Official Protocol Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Determine the Efficacy and Safety of CMB305 in Unresectable Locally-advanced or Metastatic NY-ESO-1+ Synovial Sarcoma Subjects Following First-line Systemic Anti-cancer Therapy
NCT number:	NCT03520959
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***NOTE:** This Statistical Analysis Plan (SAP) exists only as a draft version, as the trial was terminated before SAP finalization.

Statistical Analysis Plan

Title: A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Determine the Efficacy and Safety of CMB305 in Unresectable Locally-advanced or Metastatic NY-ESO-1+ Synovial Sarcoma Subjects Following First-line Systemic Anti-cancer Therapy

Protocol Number: IMDZ-04-1702

Study Drug: CMB305 (sequentially administered LV305 [lentiviral vector encoding New York esophageal squamous cell carcinoma-1 {NY-ESO-1} gene] and G305 [NY-ESO-1 recombinant protein plus glucopyranosyl lipid A stable emulsion {GLA-SE}])

Sponsor: Immune Design Corp. (IMDZ)

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Version: Draft 1.0

Date: 2018-05-25

SIGNATURES

The undersigned have approved this Statistical Analysis Plan for use in this study.

_____	_____
Name	(Date)
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Name	(Date)

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine transaminase (SGPT)
ANC	Absolute neutrophil count
AST	Aspartate transaminase (SGOT)
ATC	Anatomical therapeutic chemical classification
BUN	Blood urea nitrogen
BMI	Body mass index
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DMC	Data monitoring committee
eCRF	Electronic case report form
ECOG	Eastern cooperative oncology group
ECG	Electrocardiogram
EE	Efficacy evaluable
ELISA	Enzyme-linked immunosorbent assay
EQ-5D-5L	EuroQol 5-Dimension 5-Level
EQ-5D-Y	EuroQol 5-Dimension Youth
FNCLCC	French Federation of Comprehensive Cancer Centers
GLA-SE	Glucopyranosyl lipid A stable emulsion
HCT	Hematocrit
HepB	Hepatitis B
HepC	Hepatitis C
HGB	Hemoglobin
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization

IHC	Immunohistochemistry
IM	Intramuscular(ly)
IMDZ	Immune Design Corp.
IPD	Important protocol deviation
IRC	Independent review committee
ITT	Intent to treat
IV	Intravenous
LAUR	Locally advanced unresectable
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
MEOI	Medical event of interest
MRI	Magnetic resonance imaging
NED	No evidence of disease
NCI	National cancer institute
NY-ESO-1	New York esophageal squamous cell carcinoma-1
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PT	Preferred term
PTT	Partial thromboplastin time
QoL	Quality of life
QTc	Heart rate-corrected QT interval
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Stable disease
SOC	System organ class

TEAE	Treatment Emergent Adverse Event
TTNT	Time-to-next treatment
VAS	Visual analogue scale
WBC	White blood cell (count)
WHO	World Health Organization

1 INTRODUCTION

This study is a global, randomized, double-blind, placebo-controlled, phase 3 study designed to evaluate the efficacy and safety of the CMB305 vaccine regimen versus placebo in subjects with synovial sarcoma expressing NY-ESO-1.

This document describes the detailed statistical methodology applied in analyzing data of the study IMDZ-04-1702. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock.

The material presented in this section is based on the trial protocol version 2.0, dated 27 April 2018. This plan may be revised during the study to accommodate protocol amendments.

2 STUDY OBJECTIVE

2.1 Primary Objective

The primary objective is to evaluate the efficacy of CMB305 versus placebo in subjects with synovial sarcoma expressing NY-ESO-1 through the analysis of progression-free survival (PFS) and overall survival (OS).

- Progression-free survival (PFS), by investigator assessment, using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Overall survival (OS)

2.2 Secondary Objective

- To evaluate the efficacy of CMB305 versus placebo using:
  - Time- to-next treatment (TTNT)
  - Distant metastasis-free survival (DMFS)
  - Objective response rate (ORR) (defined by RECIST v1.1)
- To evaluate the safety and tolerability of CMB305 versus placebo
- To evaluate quality of life (QoL)

2.3 Exploratory Objective

- To evaluate the anti-NY-ESO-1 immune response and histologic and molecular changes in peripheral blood and tumor tissue and their association with clinical outcomes.

3 STUDY DESIGN

3.1 Overall Plan

This is a global, randomized, double-blind, placebo-controlled, phase 3 study designed to evaluate the efficacy and safety of the CMB305 vaccine regimen versus placebo in subjects with synovial sarcoma expressing NY-ESO-1.

To be eligible, subjects must be receiving a first-line systemic anti-cancer therapy for unresectable locally-advanced or metastatic synovial sarcoma and have no evidence of progression at the time of randomization.

3.1.1 Study Treatment

Subjects who meet eligibility criteria will be randomly assigned in a 1:1 ratio to receive one of the following centrally randomized treatments: placebo and CMB305

Arm A: Placebo

Placebo = LV305 placebo + G305 placebo (NY-ESO-1 placebo + GLA-SE placebo)

Matching placebo for LV305 and NY-ESO-1 will be normal saline, and matching placebo for the GLA-SE component of G305 will be the non-active stable emulsion (SE).

Arm B: CMB305

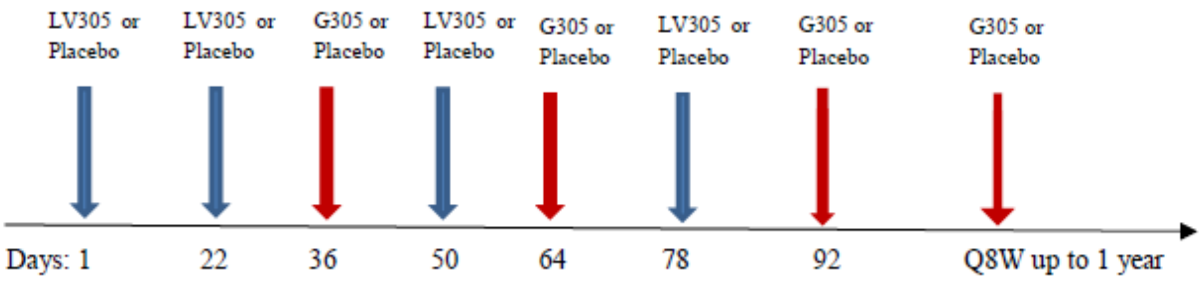
CMB305 = LV305 + G305 (NY-ESO-1 + GLA-SE)

- LV305 is a dose of 4 × 1010 vector genomes (vg).
- G305 is composed of 5 µg GLA-SE admixed with 250 µg of NY-ESO-1 protein.

3.1.2 Treatment Administered

The CMB305 or matching placebo dosing regimen is presented in Figure 1.

Figure 1 CMB305 or Matching Placebo Dosing Regimen



LV305 or matching placebo is administered as 4 separate 1-mL SC on Days 1, 22, 50, and 78, each preferably administered in a separate upper or lower limb (or stump if the subject has had a resection), or administered at least 3 cm from the neighboring injection site if on the same limb/stump.

G305 or matching placebo is administered IM on Days 36, 64, and 92, and then at 8-week intervals up to 1 year or until investigator-determined PD (using RECIST v1.1) is documented or unacceptable toxicity, whichever occurs first..

Three placebos (fully matched to characteristics of LV305, the NY-ESO-1 protein, and GLA-SE) will be provided for this study and will be administered on the same schedule and by the same route as the corresponding experimental therapy components to ensure that the sponsor, site personnel (including pharmacist), and subjects remain blinded to study drug for the duration of the study.

3.2 Study Population

Approximately 248 subjects who have synovial sarcoma expressing NY-ESO-1 will be enrolled and randomly assigned in a 1:1 ratio to treatment with CMB305 or placebo.

The subjects in this study must have documented histologic diagnosis, and unresectable locally-advanced or metastatic synovial sarcoma with at least 6 months life expectancy, have IHC test results from tumor biopsy for NY-ESO-1 that are positive, and be no younger than 12 years old without any evidence of disease progression during/after the first-line systemic anti-cancer therapy in Pre-screening period.

The subjects are excluded if they have received prior anti-NY-ESO-1 therapy, or have history of brain metastasis, or have inadequate organ function, significant electrocardiogram (ECG) finding or cardiovascular disease, or have active tuberculosis or hepatitis B (HepB), hepatitis C (HepC), or human immunodeficiency virus (HIV) infection.

For the full list of inclusion and exclusion criteria, please refer to section 4.2 and 4.3 of the study protocol.

3.3 Randomization, Stratification and Blinding

3.3.1 Randomization and Stratification

Subjects will be randomly allocated in a 1:1 ratio to receive placebo (Arm A) or CMB305 (Arm B) according to a centrally randomized treatment schedule.

An IRT system will use the following stratification factors at the time of randomization:

- Disease status at screening: locally advanced unresectable (LAUR) vs metastatic
- Tumor response during screening: stable disease (SD)/partial response (PR) vs complete response (CR)/no evidence of disease (NED)

- Baseline presence of anti-NY-ESO-1 antibody (yes vs no).

3.3.2 Blinding

The study subjects, investigators, study site personnel, including the pharmacist, safety laboratory personnel, central imaging readers, sponsor, and representatives of the sponsor involved in the conduct and/or management of the study will be blinded to treatment assignment.

LV305 and its placebo will be identical in appearance; G305 and its placebos will be identical in appearance.

All study treatments (CMB305 or placebo) will be labeled with the study number, a unique number, and any additional information required in accordance with government regulations. Further details will be contained in the Pharmacy Manual provided to study sites.

The blind is only to be broken in cases of emergency where, upon documentation provided by investigator and verified by sponsor, immediate unblinding of the treatment is necessary in order to evaluate further course of action. For all cases requiring unblinding, the investigator is to contact the sponsor's medical monitor or designee, per local country regulatory authority.

3.4 Study Assessments

Safety, tolerability and efficacy of CMB305 will be assessed during the study.

The study will consist of 5 periods: Pre-screening, Screening, Treatment, Post-treatment, and Long-term Follow-up.

Pre-screening: subjects will attend a pre-screening visit within up to 151 days (Day -180 to Day -29) from the pre-screening informed consent form (ICF).

During the pre-screening period, subjects must still be receiving treatment with first-line systemic anti-cancer therapy, evaluate radiographic disease response and take immunohistochemistry (IHC) test for the presence of NY-ESO-1.

Once the investigator confirms 1) the subject has no evidence of progression (using RECIST v1.1) and 2) the IHC test results for NY-ESO-1 are positive (≥1% expression), then the Main Study ICF will be signed and subject will go to screening period.

Screening: The duration of the Screening period is 28 days (Day -28 to Day -1) and begins on the date of the Main Study ICF was signed and ends at time of randomization.

Subjects will undergo additional eligibility assessments and the investigator will confirm there is no evidence of progression (using RECIST v1.1).

Treatment: The Treatment period will begin on the day of randomization (Day 1), and continue until investigator-determined progressive disease (PD) (using RECIST v1.1), unacceptable toxicity, or 1 year after the first dose, whichever occurs first.

Post-treatment: For subjects who discontinue study treatment for reasons other than disease progression, the post-treatment period will begin at the end of treatment and will continue until investigator-determined radiographic PD (using RECIST v1.1) is documented.

Long-term Follow-up: The Long-term Follow-up period will begin at the time investigator-determined PD (using RECIST v1.1) is documented and will continue for up to 5 years, until the date of death, or until sponsor notification of study closure.

The detailed assessment plan is listed in table 1 and 2.

Table 1 Schedule of Events for the Pre-Screening and Screening Periods

	Pre-Screening Period[a]	**Screening Period[b]**
Visit	**1**	**2**
Timeline – Day(s)	**Day-180 to Day-29**	**Day -28 to Day -1**
Procedures		
Informed consent/assent[c]	X	X
Obtain or collect tumor sample for IHC testing of NY-ESO-1 expression[d]	X	
Collect fresh tumor sample to assess tumor biomarkers (frozen and FFPE) at select U.S. sites		X
Investigator review of tumor response to first-line systemic anti-cancer therapy using RECIST v1.1[e]	X	
Obtain images collected at the standard-of-care time point for the first evaluation of response to first-line systemic anti-cancer therapy[f]	X	
Tumor imaging (CT/MRI) for baseline tumor response assessment[g]		X
Inclusion and exclusion criteria		X
Demographics and medical history		X
Tumor-specific therapy history		X
Record prior and concomitant medications		X
Blood for chemistry laboratory tests[h]		X
Blood for hematology laboratory tests[h]		X
Blood for coagulation tests laboratory tests[h]		X
HIV, hepatitis B (HepB), and hepatitis C (HepC) tests[h]		X
Blood for anti-NY-ESO-1 plasma ELISA[i]		X
Blood for circulating tumor genomics[j]		X
Urinalysis[h]		X
Pregnancy test[k]		X
Vital sign measurements[l]		X
Physical examination[m]		X
12-lead electrocardiogram		X
ECOG		X
QoL assessment		X
Blood for LV305 persistence		X

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; ELISA = Enzyme-linked immunosorbent assay; HIV = human immunodeficiency virus; ICF = informed consent form; IHC =

immunohistochemistry; MRI = magnetic resonance imaging; NY-ESO-1 = New York esophageal squamous cell carcinoma-1; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors

[a] The Pre-screening period is up to 151 days (Day -180 to Day -29) and is the time from the subject and/or their legally authorized representative signing the Pre-screening ICF/assent form to the time of signing the Main study ICF/assent form. The Pre-Screening can commence at any time after first dose of first-line systemic anti-cancer therapy.

[b] The duration of the Screening period is 28 days (Day -28 to Day -1) and begins on the date the subject and/or their legally authorized representative sign the Main study ICF/assent form. At Day 1, subjects must have documented completion of first-line systemic anti-cancer therapy and must have received at least 4 to 8 cycles of therapy (or no more than 180 days of systemic anti-cancer therapy).

[c] Two informed consents (subjects aged ≥18 years and legally authorized representatives of subjects aged 12 to <18 years) or assents (subjects aged 12 to <18 years) will be used in this study. The Pre-screening ICF/assent form will allow for IHC testing of the tumor sample (fresh or archival) for the presence of NY-ESO-1 and review of the tumor images (CT or MRI) collected before administration of the first dose of first-line systemic anti-cancer therapy and at the subsequent standard-of-care time point for the first evaluation of response to first-line systemic anti-cancer therapy. The Main study ICF/assent must be signed before any Screening study-related procedures are initiated. Before the Main study ICF/assent can be signed, results of IHC testing for the presence of NY-ESO-1 (≥1% expression) must be available from the central laboratory, and the investigator-evaluated tumor response (using RECIST v1.1) to first-line systemic anti-cancer therapy must be documented.

[d] At Pre-screening, a tumor sample (fresh or archival) will be collected or obtained for the IHC testing by the central laboratory for the presence of NY-ESO-1 expression (≥1% expression). Archival tumor tissue or fresh tumor tissue will be obtained from a biopsy or a resected tumor lesion, as appropriate (tumor tissue may be from a sample obtained within 18 months before signing the Pre-screening ICF/assent form).

[e] Obtain images (CT or MRI) collected before administration of the first dose of first-line systemic anti-cancer therapy. Images will be assessed by the investigator using RECIST v1.1. Investigator assessment of all target and non-target lesions and tumor response assessment will be captured in the eCRF. Subjects who have a tumor response of stable disease with evidence of ≥15% to 20% increase in tumor burden will be submitted for central review to adjudicate the investigator's assessment of tumor response prior to randomization.

[f] Obtain and review images (CT or MRI) collected at the standard-of-care time point for the first evaluation of response to first-line systemic anti-cancer therapy. The subject's response to first-line systemic anti-cancer therapy will be assessed by the investigator using RECIST v1.1 and documented in the eCRF.

[g] Tumor imaging (CT or MRI) will be performed after completion of the planned 4-cycles to 8-cycles of first-line systemic anti-cancer therapy for the evaluation of response at baseline, as assessed by the investigator using RECIST v1.1. The images collected at this time point will serve as the baseline assessment for the efficacy evaluations. These images must be collected within 28 days after the date of last dose of first-line systemic anti-cancer therapy.

[h] Results from the central laboratory will be used to determine eligibility and for the safety analysis. Laboratory tests performed by the central laboratory will include: chemistry with liver function tests, lactate dehydrogenase, alkaline phosphatase, albumin, hematology with complete blood count with differential, HIV, HepB, and HepC. Coagulation samples will be drawn only at Screening and shipped to the central laboratory (prothrombin time, partial thromboplastin time, and international normalized ratio) for analysis. Urinalysis will be conducted at the central laboratory. All laboratory assessments to be performed are listed in protocol Table 4.

[i] The peripheral blood on all subjects must be collected Day -28 to Day -7 during Screening and will be used for plasma ELISA testing; results of the assessment will be used for stratification and randomization.

[j] For circulating tumor genomics, please see lab manual.

[k] For FCBP, serum pregnancy testing will be performed during Screening.

[l] Vital sign measurements will include body temperature, heart rate, respiratory rate, and resting systolic and diastolic blood pressure.

[m] At Screening, the physical examination should include an evaluation of organ systems, including, but not limited to, head and neck; chest and lungs; cardiac; gastrointestinal; neurologic; endocrine; and musculoskeletal and integument. Other organ systems should be evaluated as directed by medical history or current symptoms. Measurements of body weight and height will be obtained.

Table 2 Schedule of Events for the Treatment Period through Long-term Follow-up Period

	Treatment Period								Post-Treatment Period[c]	Long-term Follow-up Period[d]
	Prime Phase							Boost Phase	Follow-up	Follow-up
Visit	3	4	5	6	7	8	9	10+		
Timeline – Week(s)	1	3	5	7	9	11	13	Every 8 weeks[b]	Every 3 months until documentation of disease progression	Every 3 months for up to 5 years or until date of death
Timeline – Day(s)	1[a]	22	36	50	64	78	92	Up to 1 year		
Allowed Visit Window - Days	+3	±3	±3	±3	±3	±3	±3	±7	±7	±14
Procedures										
Enrollment, stratification, and treatment allocation[e]	X									
Record prior and concomitant medications	X	X	X	X	X	X	X	X	X	X
Blood for central laboratory chemistry laboratory tests[f]	X	X		X	X		X			
Blood for central laboratory hematology[f]	X	X		X	X		X			
Urinalysis[f]	X						X			
Blood for anti-NY-ESO-1 plasma ELISA[g]	X						X			
Blood for immunity assessments[g]	X						X	X		
Blood for circulating tumor genomics[h]	X						X			
Pregnancy test[i]	X						X			
Vital sign measurements[j]	X	X	X	X	X	X	X	X		
Physical examination[k]	X	X	X	X	X	X	X	X		
12-lead electrocardiogram							X			
Tumor imaging with response assessment by RECIST v1.1 (CT scan or MRI)[l]					X			X	X	
ECOG Performance Status	X	X	X	X	X	X	X			
QoL assessment[m]	X						X	X		
Report AEs and SAEs[n]	X	X	X	X	X	X	X	X	X	X

	Treatment Period								Post-Treatment Period[c]	Long-term Follow-up Period[d]
	Prime Phase							Boost Phase	Follow-up	Follow-up
Visit	3	4	5	6	7	8	9	10+		
Timeline – Week(s)	1	3	5	7	9	11	13	Every 8 weeks[b]	Every 3 months until documentation of disease progression	Every 3 months for up to 5 years or until date of death
Timeline – Day(s)	1[a]	22	36	50	64	78	92	Up to 1 year		
Allowed Visit Window - Days	+3	±3	±3	±3	±3	±3	±3	±7	±7	±14
Study drug administration: Placebo (Arm A) LV305 (Arm B)	X	X		X		X				
Study drug administration: Placebo (Arm A) G305 (Arm B)			X		X		X	X[b]		
Blood for LV305 persistence[p]							X	X	X	X
Tumor biopsy[q]							X			
Survival status[r]									X	X

AE = adverse event; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; IHC = immunohistochemistry; MRI = magnetic resonance imaging; NY-ESO-1 = New York esophageal squamous cell carcinoma-1; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event

a Day 1 will occur within 28 days after the last dose of first-line systemic anti-cancer therapy or the last day of local regional therapy. Day 1 procedures must occur within 72 hours of randomization.

b In the Boost Phase, tumor imaging will be performed every 8 weeks for 1 year or until investigator-determined progressive disease, using RECIST v1.1, is documented.

c The Post-treatment period will begin at the end of treatment and will continue until investigator-determined progressive disease, using RECIST v1.1, is documented. If a subject has reached 12 months on study without disease progression, tumor imaging will be performed every 12 weeks ±7 days until disease progression.

d The Long-term Follow-up period will begin at the time investigator-determined progressive disease (using RECIST v1.1) is documented and will continue for up to 5 years, until the date of death, or until sponsor notification of study closure.

e The following information must be available at Day 1: subjects must have documented completion of first-line systemic anti-cancer therapy and must have received at least 4 to 8 cycles of therapy (or no more than 180 days of systemic anti-cancer therapy); results of IHC testing for the presence of NY-ESO-1 (≥1% expression) must be available from the central laboratory; and the investigator-evaluated tumor response, using RECIST v1.1, to first-line systemic anti-cancer therapy must be documented.

[f] During the study dosing period, all laboratory assessments are to be performed prior to dosing. Hematology and clinical chemistry samples will be shipped to the central laboratory for safety analyses, and will include: chemistry with liver function tests, lactate dehydrogenase, alkaline phosphatase, albumin, thyroid function, and hematology with complete blood count with differential. Urinalysis will be conducted at the central laboratories. All laboratory tests to be performed are listed in protocol Table 4.

[g] Blood for anti-NY-ESO-1 T cell assessments to be collected only for subjects on prior to dosing on Day 1 and Day 92 only at select US sites. Additional blood samples for immunity assessments will be drawn for any subject who has no evidence of tumor progression by RECIST v1.1 at 1 year at the same select US sites.

[h] For circulating tumor genomics, please see lab manual.

[i] For FCBP, serum and confirmation urine pregnancy testing will be performed by the local laboratory prior to dosing on Day 1; results must be negative. Serum pregnancy testing will be performed by the local laboratory prior to dosing on Day 92; results must be negative. Pregnancy testing will be performed more frequently as required per local regulatory authority.

[j] Vital sign measurements will include body temperature, heart rate, respiratory rate, and resting systolic and diastolic blood pressure. On the day of each dosing, vital signs will be obtained no more than 60 minutes before dosing and 30 minutes after dosing (±10-minute window).

[k] Once the Screening physical examination has been conducted, a simple symptom-directed physical examination should be performed for all subsequent visits. Measurements of body weight will be obtained at every visit.

[l] Beginning in the Treatment period, imaging will be performed at 8-week intervals after Day 1 administration of the first dose of the study drug for up to 1 year or until the time investigator-determined progressive disease, using RECIST v1.1, is documented.

[m] QoL assessments will be conducted at the study site. In addition to the screening QoL assessment, the QoL assessment will be obtained on Day 1 prior to the first dose of study drug, at Day 92, and at 6 months and 12 months after Day 1. All subjects, regardless of their disease response status, will continue to have QoL assessments performed for 12 months after Day 1.

[n] All AEs and SAEs will be collected until 30 days after administration of the last dose of the study drug. Information on any SAEs and new malignancies that come to the attention of the site staff that are considered at least possibly related to CMB305 will be collected until the time of last subject contact.

[o] After Day 92, G305 or placebo will be given on Day 148 and at 8-week intervals as a boost for up to 1 year, or until unacceptable toxicity, or investigator-determined progressive disease, using RECIST v1.1, is documented, whichever occurs first. AEs will be reported at the subsequent visit and until at least 30 days after the last dose.

[p] Peripheral blood will be collected at the following times after administration of the first dose of study drug on Day 1: no sooner than Day 92 (3 months) but up to 4 months; 6 months up to 9 months; and 1 year up to 15 months; and then yearly at no sooner than every 12 months but not more than 15 months up to the time of study closure. If all post-treatment assays are negative during the first year, then the yearly samples should be archived. Samples will be used for an assay to test for persistence of LV305.

[q] The Day 92 biopsy may be obtained within ±2 weeks of Day 92, Day 365, and at time of progression event will be encouraged at the same selected US sites per footnote “g”.

[r] Survival status will be obtained by any means, which includes, but is not limited to, public records where allowed per local authority, telephone contact, during an in-clinic visit, chart review, or via communicating with an individual (e.g., family, friend, referring health care provider) who is knowledgeable of the subject’s survival status. More frequent survival status updates may be obtained at the request of the sponsor.

4 SAMPLE SIZE DETERMINATION

A total of 248 subjects will be randomly assigned in a 1:1 ratio such that 124 subjects will be included in each of the 2 treatment arms. The study is powered at 90% with 179 death events required to detect a HR of 0.59, which corresponds to a 41% reduction in the risk of death, and an approximately 69% increase in median survival compared with a placebo median survival of 20 months, and uses a 1-sided log-rank test, with an alpha of 0.0125, a 1:1 randomization ratio, and an interim OS non-binding futility analysis with boundary of HR = 1.0 at 67% of information time (120 death events from the 179 required death events for the final OS analysis). A total of 248 subjects will yield the 179 events required, under the assumption of 24 months for enrollment (25% of subjects enrolled in the first year and 75% of subjects enrolled in the second year) plus 42 additional months of follow-up.

With 141 PFS events, the study is powered at 90% to detect a HR of 0.55, which corresponds to a 45% reduction in the risk of PFS events (either disease progression or death), and an approximately 82% increase in median PFS compared with a placebo median PFS of 4 months, and uses a 1-sided log-rank test, with an alpha of 0.0125, and a 1:1 randomization ratio.

5 STUDY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint

Two primary efficacy endpoints of PFS by investigator's assessment and OS will be compared between CMB305 and placebo.

5.1.1.1 Progression-free Survival (PFS)

PFS by investigator's review will be the primary endpoint. PFS by investigator's assessment is defined as the time from randomization to the investigator-determined (using RECIST v1.1) date of disease progression or death, whichever comes first:

[PFS = investigator-determined PD date or death date – randomization date + 1].

Investigator-determined PD event includes the followings:

- Disease progression per RECIST v1.1
- Symptomatic deterioration (global health deterioration) as described by RECIST v1.1
- For subjects with NED at time of randomization, any new malignant lesion that occurs after randomization per RECIST v1.1

PFS will be right-censored based on Table 3 for subjects who meet the following conditions:

Table 3: Censoring Rules for PFS Analysis

Situation	Date of Censoring	Outcome
No investigator-determined PD or death at the time of study discontinuation	Date of last adequate tumor assessment with no evidence of PD on or before study discontinuation	Censored
Investigator-determined PD or death after 2 or more consecutive missed tumor assessments	Date of last adequate tumor assessment with no evidence of PD that is before the first missed assessment	Censored
Investigator-determined PD or death after the start of subsequent intervention	Date of last adequate tumor assessment with no evidence of PD that is before the first subsequent intervention	Censored
No baseline and/or adequate post baseline tumor assessments or death at time of study discontinuation	Date of randomized	Censored

* Adequate tumor assessment: tumor assessments with CR, PR, or SD as overall tumor response.

PFS by independent radiological review, if required, will be the supportive endpoints and follow similar definition and censorship as PFS by investigator's assessment, except that only PD from independent radiological review will be included as PD (symptomatic deterioration and clinical PD will not be included as PD).

5.1.1.2 Overall Survival (OS)

OS is defined as the time from randomization to the date of death from any cause:

[OS = death date – randomization date + 1].

Any subject without a date of death in the database at the time the survival analyses are performed will be censored at the date of last known alive. The date of death is recorded on the death report form page. The last known alive date is defined as the last date the subject was known to be alive at the study. The last known alive date will be the latest date among the following:

- Last assessment date among, e.g., vital signs assessment, performance status assessment, tumor imaging, and assessment date in third-party data such as central laboratory, ECG etc.
- Last adverse events date
- Last known alive date collected on the 'Long-term Follow-up' page of eCRF
- Date of last contact in 'End of Study' page of the eCRF

- Last date among last study treatment, and last concomitant medications, subsequent interventions administered after study treatment discontinuation.

5.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of TTNT, DMFS, ORR and QoL using the EQ-5D-5L or EQ-5D-Y will be compared between treatment arms.

5.1.2.1 Time to Next Treatment (TTNT)

TTNT is defined as the time from randomization to the start of post-study treatment subsequent intervention:

[TTNT = start date of subsequent intervention – randomization date + 1].

Subsequent intervention includes anticancer therapy, cancer-related surgery and local regional therapy. Subjects who do not start any post-study treatment intervention will be censored at their last known date of being alive (same as OS).

5.1.2.2 Distant Metastasis-Free Survival (DMFS)

DMFS is defined as the time from randomization to evidence of a new distant metastasis not documented at time of randomization:

[DMFS = a new distant metastasis documented date – randomization date + 1].

Subjects who do not have any new distant metastasis will be censored at their last tumor assessment.

5.1.2.3 Objective Response Rate (ORR)

The ORR is defined as the percent of subjects who achieve either CR or PR per RECIST1.1 by investigator's assessment as best response:

[ORR = (CR+PR)/total number of subjects].

The best overall response is determined once all the data for the subject is known. No confirmatory measurement for CR or PR is required in this study. The best overall response is defined as the best response (in the order of CR, PR, SD, and PD) among all overall responses recorded from randomization until the last radiographic tumor assessment (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). All tumor assessments after the first PD will be ignored.

ORR by independent radiological review, if required, will be the supportive endpoints and its definition and censorship are similar to the ORR by investigator's assessment defined above.

5.1.2.4 Quality of Life (QOL) - EQ-5D-5L and EQ-5D-Y

QOL will be evaluated using the EuroQol 5-Dimension 5 Level (EQ-5D-5L) for subjects ≥18 years of age and for subjects 12 to <18 years of age.

EQ-5D-5L

The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (EQ VAS). The descriptive system comprises 5 dimensions: mobility, self care, usual activities, pain/discomfort, anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state.

EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, will be converted into a single index value. The index values, presented in country specific value sets, are a major feature of the EQ-5D instrument. EQ-5D-5L scoring will be based on EQ-5D-5L User Guide 2015 (UK Version 2, please refer to Appendix 2 for index score weights).

5.1.3 Exploratory Efficacy Endpoint

Intratumoral and peripheral blood anti-NY-ESO-1 immune changes biomarker analysis will be included in a Supplemental Statistical Analysis Plan (SSAP). This includes anti-NY-ESO-1 immune response and histologic and molecular changes in peripheral blood and tumor tissue and their association with clinical outcomes.

5.2 Safety Endpoints

5.2.1 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any AE that newly appeared or worsened in severity following initiation of the study treatment administration until 30 days after last dose of the study treatment. In additional, all study treatment related AEs are treated as TEAE.

Medical Event of Interest (MEOI) is defined as selected non-serious AEs are classified as MEOIs, refer to protocol section 6.4.7.5 for more details.

Immune-mediated event --

5.2.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include hematology, serum chemistry, urinalysis, coagulation and viral tests.

Hematology: Hematocrit (HCT); hemoglobin (HGB); mean corpuscular hemoglobin (MCH); mean corpuscular hemoglobin concentration (MCHC); mean corpuscular volume (MCV); platelet count; red blood cell (RBC) count; white blood cell (WBC) count with differential; absolute neutrophil count (ANC); absolute lymphocyte count.

Serum Chemistry: Albumin; alkaline phosphatase; alanine aminotransferase (ALT); aspartate aminotransferase (AST); total protein; blood urea nitrogen (BUN); calcium; carbon dioxide; chloride; creatinine; creatinine clearance; uric acid; gamma-glutamyl transferase (GGT); glucose; lactate dehydrogenase (LDH); phosphorus; potassium; sodium; total bilirubin; direct bilirubin; thyroid stimulating hormone (TSH) (if TSH abnormal then T3, T4 to be evaluated).

Urinalysis: Appearance; bilirubin; color; glucose; ketones; microscopic examination of sediment; nitrite; occult blood; pH; protein; specific gravity; urobilinogen.

Coagulation: Prothrombin time (PT); partial thromboplastin time (PTT); international normalized ratio (INR).

Viral Tests: Hepatitis B (HepB), hepatitis C (HepC), or human immunodeficiency virus (HIV) infection.

5.2.3 Vital Signs

Vital Signs include body temperature, heart rate, respiratory rate, and resting systolic and diastolic blood pressure. On the day of each dosing, vital signs will be obtained before dosing and 30 minutes after dosing (±10 minute window). Blood pressure and heart rate will be measured no more than 60 minutes before the scheduled dosing.

5.2.4 Electrocardiogram (ECG)

ECG includes heart rate, PR interval, RR interval, QRS duration, QT interval, QTc interval and overall interpretation.

5.2.5 Other Safety Endpoints

ECOG, physical examination by body system, dosing and extent of exposure, prior and concomitant medication, and LV305 persistence will be also included to evaluate the safety of study treatment.

6 ANALYSIS SETS

Three analysis sets are considered in the statistical analysis of the study: Intent-to-Treat set (ITT), Efficacy Evaluable set (EE), and Safety set.

6.1 ITT Set

The ITT set consists of all subjects randomized. All analyses of this set will be based on the randomized treatment arm to which the subjects are assigned. Efficacy analyses performed in the ITT set will be considered to be the primary indicator of efficacy.

6.2 EE Set

The EE set consists of all subjects without major protocol violations, who have received at least 1 dose of study treatment, and have the baseline and at least 1 post-baseline tumor assessments available. The EE set will be analyzed according to the treatment received. Efficacy analyses performed in the EE set will be considered to be supportive.

6.3 Safety Set

The Safety set consists of all subjects taking any amount of study drug. The safety set is the primary set for safety analyses including AEs and clinical laboratory data. Study treatment exposure also will be summarized using the safety set.

7 GENERAL STATISTICAL CONSIDERATIONS

7.1 Data Summaries and Conventions

Formal statistical tests will be performed for inference, unless otherwise specified, P-values will be reported to four (4) decimal places and those less than 0.0001 will be reported as <0.0001, 2-side 95% confidence intervals will be presented where appropriate. All analyses will be presented by treatment arm and overall.

Unless specified otherwise, all summaries will be comprised of standard descriptive statistics. Standard descriptive statistics include:

- For continuous parameters: number of observations (or subjects), mean, standard deviation, median, minimum and maximum
- For categorical parameters: frequency and percent of observations in each category

The following rules will be used for the days to months/years conversion:

- 1 month = 30.4375 days
- 1 year = 365.25 days

As appropriate, all data collected on the electronic case report form (eCRF) will be presented in data listings. All statistical analyses will be performed using SAS® version 9.4 or above.

7.2 Handling of Dropouts or Missing Data

In order to achieve the goal of a well-conducted clinical study according to Good Clinical Practice, every effort will be made to collect all data. However, despite best efforts, it may be inevitable that some data may be missing or incomplete.

In the subject data listing all available data, including partial data, will be presented as they are recorded on the case report forms (CRFs).

Time to event or duration of event endpoints will be calculated based on the study day of the event date (or censoring date) rather than visit number or visit label. Missing efficacy or safety data will not be imputed unless otherwise specified.

7.2.1 Partial Dates for Adverse Events

For adverse events (AEs) with partially missing start dates, it's necessary to impute an AE start date to define TEAE. For the partial date of AE start date (missing day and/or month and/or year), the following imputation rules will be applied:

- If year of the AE start date is missing, no date imputation will be made and the AE will not be considered treatment-emergent unless the investigator has deemed it to be treatment-related.
- If both day and month of the AE start date are missing but year is known, the day and month will be imputed with the day and month of the first study dose date if the year is equal to the year of first dose. Otherwise, the month and day is imputed as the first day of the year (01 Jan).
- If only day is missing, and if the year and month are equal to the first dose date, the day will be imputed as day of the first dose date. Otherwise, the day will be imputed as "01."

Partial AE end dates will be imputed for non-ongoing AEs as follows:

- If year of the AE end date is missing, no date imputation will be made.
- If both day and month of the AE end date are missing but year is known, the date of the last dose of study drug will be used as the end date of the AE. Otherwise, December 31 will be used as the end of the AE.
- If only day is missing, the date of last dose of study drug will be used as the end date of the AE. Otherwise, the last day of the month will be used as the end of the AE.

7.2.2 Partial Dates for Concomitant Medication

For concomitant medications (CM) 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:

- If year of the CM start date is missing, no date imputation will be made.
- If both day and month of the CM start date are missing but year is known, the day and month will be imputed with the day and month of the first study dose date if the year is equal to the year of first dose. Otherwise, the month and day is imputed as the first day of the year (01 Jan).
- If only day is missing, and if the year and month are equal to the first dose date, the day will be imputed as day of the first dose date. Otherwise, the day will be imputed as "01."

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

- If year of the CM end date is missing, no date imputation will be made.
- If both day and month of the CM end date are missing but year is known, 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.
- If only day is missing, 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.

7.3 Multiplicity

The study is to be conducted with PFS and OS as 2 primary endpoints with the goal of a regulatory approval based on either PFS or OS. The overall type I error probability is specified to be 1-sided 0.025 with success for either of the 2 primary endpoints defining study success using the Bonferroni method to specify that each endpoint will be evaluated using a type I error probability of 1-sided 0.0125 in order to protect the overall type I error. In case both final PFS analysis and final OS analysis have 1-sided $0.0125 \leq p < 0.025$, or one of the analyses has 1-sided $0.0125 \leq p < 0.025$ while the other has 1-sided $p < 0.0125$, the overall type I error will be controlled at 1-sided 0.025 with statistical significance applied to both PFS and OS analyses using the Hochberg method.

7.4 Interim Analyses and Data Monitoring

A data monitoring committee will be established with the responsibility of safeguarding the interest of study subjects and maintaining the overall integrity of the study. The DMC will review safety data periodically during the study as described under Section 8.17 (Data Monitoring Committee) of the protocol and will evaluate the results of final PFS analysis and a planned interim OS analysis to assess futility with the possibility of a recommendation for stopping the study early because of futility. The OS non-binding futility boundary is set to be HR = 1.0. It will be conducted at 67% of information time (120th death event from the 179 required death events for final OS analysis). If deemed necessary by the DMC, unblinded data may be reviewed on a case-by-case basis. The sponsor will remain blinded to study treatment until either

1 of the 2 primary endpoints is met or until the study has been stopped early. Details of DMC function will be governed by a DMC Charter developed by the sponsor and accepted by DMC members.

8 STATISTICAL ANALYSIS

8.1 Study Population

8.1.1 Subject Disposition

Subject disposition and the incidence of study discontinuation (and reason for discontinuation) will be tabulated for all enrolled patients by treatment arm. The information will be summarized as follows for subject disposition per treatment arm and overall:

- Subject Status (Prime Phase [Day 1 to 92], Boost Phase [Day 92 up to Day 365], Post Treatment Period [Last dose to PD], and Long Term Follow-up [PD to end of study])
- Treatment Completed
- Primary Reason for Treatment Discontinuation (as reported on CRF)
- Study Completed
- Primary Reason for Study Discontinuation (as reported on CRF)

At the same time, the number and percentage of subjects in each analysis set and reason for excluding from the specified analysis set will also be tabulated.

Listings will be presented for data relevant to subject disposition.

8.1.2 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. The subject incidence of CSR reportable protocol deviation (IPD) will be summarized by deviation type based on safety set.

A listing will be provided for all protocol deviations.

8.1.3 Demographic and Baseline Characteristics

All demographics and baseline characteristic variables will be summarized by treatment arm and overall for ITT set.

- Demographic and baseline characteristics data, including age (continuous and grouped as <65, or ≥65 years), sex, childbearing potential, race, ethnicity, weight, height, BMI and ECOG will be summarized.
- Disease history and characteristics will be summarized and include:
  - Time from Initial Diagnosis (month) [(date of randomization – date of initial diagnosis + 1)/30.4375]
  - TNM separated stage at initial diagnosis
  - AJCC stage at initial diagnosis
  - Grade (French or FNCLCC) at initial diagnosis
  - t(X;18) Translocation
  - BCOR 6 Present
  - Tumor Monophasic or Biphasic
  - Any Prior Cancer Related Treatment (Yes, No)
  - Any Prior Cancer Related Surgery (Yes, No)
  - Type of prior therapy (adjuvant/neoadjuvant chemotherapy and surgery and/or radiotherapy)
  - First-Line systemic anti-cancer therapy (regimen, number of cycles, type, best response, total dose)

8.2 Efficacy Analyses

The efficacy analysis will be performed based on ITT set and supportive analysis will be performed based on EE set.

For PFS and ORR, primary analyses will be performed for the scan results determined by the investigator assessment, scan results by independent radiological review (IRC), if required, will be the supportive analysis.

8.2.1 Analytic Standard

8.2.1.1 Data Cutoff Date

Associated with each analysis is a data cutoff date. The key analyses will use the data cutoff date to censor event dates, and this may result in an event date turning into a censored date. Additional sensitivity analyses without data cutoff censoring will also be done when there has been data cutoff censoring, especially when data cutoff censoring results in loss of events.

8.2.1.2 Assessing Clinical Site Homogeneity

It is important to assess clinical site homogeneity with respect to the primary and secondary outcomes. Following is the method that will be used to obtain a descriptive assessment of clinical site homogeneity.

Assume each clinical site is identified by a unique code. It is often the case that one or more clinical sites will fail to have at least one subject assigned to each arm. All such clinical sites are to be pooled into a new pseudo clinical site with a new unique code. This new pseudo clinical site is to be used in the following analyses. A forest graph with sites or a grouping of sites will be created where the effect estimate will be displayed along with the 95% confidence interval. This graph is most effectively displayed if the estimates are sorted by estimate size.

8.2.2 Analysis of Primary Efficacy Variables

8.2.2.1 Primary Analyses

The null hypothesis of no difference in PFS/OS between CMB305 and placebo, in the ITT set, will be tested using a stratified log-rank test stratified by randomized stratification factors: disease status at screening (locally advanced unresectable versus metastatic), tumor response during screening (PR/SD versus CR/NED), and by baseline presence of anti-NY-ESO-1 antibody (yes versus no)).

The null hypothesis will be rejected and it will be concluded that PFS/OS on CMB305 is superior to that on placebo if the 1-sided p value at the final analysis for the stratified log-rank test is less than the pre-specified alpha as discussed in Multiplicity Section. Success for either of the 2 primary endpoints defines study success.

The Kaplan-Meier curve will summarize PFS/OS graphically by treatment arm. Tabular summaries of the Kaplan-Meier curves, including the median and 2-side 97.5% and 95% CI will be provided by treatment arm. The 4, 6, 8, and 10 month PFS rate and 12, 18, 24, and 30 month OS rate will be provided by treatment arm.

The associated HR and its 2-sided 97.5% and 95% CI will be provided using the stratified Cox proportional hazard model for PFS/OS, comparing treatment arm, stratified by the randomized stratification factors .

The final PFS analysis will be conducted when a total of 141 PFS events occur. The final OS analysis will be conducted when a total of 179 deaths occur.

8.2.2.2 Sensitive Analysis of Primary Endpoints (PFS/OS)

The sensitive analyses of primary endpoints will include:

- OS using the Safety set, according to the treated arm

- PFS by investigator assessment and OS using the EE set
- PFS by investigator assessment in the ITT set, with start of subsequent anti-cancer therapy as a PFS event
- PFS based on the IRC response assessment, if required, for both ITT and EE sets as supportive analysis

- Stratified Cox proportional hazard model for PFS or OS, in ITT set, with additional covariates of number of cycles in first line chemotherapy, and/or type of prior therapy (adjuvant/neoadjuvant chemotherapy and surgery and/or radiotherapy)
- PFS and OS by Fleming-Harrington weighted log-rank test with $\rho = 0$, $\gamma = 1$, for adjustment of delayed effects.
- The Fleming-Harrington weight for late effects is defined as below

  $W_n(t) = (S_n(t))^{\rho}(1 - S_n(t))^{\gamma}$
- PFS and OS by piecewise Cox proportional model in presence of non-proportional hazard for time-varying treatment effect:

  $$h\left(t \mid z_i\right) = h_o(t)\exp\left(\alpha z_{1i} + \beta_1 z_{2i} 1\left(t \le c_i\right) + \beta_2 z_{2i} 1\left(c_i < t \le c_{i+1}\right) + \beta_3 z_{2i} 1\left(t > c_{i+1}\right)\right)$$

  Where $\boldsymbol{Z_{1j}}$ is time-independent covariates such as stratification factors; $\boldsymbol{C_i}$ **and** $\boldsymbol{C_{i+1}}$ are cut points (e.g. 4 and 8 months, respectively) for time period and ***1(.)*** denotes the indicator function.

- PFS and OS not censoring events that occur after the cutoff..
- OS with competing events being taken into consideration. Competing events for death are "definite" lost to follow-up and withdrawal of consent for continued survival assessments. Both of these competing events are subject to revision for an individual subject with the passage of time. The cumulative incidence estimates will be plotted if the percent of subjects with competing events in either arm exceeds 3%.
- PFS with competing events being taken into consideration. Competing events for PFS event are lost to follow-up, withdrawal of consent, start of other anti-cancer therapy, or two or more missing scans prior to a PFS event. The cumulative incidence estimates will be plotted if the percent of subjects with competing events in either arm exceeds 3%.

8.2.2.3 Other Analyses of Primary Endpoints (PFS/OS)

- Strata homogeneity will be assessed by including arm by stratum interaction with main effect terms in the Cox proportional hazard model. If the 2-sided p value for this test of

homogeneity is significant at two-sided 0.10, then the stratum-specific hazard ratio estimates and confidence intervals will be computed. If the statistical criterion is not met then the test of homogeneity will be regarded as an exploratory analysis of the data collected. Thus, the outcome of the strata homogeneity test will not affect the interpretation of significance for the primary test, but will affect the way the results are presented or subsequently analyzed.

- Clinical site homogeneity will be assessed by including in the model site grouping multi-level main effect terms and also interaction terms for arm by categorical site grouping.
- Effect modifier analyses will be performed for putatively prognostic factors, including those explored previously in the literature as well as those hypothesized to be predictive in the context of this study. Effect modification will be assessed one factor at a time in stratified models. Each factor will be analyzed as either a natural dichotomy, a dichotomized ordered categorical with cut point chosen based on biologic considerations, or a continuous variable dichotomized at the overall median. A separate effect size estimate for arm and its 95% confidence interval will be computed for each level of the dichotomy using SAS. The four Kaplan-Meier estimates (arm by factor) for each of the factors analyzed as effect modifiers will be plotted on one graph.
- Cox proportional hazard models with multiple added prognostic covariates will be estimated. The covariates to be added will include those explored previously in the literature as well as those hypothesized to be predictive in the context of this study. Variable selection method such as stepwise method will be used to build the multivariate Cox proportional hazard model. . Interactions will also be explored for contribution to the model.

8.2.3 Analysis of Secondary Efficacy Variables

The secondary efficacy endpoints of TTNT, DMFS, ORR and QoL using the EQ-5D-5L or EQ-5D-Y will be compared between treatment arms.

The secondary efficacy endpoints will only be evaluated if at least one of the primary efficacy endpoints (PFS/OS) demonstrates superiority for CMB305 over placebo. Furthermore, to control the overall family-wise type I error rate at 1-sided $\alpha = 0.025$ for the secondary efficacy endpoints, the secondary efficacy endpoint of TTNT will be tested first at 1-sided alpha of 0.025. DMFS will be tested at 1-sided alpha of 0.025 only if TTNT shows significant improvement.

8.2.3.1 Time to Next Treatment (TTNT)

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

In the event that the percent of subjects with competing events such as death, lost to follow-up and withdrawal of consent in either arm exceeds 3%, the cumulative incidence estimates and Gray's test will be the main TTNT comparison between the treatment arms.

Example code for cumulative incidence estimates and Gray's test:

```
data risk;
      Baseline=1;
      trt=1; output;
      trt=2; output;
      format trt trtgroup.;
run;

proc phreg data=adtte (where=(paramcd='TTNT')) plots(overlay=strata)=cif;
      class trt / param=glm order=internal ref=first;
      model aval*Status(0) = trt baseline / eventcode=1;
      hazardratio 'Subdistribution Hazards' Group / diff=pairwise;
      baseline covariates=risk out=_null_ / rowid=trt;
run;
```

8.2.3.2 Distant Metastasis-Free Survival (DMFS)

DMFS will be analyzed using the same methods described for OS/PFS. In the event that the percent of subjects with competing events such as death, lost to follow-up and withdrawal of consent in either arm exceeds 3%, the cumulative incidence estimates and Gray's test will be the main DMFS comparison between the treatment arms.

8.2.3.3 Objective Response Rate (ORR)

ORR will be estimated using the ITT set and EE set by both investigator's and IRC response assessment, the percent of subjects will be provided along with their corresponding 2-sided the 95% exact CI using Clopper-Pearson method. Also the best overall tumor response (CR, PR, SD, PD and not evaluable) will be tabulated with 2-sided 95% CI in the same table.

Also, ORR will be compared between treatment arms using a logistic regression. Logistic regression will be performed with the treatment arm and all stratification factors as independent variables. Treatment arm will be compared using the likelihood ratio chi-square test.

8.2.3.4 QoL using the EQ-5D-5L or EQ-5D-Y

QOL analysis will be performed based on the ITT and EE set.

For EQ-5D-5L, number of subject and percentage will be provided by visit for each dimensions; observation, change and % change from baseline will be summarized for EQ-5D index value and VAS by each scheduled visit per treatment arm and overall.

Also, the treatment difference between CMB305 to placebo in the mean and change of the EQ-5D-5L index score/VAS from baseline to each post baseline analysis visit will be estimated using pattern mixture models. The following covariates will be considered: randomization stratification factors, baseline value of index score/VAS, treatment arm, analysis visit, analysis visit * treatment arm. Both index score/VAS values and change from baseline of each analysis visit will be included as dependent variable separately.

EQ-5D-Y will be analyzed using the same methods described for EQ-5D-5L, except for index score (no index score will be calculated for EQ-5D-Y).

Example code for mixed model for repeated measures for change from baseline of index score/VAS:

```
proc mixed data = data.qol method=REML;
      class subjid trt avisit stratum1 stratum2 stratum3;
      model socre_change = baseline stratum1 stratum2 stratum3 trt avisit
trt*avisit
      /NOINT SOLUTION DDFM=SAT;
      repeated avisit/ type = UN subject = subjid r;
      Lsmeans trt*avisit/diff CL;
run;
```

In the case of non-convergence, the covariance structure type and computation method will be adjusted until convergence achieves without errors.

8.2.4 Analysis of Exploratory Efficacy Variables

The baseline 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. 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.

8.3 Safety Analyses

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

Baseline is defined as the last non-missing value prior to the first dose date on day 1, unless otherwise noted.

8.3.1 Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded to a system organ class (SOC) and a preferred term (PT) using the current Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher. The severity of adverse events is assessed in National Cancer Institute (NCI) common toxicity criteria for adverse events (CTCAE) Version 4.03 or higher. Only TEAEs occurring from the time of the first dose through 30 days after the last dose of the study drug and medical events of interest, immune-mediated events and related AEs will be summarized, while all AEs captured in eCRF will be listed in data listings.

TEAE will be summarized by system SOC and PT, by severity, by relationship to study treatment, and by action taken. Tables will be sorted by frequency in incidence (the highest to lowest incidence in total column).

The following TEAEs will be tabulated and organized as follows:

- Overall Summary of Treatment Emergent Adverse Events
- TEAEs by system organ class and preferred term
- TEAEs by system organ class, preferred term and worst NCI CTCAE grade
- Severe TEAEs (Grade 3 or higher) by system organ class and preferred term
- SAEs by system organ class and preferred term and worst NCI CTCAE grade
- Related TEAEs by system organ class and preferred term
- Related SAEs by system organ class and preferred term
- Related TEAEs by system organ class, preferred term and worst NCI CTCAE grade
- Related SAEs by system organ class and preferred term and worst NCI CTCAE grade
- TEAEs leading to treatment discontinuation by system organ class and preferred term
- Related TEAEs leading to treatment discontinuation by system organ class and preferred term
- TEAEs classified as Medical Event of Interest (MEOI) by system organ class and preferred term
- TEAEs resulting in death by system organ class and preferred term

TEAEs will be summarized by presenting the number and percentage of subjects having at least one TEAE in each system organ class and preferred term. A subject with multiple occurrences of the same TEAE will be counted only once in the AE category.

Separate TEAE summaries will be presented by system organ class, preferred term, and maximum CTCAE (4.03 or higher) grade. A subject with multiple CTCAE grades for the same TEAE will be summarized under the maximum CTCAE grade recorded for the event.

AEs will also be listed for individual subjects, along with information regarding onset, duration, grade, relationship to the study drug, and outcome.

8.3.2 Clinical Laboratory Evaluations

All laboratory values will be converted to SI units and classified as normal, low, or high based on the normal ranges of local/central lab. All gradable laboratory parameters will be graded using the NCI CTCAE v4.03 or higher. The worst post-baseline toxicity grade will be summarized for hematologic, chemistry and coagulation parameters for all gradable laboratory parameters, otherwise, the worst abnormal will be presented instead.

Standard descriptive statistics will be presented for clinical laboratory tests, at baseline, each scheduled visit and change from baseline on safety set by each treatment arm and overall.

If lab results contain symbols like "<", ">", '>=" or "<=", extract the numeric value as the limit, Example: if result is ">0.1", "0.1" will be used for analysis.

Subject listings of laboratory test results for hematology, chemistry, urinalysis, coagulation and other laboratory tests will be provided separately. Values with CTC grade as 3 or above will be flagged in the listings.

8.3.3 Vital Signs

Vital signs are composed of systolic/diastolic blood pressure, respiratory rate, heart rate, and body temperature. Summary statistics for baseline, each post-baseline measurement, and change from baseline for each post-baseline measurement will be presented for each treatment arm and overall, by each vital sign parameter.

Baseline is defined as the pre dose observation value of each dosing visit.

Also all vital sign values will be listed in data listings.

8.3.4 ECG

ECG absolute individual parameters and the change from baseline will be summarized by treatment arm and overall per assessment as continuous measurements.

QTc and maximum QTc (including changes from baseline) will be summarized as both continuous and categorical measurements, where the categorical for QTc, and change from baseline QTc are as follows, respectively:

- Observed post baseline value: >450-≤480; >480-≤500 and >500 (msec)
- Change from baseline: >30-≤60 and >60 (msec)

All ECG measurements will be presented in data listings.

8.3.5 Physical Findings

Physical examination results will be presented in a listing, including screening and each post treatment visit.

8.3.6 Dosing and Extent of Exposure

Treatment exposure will be provided by treatment arm. The number of CMB305 or placebo injections, duration of exposure, and number of subjects with dose reductions/interruptions will be summarized by treatment arm based on the Safety set.

Dosing and Extent of Exposure

The duration of exposure is defined as the total number of days on the planned study treatment, temporary treatment discontinuation and planned treatment misses will be ignored.

The following algorithm will be used to calculate the duration of study treatment exposure for subjects who took at least one dose of study treatment:

Duration of exposure (days) = [(date of last administration of study treatment) – (date of first administration of study treatment) + 1]

8.3.7 Prior and Concomitant Medications

All concomitant medications and prior medications will be coded to therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug Classification. The incidence of prior and concomitant medication usage will be summarized by treatment arm, by therapeutic drug class, and generic drug names on safety set separately.

Concomitant medication is any medication with start date on or after the initial dosing of study treatment.

Prior medication is defined as any medication with start date on or before the first day of study treatment, or medication with start date missing.

Each subject will be counted once only for each therapeutic drug class, generic drug names, and for the overall summary.

Prior and concomitant therapies will also be presented in data listings.

8.3.8 Analysis of Other Safety Variables

Analyses for other safety variables will be performed based on the nature of the parameters and assessment schedule as needed.

A shift table for ECOG comparing the worst post baseline to baseline will be presented by treatment arm and overall.

9 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.

10 REFERENCES

1. CMB305 IMDZ-04-1702 Protocol Version 2.0 dated on 27Apr, 2018.
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11 APPENDICES

Mockups for listings, tables and figures are detailed in separate mockup files.