free Survival (Includes investigator assessment)

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Date of randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of radiological assessment showing new lesion (if progression is based on new lesion); or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
Symptomatic deterioration before first PD assessment	Date of Symptomatic deterioration	Progressed
Symptomatic deterioration between adequate assessment visits	Date of Symptomatic deterioration	Progressed
Symptomatic deterioration after two or more missed visit	Date of last tumor assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after two or more missed visit	Date of last tumor assessment	Censored
New anti-cancer therapy or radiotherapy or surgery at a lesion site prior to confirmed progression (or death)	Date of last tumor assessment where the patient was documented as progression free prior to the intervention	Censored
No progression or Death	Date of last tumor assessment	Censored

5.1.1.2 Overall Survival (OS)

Overall survival in months will be calculated as: (date of death (any cause) – date of randomization) +1)/30.4375. Patients who were alive at the end of study will be censored at the last date the patient is known to be alive or data analysis cutoff date, whichever is earlier.

5.1.2 Secondary Efficacy Endpoint

5.1.2.1 PFR at 6 Months

PFR at 6 months will be calculated using Kaplan-Meier method.

5.1.2.2 Immune response and histologic and molecular tissue changes in tumor tissue or peripheral blood

Baseline and post treatment anti-NY-ESO-1 immune response and histologic and molecular changes in peripheral blood data will be collected.

5.1.2.3 Time to Next Treatment (TTNT)

Time to next treatment in months will be calculated as: (start date of subsequent therapy – date of randomization) +1)/30.4375. Patients who did not receive subsequent therapy will be censored at the last date the patient is known to be alive or data analysis cutoff date, whichever is earlier.

5.1.2.4 Distant Metastasis-Free Survival (DMFS)

Distant metastasis free survival (DMFS) in months is calculated as (first metastasis new lesion scan date or death date within 2 missed scheduled tumor assessment – date of randomization + 1)/30.4375. Patients without metastasis and death are censored at the date of the last disease assessment. Patients without post-baseline disease assessment are censored at randomization date.

5.1.3 Exploratory Efficacy Endpoints

5.1.3.1 Tumor Growth Rate and Progression Arrest Rate

Progression status as determined by investigator performed by using outside images off protocol at screening will be collected in study.

At the baseline tumor assessment, the sum of the longest diameters (SLD) of all index lesions (2 target lesions per organ, up to 5 target lesions in total) will be calculated. At each subsequent tumor assessment, the SLD of the index lesions and of new, measurable lesions is calculated: SLD = SLD index lesions + SLD new, measurable lesions

Percentage changes in SLD per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear.

5.1.3.2 Overall Response Rate (ORR) and Duration of Response (DOR)

Overall response rate (ORR) will be defined as the number of patients whose best overall response is complete response (irCR) or partial response (irPR) divided by the number of evaluable patients. Overall response rate based on unconfirmed response and confirmed response will both be summarized.

Duration of response (DOR) will be defined only for the patients whose confirmed best response is irCR or irPR as the time interval between the date of the earliest qualifying confirmed response and the date of progressive disease (PD) or death for any cause, whichever occurs first. DOR in months will be calculated as: (date of PD or death, whichever occurs first – date of first confirmed irCR or irPR + 1)/30.4375.

For patients who are alive without documentation of disease progression following the qualifying response, duration of response will be censored following the same rule defined for PFS.

5.1.3.3 Clinical Benefit Rate (CBR) and Duration of Clinical Benefit

Clinical benefit rate (CBR) will be defined as the number of patients whose best overall response is complete response (irCR), partial response (irPR) or stable disease (irSD) divided by the number of evaluable patients. Clinical benefit rate based on unconfirmed response and confirmed response will both be summarized.

Duration of clinical benefit will be defined only for the patients whose confirmed best response is irCR, irPR or irSD as the time interval between the date of the earliest qualifying confirmed response and the date of progression disease (PD) or death for any cause, whichever occurs first. Duration of clinical benefit in months will be calculated as: (date of PD or death, whichever occurs first – date of first confirmed irCR, irPR or irSD + 1)/30.4375.

For patients who are alive without documentation of disease progression following the qualifying response, duration of clinical benefit will be censored following the same rule defined for PFS.

5.1.3.4 Time to New Lesion

Two time to new lesion definitions are included in the analysis: one excludes death, the other includes death as an event.

- Definition 1: calculated as (first new lesion scan date – date of randomization + 1)/30.4375. Patients without new lesion scanned are censored at the date of the last disease assessment. Patients without post-baseline disease assessment are censored at randomization date.
- Definition 2: calculated as (first new lesion scan date or death date within 2 missed scheduled tumor assessment – date of randomization + 1)/30.4375. Patients without new lesion scanned and death are censored at the date of the last disease assessment. Patients without post-baseline disease assessment are censored at randomization date.

5.2 Safety Endpoints

The safety endpoints for the study include the nature, frequency, and severity of adverse events and clinically significant abnormalities. Laboratory tests, vital signs, ECOG performance status, physical exams, and 12-lead ECG will be summarized and/or analyzed to inspect for trends of abnormalities and deteriorations of any pre-existing conditions.

All clinically significant abnormalities and deteriorations identified in laboratory tests, vital signs, physical exams and 12-lead ECG will be entered in the case report forms (CRFs) as Adverse Events and graded according to the NCI CTCAE v4.03.

6 ANALYSIS SET

6.1 Intent-to-Treat Set

The Intent-to-treat (ITT) analysis set consists of all randomized patients. All analyses of this set will be based on the treatment arm to which the subjects are randomized.

6.2 Safety Set

The Safety analysis set includes all enrolled patients who received any of the CMB305 components (LV305, G305) or atezolizumab. The Safety analysis set is the primary set for safety analyses including adverse events (AEs) and clinical laboratory data. Trial product exposure will also be summarized using the Safety set.

6.3 Efficacy Set

The Efficacy analysis set includes all randomized patients who have received at least one injection/dose of any of the CMB305 components (LV305 and G305) or atezolizumab and had at least one post-baseline scan or discontinued or died prior to 2 missed tumor assessments.

7 STATISTICAL ANALYSES

7.1 Data Summaries and Conventions

All data collected on CRFs will be provided in listings, except data collected only for confirmation of study entry criteria and for study administrative purposes. If any enrolled patient is found to not have valid documented informed consent, that patient's data will be excluded from the report, except as necessary to document the error.

Except where specified all continuous variables will be summarized with descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum and maximum) and all categorical variables will be summarized with frequency counts and percentages, by treatment arm (combination arm vs. control arm).

7.2 Missing Data

For adverse events and concomitant medication, the imputation rule for start date and end date are defined in below section. For other analysis when necessary (e.g., OS analysis), dates without a specific day of the month (i.e., JAN2010) will be assigned the 15th day of the month and dates without a specific day or month (i.e., 2010) will be assigned the 15th day of June.

7.2.1 Partial Dates for Adverse Events

If the AE start date is partial or missing, then:

- If AE start date is completely missing, then the AE is considered as treatment-emergent.
- If both AE start month and day are missing and AE start year is the same or after the first dose year, then the AE is considered as treatment-emergent.
- If AE start day is missing and AE start year and month are the same or after the first dose year and month, then the AE is considered as treatment-emergent.

7.2.2 Partial Dates for Concomitant Medication

For medications with incomplete dates, imputation will be used to convert to a complete date. Imputed dates will be used to determine Study Day.

Partial medication start dates will be imputed as follows:

1. Only the year is reported: If the subject started to receive study drug in the year reported, then the date of the first dose of study drug will be used as the starting date of the medication. Otherwise, January 1 will be used as the start of the medication.
2. The month and year are reported: If the subject started to receive study drug during the month and year reported, then the date of first dose of study drug will be used as the starting date of the medication. Otherwise, the first day of the month will be used as the start of the medication.

Partial medication end dates will be imputed for non-ongoing medications as follows:

1. Only the year is reported: If the subject stopped to receive study drug in the year reported, then the date of the last dose of study drug will be used as the end date of the medication. Otherwise, December 31 will be used as the end of the medication.

2. The month and year is reported: If the subject stopped to receive study drug during the month and year reported, then the date of last dose of study drug will be used as the end date of the medication. Otherwise, the last day of the month will be used as the end of the medication.

If an imputation results in an imputed start date after the stop date, the start date will be set to the day prior to the stop date.

7.3 Subject Disposition

Patient disposition information will be summarized by treatment group and in total for ITT set. The number and percentages of patients in safety set and efficacy set will be summarized by treatment group and in total.

The below numbers based on ITT set will be presented in table.

- Number of patients complete all doses of LV305 per protocol
- Number of patients discontinued from LV305 and reason for discontinuation,
- Number of patients complete all doses of G305 per protocol
- Number of patients discontinued from G305 and reason for discontinuation
- Number of patients complete all dose of atezolizumab
- Number of patients discontinued from atezolizumab and reason for discontinuation
- Number of patients receive all doses of CMB305 up to visit 12 based on dose administration page
- Number of patients receive all doses of atezolizumab up to visit 12 based on dose administration page
- Number of patients receive all doses of CMB305 and atezolizumab up to visit 12 based on dose administration page
- Number of patients complete all dose of LV305, G305 and atezolizumab
- Number of patients entered Long Term Follow-Up
- Number of patients completed LTFU Visit (Month 3, 6, 9, 12, 15, 18, 21 >=24)
- Number of patients completed study per protocol
- Number of patients discontinued from study and reason for discontinuation

7.4 Protocol Deviations

The clinical study team will define CSR reportable protocol deviation and major protocol deviation to be excluded from efficacy evaluable set. They clinical team will have quarterly review of all potential CSR reportable and major protocol deviations during study conduct and prior to database lock. CSR reportable and major protocol deviations will be categorized by deviation type.

A listing will be provided for all protocol deviations.

7.5 Demographic and Baseline Characteristics

Demographics, cancer history and tumor specific therapy history will be summarized by treatment arm for the ITT and safety analysis set. Demographics, cancer history, medical history and tumor specific therapy history will be presented in a data listing for all patients in ITT Analysis Set.

Baseline demographic and baseline characteristics summary will include the following:

- Age in years, calculated as integer part of (date of informed consent – date of birth + 1)/365.25.
- Age categories of (>= 70 years, >= 80 years)
- Sex (Male and Female) and Childbearing Potential status for Female
- Race
- Ethnicity
- Height (cm) at baseline, defined as the last non-missing value prior to first dosing.
- Weight (kg) at baseline, defined as last non-missing value prior to first dosing
- ECOG Performance Status at baseline, defined as last non-missing value prior to first dosing
- Number of Target/Non-Target Lesions at Baseline
- Number of Target Lesions at Baseline
- Number of Non-Target Lesions at Baseline
- Sum of Target Lesion Diameters at Baseline (mm)

Cancer History summary will include the following:

- Type of Sarcoma (Myxoid/Round Cell Liposarcoma and Synovial Sarcoma)
- Time from diagnosis (Month), calculated as (first dosing date – date of diagnosis + 1) /30.4375. In case of partial date, "15" is used for missing day, "Jun" is used for missing month.
- Stage at Diagnosis
- Disease Status at Study Start
- Soft Tissue Sarcoma Grade at Diagnosis
- Current Tumor Staging (Stage T, Stage N, Stage M and Stage TNM)
- NY-ESO-1 Expression (%) and categories of NY-ESO-1 (1%-25%, >25% - 50%, >50% - 75%, >75% - 100%)
- Progression Status at Screening

Medical and surgical history includes diagnosis or surgery entered on the medical and surgical history form.

Prior tumor specific therapy history includes therapy/treatment entered on the prior anti-cancer therapy form. The summary will include the following:

- Any prior therapy
- Type of therapy (Radiotherapy, Immunotherapy, Chemotherapy, Other Therapy)
- Number of lines of prior therapy (1, 2, >=3). Line of therapy will be assigned and reviewed by medical team at several milestone time points.
- Number of prior chemotherapy agents
- Frequency and percentage by prior chemotherapy agents
- Best response of prior chemotherapy
- Reason for discontinuation from prior chemotherapy

7.6 Efficacy Analyses

The efficacy analysis will be performed based on ITT set and supportive analysis will be performed based on Efficacy set and subgroup of ITT and efficacy set.

7.6.1 Analysis of Primary Efficacy Variables

7.6.1.1 Progression-Free Survival (PFS) and Overall Survival (OS)

PFS and OS analyses by treatment arm using Kaplan-Meier methodology based on the ITT set will be performed. Median with 95% CIs by treatment arm will be provided by treatment arm. The Kaplan-Meier plots will be displayed. The SAS code used to calculate the median (and 95% CI) and create the Kaplan-Meier plot is listed in Appendix 2.

As an exploratory analysis, PFS and OS between CMB305+atezolizumab arm vs. atezolizumab alone arm for all ITT patients will be compared. Hazard ratio, its corresponding 95% confidence interval (CI), and p-value (based on a 2-sided stratified log-rank test) from a Cox proportional hazards model stratified by disease type will be presented. Unstratified analysis will also be performed to estimate the hazard ratio and the corresponding 95% CIs and p-values. Since the sample size is not based upon a hypothesis to be tested regarding the differences in PFS between treatment arms, the statistical analyses to compare PFS and OS differences between treatment arms should be considered exploratory.

Exploratory analyses of OS at 6, 12, 18, and 24 months, and PFS at 3 and 12 months will also be assessed. The survival rate estimates between the two treatment arms will be compared using the following:

Z= difference in x-month survival rates / square root of sum of variance

where variance=square of survival standard error from Product Limit Estimate from SAS PROC LIFETEST, assuming independence of the two treatment arms, and the survival standard error for x-month is the same as the survival standard error at the event time prior to x-month if x-month is not an event time.

A forest plot of hazard ratios and their two-sided 95% confidence intervals will be presented for the subgroups defined in section 7.7 of this document, based on the ITT analysis set. The interaction p-value from Cox proportional hazards model will be also shown in the plot.

Progression-free survival and overall survival data will be presented in data listing.

7.6.2 Analysis of Secondary Efficacy Variables

7.6.2.1 PFR at 6 Months

PFR at 6 months using Kaplan-Meier method, with 95% and 80% confidence intervals (CIs) by treatment arm will be presented. If the Lower Confidence Limit of the 80% CI is greater than the assumed unaccepted PFR rate of 25%, it would serve as a signal that PFR at 6 months is higher than 25%.

7.6.2.2 Immune response and histologic and molecular tissue changes in tumor tissue or peripheral blood

Baseline and post treatment anti-NY-ESO-1 immune response and histologic and molecular changes in peripheral blood and tumor tissue and their association with clinical outcomes will be explored. Pre and post dosing antibody and T cell (+ vs -) will be summarized. In addition, a relationship between an induced anti-NY-ESO-1 immune response as well as tumor tissue changes during study treatment and clinical outcomes will be evaluated using peripheral blood and tumor tissue biopsies collected during study treatment at select sites. Association between Pre and post dosing antibody and T cell (+ vs -) and clinical outcome (PFS, OS) will be explored. Stepwise Cox regression analysis will be explored to investigator prognostic baseline factors associated with clinical outcome (OS, PFS).

7.6.2.3 Time to Next Treatment (TTNT)

TTNT will be analyzed using the same methods described for OS/PFS.

7.6.2.4 Distant Metastasis-Free Survival (DMFS)

DMFS will be analyzed using the same methods described for OS/PFS.

7.6.3 Exploratory Analyses

7.6.3.1 Tumor Growth Rate and Progression Arrest Rate

PD/SD at screening will be summarized.

Post treatment initiation, spider plot (% change and change from baseline in sum of longest diameter of target lesions) for all visits will be presented.

7.6.3.2 Overall Response Rate (ORR) and Duration of Response (DOR)

ORR will be estimated using the ITT set and EE set will be provided along with their corresponding 2-sided the 95% exact CI using Clopper-Pearson method. Best Overall Response (CR, PR, SD, PD and not evaluable) will be tabulated with 2-sided 95% CI in the same table.

ORR will be compared between treatment arms using a logistic regression. Logistic regression will be performed with the treatment arm and stratification factor of disease type as independent variables.

Lesion assessment (lesion type, organ site, evaluation method, diameter, lesion status and overall response) at each visit will be presented in a data listing.

Median DOR with the corresponding 95% CI will be estimated using the Kaplan-Meier method in each treatment arm. The Kaplan-Meier plots will be displayed.

DOR data will be presented in a data listing.

7.6.3.3 Clinical Benefit Rate (CBR) and Duration of Clinical Benefit

CBR and Duration of clinical benefit will be analyzed using the same methods described for ORR and DOR.

7.6.3.4 Time to New Lesion

Time to New Lesion will be analyzed using the same methods described for OS/PFS.

7.7 Subgroup Analysis

The following subgroups will be used for primary PFS and OS analysis in ITT and Efficacy set.

- Excluding safety run-in patients
- Patients with confirmed CR/PR/SD on study
- Patients with unconfirmed CR/PR/SD on study
- Patients with confirmed PD on study
- Type of Sarcoma (Myxoid/Round Cell Liposarcoma and Synovial Sarcoma)
- NY-ESO-1 (%) categories (1-<100, 100)
- NY-ESO-1 (%) categories (1-75, >75-99)
- Age (<48 Years, >=48 Years)
- Sex (Female, Male)
- Baseline ECOG (0, 1)
- Time from Diagnosis (<30.3 months, >= 30.3 months)
- Time from Diagnosis (<18.4 months, 18.4 - <46.8 months, >= 46.8 months)
- Disease Status at Study Start (Locally Advanced, Metastatic)
- Metastatic Status (Relapsed/Recurrence of prior metastatic, Relapsed/Recurrence of prior locally advanced)
- Stage at Diagnosis (I/II/III, IV)
- Race (White, Other)
- Progression Status at Screening (SD, PD)
- Number of lines of prior chemotherapy (1, 2, >=3)
- Number of Target/Non-Target Lesions (<=3, >=4)
- Number of Target lesions (<=2, >=3)
- Patient with 1 prior line of chemotherapy and with response SD or better in prior therapy
- Synovial Sarcoma patient with 1 line of chemotherapy and with response SD or better in prior therapy

The below subgroups are defined for PFS analysis only.

- New target lesion on study (Yes, No)
- Total size of target lesion at baseline (0-15 mm, 16-50 mm, > 50 mm)
- Number of organs with target/non-target lesions at baseline (1, 2, >=3)
- Prior Anthracyclines Use (Yes, No)

7.8 Safety Analyses

All analyses for the safety evaluation variables will be performed on safety set by treatment arm and overall.

7.8.1 Adverse Events

A treatment-emergent adverse event (TEAE) is an AE with an onset on or after the initiation of study treatment, or a pre-existing condition that worsens after initiation of study treatment (i.e.,

increase in severity), up to 30 days after the last dose of study treatment (LV305, G305, or atezolizumab, whichever occurs last). AEs that occur more than 30 days after the last dose, if deemed as related to the study drug, will also be included as TEAEs.

The incidence of a TEAE will be defined as the number and percent of patients experiencing an event. TEAEs will be summarized by severity, system organ class, and preferred term in each treatment arm. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA 20.1 or newer). A patient with more than one different adverse event in a system organ class (SOC) will be counted only once in the total of patients experiencing adverse events in that particular SOC. A patient having experienced the same event (AE preferred term) more than once during the study will be counted only once in the number of patients with that event. If an event changes in intensity or in seriousness during the study, it will be counted only once with the worst grade and seriousness respectively.

An AE with missing severity will be deemed as severe. Imputed values will not be listed in data listings. An AE with a missing relationship to study drug will be deemed as definitely related. Imputed values will not be listed in data listings.

The following adverse events summaries will be reported:

- Overall summary of safety, including TEAEs, treatment-related TEAEs, serious TEAEs, treatment-related serious TEAEs, TEAEs of grade 3 and above, treatment-related TEAEs of grade 3 and above, TEAEs leading to treatment interruption, TEAEs leading to study drug administration, TEAEs leaing to treatment interuption or discontinuation, TEAEs leading to death reported during the study, dose limiting toxicities (DLTs), medical events of interest (MEOIs)
- Incidence of TEAEs by severity
- Incidence of TEAEs related to study drug by severity
- Incidence of TEAEs related to CMB305 by severity
- Incidence of TEAEs related to atezolizumab by severity
- Incidence of treatment-emergent serious adverse events by severity
- Incidence of treatment-emergent serious adverse events related to study drug
- Incidence of Grade 3 or higher treatment-emergent adverse events (TEAEs) by severity
- Incidence of TEAEs leading to study drug discontinuation
- Incidence of TEAEs related to study drug leading to study drug discontinuation
- Incidence of TEAEs related to CMB305 leading to study drug discontinuation
- Incidence of TEAEs related to atezolizumab leading to study drug discontinuation
- Incidence of TEAEs leading to death
- Incidence of TEAEs related to study drug leading to death
- Incidence of treatment-emergent dose limiting toxicities by severity
- Incidence of treatment-emergent MEOI by severity

All AEs in safety analysis set will be presented in a data listing.

7.8.2 Deaths

Deaths (and cause of death) will be provided in table and listing.

7.8.3 Dosing and Extent of Exposure

The number of injections with LV305, G305, and atezolizumab that patients have received will be used to assess whether the planned study regimen components and the doses are administered.

Number of LV305 dose administered, G305 dose administered, and atezolizumab dose administered will be summarized by frequency and descriptive statistics.

Total cumulative atezolizumab dose (mg) will be summarized and calculated as cumulative dose of atezolizumab administered to the patient over all cycles.

Treatment duration of atezolizumab (weeks) will be calculated as (date of last atezolizumab dose administered – date of first atezolizumab dose administered + 21 days) / 7 days.

The compliance to each study drug (whether entire dose was administered, or missing dose) will also be presented.

CMB305 components (LV305 and G305) and atezolizumab dosing administration will be summarized by treatment arm and all study drug information will be displayed in a listing.

7.8.4 Clinical Laboratory Evaluations

Except urinalysis performed only at baseline visit (visit 1), hematology and blood chemistry will be assessed at baseline visit (visit 1), visits 2, 3, 4, 5, 6, 7, 8, 9, 10, 12 and 3-weekly visits during the maintenance phase treatment and follow-up. Laboratory assessments included the following:

- Hematology: WBC count with differential, absolute neutrophil count (ANC), red blood cell (RBC) count, hemoglobin, hematocrit, platelet count, prothrombin time (PT)/partial thromboplastin time (PTT) and international normalized ratio (INR)
- Clinical chemistry (or local panel if inclusive of the following): sodium, chloride, potassium, glucose, blood urea nitrogen (BUN), creatinine, calcium, aspartate aminotransferase (AST)/SGOT, alanine aminotransferase (ALT)/SGPT, total bilirubin, alkaline phosphatase, lactic acid dehydrogenase (LDH), total protein, albumin
- Urinalysis (baseline only): protein, glucose, blood, leukocytes, nitrites, urobilinogen, bilirubin, pH, specific gravity, ketones
- Thyroid function (Screening, Day 84 and every 3 months during the follow-up): T_3, T_4 and TSH

All local laboratory data will be stored in the database with the units in which they are originally reported. Laboratory data in summary tables and patient data listings will be presented in the international system of units (SI Units). Laboratory data not reported in SI units will be converted to SI units before further processing or data analysis.

Summary statistics (mean, median, standard deviation, and range) of laboratory values for hematology tests and chemistry tests and their changes from baseline values will be tabulated for each visit, by treatment arm. Baseline is defined as the last value prior to first dosing.

Laboratory tests will be graded using NCI-CTCAE v4.03 toxicity grading (see Appendix 1).

Worst change from baseline in toxicity grade for selected laboratory parameters will be presented in shift tables: in each treatment arm, the patient's baseline grade will be cross-

tabulated by the patient's maximum post-baseline grade during the treatment. Data from scheduled and unscheduled visits will be used for finding maximum post-baseline NCI-CTCAE grade of laboratory values.

All laboratory measurements will be presented in a listing.

7.8.5 Vital Signs

Vital sign measurements include temperature, pulse (heart rate), respiratory rate, resting systolic and diastolic blood pressure. Temperature, pulse (heart rate), respiratory rate, resting systolic and diastolic blood pressure will collected at screening visit (visit 1), and all visits through weeks 0-12 treatment, post-CMB305 treatment, and maintenance phase.

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 [± 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.

For first infusion, measurements collected in all time points will be summarized in table. For subsequent infusion, only the measurements collected at time point pre-dosing and 30 minutes after dosing need be summarized.

Summary statistics (mean, median, standard deviation, and range) of baseline and post-baseline vital signs measurements (temperature, pulse, respiratory rate, resting systolic and diastolic blood pressure), as well as the changes from baseline, will be tabulated for each visit, by treatment arm. Baseline is defined as the last value prior to initial LV305 or atezolizumab dosing, whichever occurs first.

All vital signs measurements will be presented in a listing. The visits with clinically significant abnormalities in vital sign measurements will be flagged in the vital signs listing.

7.8.6 ECG

12-Lead ECG measurements collected in both scheduled and unscheduled visits will be presented in data listings.

7.8.7 Physical Findings

Physical examination abnormalities will be included in the adverse event (abnormalities after the start of study drug) or medical history (abnormalities before the start of study drug) summaries and listings

7.8.8 Pregnancy Test

Pregnancy test will be performed at baseline (visit 2) and at each dosing visit. Pregnancy data will be presented in a listing.

7.8.9 ECOG Performance Status

ECOG performance status will be summarized by visit and presented in a listing.

7.8.10 Prior and Concomitant Medications

Verbatim terms of prior and concomitant medications will be coded using the most current version of the World Health Organization (WHO) Drug Dictionary (3Q 2018 or newer).

All concomitant medications will be summarized by ATC class and preferred term and all prior and concomitant medications will be presented in a listing. A patient with more than one different medication in a medication class will be counted only once in the total of patients taking that medication class. A patient having the same medication more than once during the study will be counted only once in the number of patients with that medication.

Concomitant medication/treatment is any medication/treatment with start date on or after the initial dosing of LV305 or atezolizumab, whichever occurs first.

Prior medication is defined as any medication with start date on or before the first day of study drug (LV305 or atezolizumab, whichever occurs first), or medication with start date missing.

Any medication/treatment which cannot be identified as prior or concomitant will be considered prior and concomitant.

7.8.11 Subsequent Anti-Cancer Therapies and Procedures

Subsequent anti-cancer therapies and procedures will be collected throughout weeks 0-12 treatment visits as well as long-term treatment and follow-up visits. The following will be summarized by treatment arm in safety analysis set and will be presented in a listing.

- Any subsequent anti-cancer therapy
- Type of therapy
- Number of lines of therapy

Line of therapy will be reviewed and assigned by medical monitor. For first line, second line and third line treatment, number of subsequent chemotherapy agents and number of patients in each chemotherapy regimen/agents, best response of chemotherapy and reason for discontinuation of chemotherapy will be summarized in each line.

Subsequent procedures will be presented in a separate listing.

7.9 Multiplicity

Where possible, parameters will be quantified for direct comparisons between the treatment arms. Since the sample size is not based upon a hypothesis to be tested regarding the differences in primary and secondary endpoints between treatment arms, the statistical analyses to compare differences in parameters between treatment arms should be considered exploratory. All other statistical tests (where performed) will be two-sided and tested at the alpha=0.05 level of significance; all these p-values produced should be deemed descriptive. There will be no adjustment to multiplicity.

7.10 Interim Analyses and Data Monitoring

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 Protocol Section 10.3, 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.

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

8 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued, and the SAP will prevail.

9 REFERENCES

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Appendix 1: NCI CTCAE V4.03 Grades for Laboratory Parameters

Panel: Chemistry

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Albumin	g/L	[30, LLN)	[20, 30)	[0, 20)	Life-threatening consequences; urgent intervention indicated
Alkaline Phosphatase	U/L	(ULN, 2.5*ULN]	(2.5*ULN, 5*ULN]	(5*ULN, 20*ULN]	>20*ULN
ALT (increased)	U/L	(ULN, 3.0*ULN]	(3.0*ULN, 5.0*ULN]	(5*ULN, 20*ULN];	>20*ULN
AST (increased)	U/L	(ULN, 3.0*ULN]	(3.0*ULN, 5.0*ULN]	(5*ULN, 20*ULN];	>20*ULN
Bilirubin	umol/L	(ULN, 1.5*ULN]	(1.5*ULN, 3*ULN]	(3*ULN, 10*ULN]	>10*ULN
Calcium high (Hypercalcemia)	mmol/L	(ULN, 2.9]	(2.9, 3.1]	(3.1, 3.4]	>3.4
Calcium low (Hypocalcemia)	mmol/L	[2.0, LLN)	[1.75, 2.0)	[1.5, 1.75) ; hospitalization indicated	[0, 1.5); life threatening consequences
Creatinine (increased)	umol/L	(1 – 1.5*baseline]; (ULN, 1.5*ULN]	(1.5 – 3.0* baseline]; (1.5*ULN, 3*ULN]	>3.0*baseline; (3*ULN, 6*ULN]	>6*ULN
Glucose high (hyperglycemia)	mmol/L	(ULN, 8.9]	(8.9, 13.9]	(13.9, 27.8] ; hospitalization indicated	>27.8; life threatening consequences
Glucose low (hypoglycemia)	mmol/L	[3.0, LLN)	[2.2, 3.0)	[1.7, 2.2)	[0, 1.7); life threatening consequences; seizures
Potassium high (hyperkalemia)	mmol/L	(ULN, 5.5]	(5.5, 6]	(6, 7]; hospitalization indicated	>7; life-threatening consequences
Potassium low (hypokalemia)	mmol/L	[3, LLN)	[3, LLN); symptomatic; intervention indicated	[2.5, 3) ; hospitalization indicated	[0, 2.5); life-threatening consequences
Sodium high (hypernatraemia)	mmol/L	(ULN, 150]	(150, 155]	(155, 160]; hospitalization indicated	>160; life-threatening consequences
Sodium low (hyponatraemia)	mmol/L	[130, LLN)	UNDEFINED	[120, 130)	[0, 120); life-threatening consequences

Panel: Hematology

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (decreased)	g/L	[100, LLN)	[80, 100)	[0, 80); transfusion indicated	Life-threatening consequences; urgent intervention indicated
Platelet count (decreased)	10^9/L	[75, LLN)	[50, 75)	[25, 50)	[0, 25)
WBC (decreased)	10^9/L	[3, LLN)	[2, 3)	[1, 2)	[0, 1)
Lymphocytes (decreased)	10^9/L	[0.8, LLN)	[0.5, 0.8)	[0.2, 0.5)	[0, 0.2)
Neutrophil count (decreased)	10^9/L	[1.5, LLN)	[1, 1.5)	[0.5, 1)	[0, 0.5)
Activated Partial Thromboplastin Time	sec	(ULN, 1.5*ULN]	(1.5*ULN, 2.5*ULN]	>2.5*ULN; hemorrhage	
Prothrombin Intl. Normalized Ratio	Ratio	(ULN, 1.5*ULN]; >1 - 1.5 times above baseline if on anticoagulation	(1.5*ULN, 2.5*ULN]; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5*ULN; >2.5 times above baseline if on anticoagulation	

Reference:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix 2: SAS Code for Statistical Analyses

The following table presents the SAS code for the analyses.

Test	Table/Figure	SAS Codes

95% Clopper-Pearson confidence interval	Tumor response based on irRC	ods listing close;
		proc freq data = xx;
		ods output BinomialCLs=CI BinomialProp=prop;
		table resp / binomial (level = 1 exact) out=freq1 (keep=objresp count);
		by trt;
		run;
		ods listing;
		
		**where resp = best overall response
		trt = treatment arm;

Median (and 95% CI) for Kaplan-Meier curve	Progression-free survival, Duration of Response	proc lifetest data=xx method=km plots=(s);
		time pfs*status (1);
		strata trt;
		run;
		
		**where pfs = time to event.
		status: 1=censoring; 0=event
		trt = treatment arm;

Hazard ratio, 95% CI, p-value based on a 2-sided stratified log-rank test	Progression-free survival, OS	Proc phreg; (Stratified) model time*status (1) = treat; strata disease_type; Run;
Hazard ratio, 95% CI, p-value based on a 2-sided unstratified log-rank test	Progression-free survival, OS	Proc phreg; (Unstratified) model time*status (1) = treat; Run;