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

The schedule of events is presented in Table 1 for the Pre-Screening and Screening periods and in Table 2 for the Treatment through the Long-term Follow-up periods. Study flow diagrams for subjects who received either a course of 4 cycles, 6 cycles, or 8 cycles of first-line systemic anti-cancer therapy are presented in Appendix 5, Figure 4, Figure 5 or Figure 6, respectively. A study flow diagram for subjects who have had local regional therapy after first-line systemic anti-cancer therapy is presented in Appendix 5, Figure 7.

Pre-screening period:

The Pre-screening period of up to 151 days (Day -180 to Day -29) commences at the time the subject and/or their legally authorized representative sign the Pre-screening informed consent form (ICF)/assent form. The Pre-screening period ends at the time the subject and/or their legally authorized representative sign the Main Study ICF/assent form.

Before any Pre-screening procedures are performed, subjects aged ≥18 years or legally authorized representatives of subjects <18 years will provide written consent on the Pre-screening ICF, and subjects aged 12 to <18 years will provide written assent. At the time of Pre-screening, subjects must still be receiving treatment with first-line systemic anti-cancer therapy. The following will be evaluated during the Pre-screening visit:

- Radiographic disease response assessment obtained at the standard-of-care time point by the investigator using RECIST v1.1
- Immunohistochemistry (IHC) test for the presence of NY-ESO-1 in an archival tumor tissue or fresh tumor tissue biopsy (tumor tissue may be from an archived sample obtained within 18 months before signing the Pre-screening ICF/assent form)

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 subject and/or their legally authorized representative will sign the Main Study ICF/assent form.

Screening period:

The duration of the Screening period of up to 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 and ends at time of randomization.

After satisfying the Pre-screening criteria, subjects aged ≥18 years and legally authorized representatives of subjects <18 years will provide written consent on the Main Study ICF, and subjects aged 12 to <18 years will provide written assent for study participation. Once the appropriate Main Study ICF/assent form is signed, subjects will undergo additional eligibility assessments and the investigator will confirm there is no evidence of progression (using RECIST v1.1). The disease status will be assessed by the investigator (using RECIST v1.1) through comparison of the most recent baseline images obtained during Screening to both 1) the images obtained prior to initiation of first-line systemic anti-cancer therapy and 2) the images obtained per standard-of-care during first-line systemic anti-cancer therapy to confirm there is no evidence of progression prior to randomization. Investigator assessment of radiographic images confirming best response (stable disease [SD] or better) to first-line systemic anti-cancer therapy using RECIST v1.1 will be entered into an electronic case report form (eCRF). Subjects who have a tumor response of SD 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. Radiographic images from both Screening and Pre-Screening will also be submitted to an independent review committee (IRC) for storage. The stored images will be available for evaluation by a central reader, if requested by the sponsor. After completion of Screening assessments and confirmation that the subject has met all eligibility requirements, the subject will be randomly assigned to one of the treatment arms using a central randomization system on Day 1.

HepC	hepatitis C
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IHC	immunohistochemistry
IM	intramuscular(ly)
IMDZ	Immune Design Corp.
INR	international normalized ratio
IRB	institutional review board
IRC	independent review committee
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
LV	lentiviral vector
MedDRA	Medical Dictionary for Regulatory Affairs
MEOI	medical event of interest
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NED	no evidence of disease
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NY-ESO-1	New York esophageal squamous cell carcinoma-1
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
Rev	Regulator of Expression of Virion Proteins (lentivirus accessory protein)
RR	response rate

- Evaluate the safety and tolerability of CMB305 versus placebo
- Evaluate subject quality of life (QoL)

2.3 Exploratory Objective

- 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

3.0 INVESTIGATIONAL PLAN

3.1 Overall Study Design and 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.

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

The schedule of events for the Pre-screening and Screening periods is presented in Table 1 and the schedule of events for the Treatment through the Long-term Follow-up periods is presented in Table 2. Study flow diagrams for subjects who received a course of 4 cycles, 6 cycles, or 8 cycles of first-line systemic anti-cancer therapy are presented in Appendix 5, Figure 4, Figure 5, or Figure 6, respectively. A study flow diagram for subjects who have had a local regional therapy after first-line systemic anti-cancer therapy is presented in Appendix 5, Figure 7.

3.1.1 Pre-screening Period

The Pre-screening period is up to 151 days (Day -180 to Day -29) and commences at the time the subject and/or their legally authorized representative sign the Pre-screening informed consent form (ICF)/assent form. The Pre-screening period ends at the time the Main Study ICF/assent form is signed.

Before any Pre-screening procedures are performed, subjects (aged ≥18 years) and legally authorized representatives of subjects <18 years will provide written consent on the Pre-screening ICF and subjects aged 12 to <18 years will provide written assent. At the time of Pre-screening, subjects must still be receiving treatment with first-line systemic anti-cancer therapy. The following will be evaluated during the Pre-screening visit:

- Radiographic disease response assessment obtained at the standard-of-care time point by the investigator using RECIST v1.1

- Immunohistochemistry (IHC) test for the presence of NY-ESO-1 in an archival tumor tissue or fresh tumor tissue biopsy (tumor tissue may be from an archived sample obtained within 18 months before signing the Pre-screening ICF/assent form)

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 subject and/or their legally authorized representative will sign the Main Study ICF/assent form.

3.1.2 Screening Period

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 and ends at time of randomization.

After satisfying the Pre-screening criteria, subjects (aged ≥18 years) and legally authorized representatives of subjects <18 years will provide written consent on the Main Study ICF and subjects aged 12 to <18 years will provide written assent for study participation. Once the appropriate Main Study ICF/assent form is signed, subjects will undergo additional eligibility assessments and the investigator will confirm there is no evidence of progression (using RECIST v1.1). The disease status will be assessed by the investigator (using RECIST v1.1) through a comparison of the most recent baseline images obtained during Screening to both 1) the images obtained prior to initiation of first-line systemic anti-cancer therapy and 2) the images obtained per standard-of-care during first-line systemic anti-cancer therapy to confirm there is no evidence of progression prior to randomization. Investigator assessment of radiographic images confirming best response (stable disease [SD] or better) to first-line systemic anti-cancer therapy using RECIST v1.1 will be entered into an electronic case report form (eCRF). Subjects who have a tumor response of SD 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. Radiographic images from both Screening and Pre-screening will also be submitted to an independent review committee (IRC) for storage. The stored images will be available for evaluation by a central reader, if requested by the sponsor. After completion of Screening assessments and confirmation that the subject has met all eligibility requirements, the subject will be randomly assigned to one of the treatment arms using central randomization system on Day 1.

3.1.3 Treatment Period

The Treatment period will begin on the day of randomization (Day 1), which is to be within 28 days after the last dose of first-line systemic anti-cancer therapy or last day of local regional therapy, if applicable, and will continue until investigator-determined progressive disease (PD) (using RECIST v1.1), unacceptable toxicity, or 1 year after the first dose, whichever occurs first.

[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 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.

	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[o]		
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.

anti-cancer therapy, the use of a placebo in this trial is warranted. This trial will evaluate whether CMB305 active therapy is better than observation alone (i.e., placebo).

Advantages for the use of placebo in the control arm of this trial include:

- Lowers the risk of altering the natural history of a subject's tumor progression so that there is a true comparator arm
- Minimizes confounding factors and bias
- Reduces the potential of study withdrawal

The study will be stratified by response to first-line treatment to maintain balance between arms. The strata will allow for statistical impact of subjects who have received local regional therapy. In addition, subjects on the study are not forgoing any standard therapy, which minimizes risks and allows for blinded analysis of not only efficacy but also of QoL and the safety of CMB305.

In summary, there remains a high unmet medical need for subjects with locally-advanced unresectable or metastatic synovial sarcoma who have no evidence of progression. Currently, there is no disease-specific therapy approved specifically for the indication of synovial sarcoma based on the underlying biology or subtype specific activity. Therapeutic options that are approved for the broader STS indication have limited efficacy in subjects with synovial sarcoma and are often associated with significant toxicities. Thus, there is a need for a novel approach on how to develop and evaluate a new targeted therapy that is safe for this ultra-rare subject population with a high unmet medical need.

3.3 Study Duration and Dates

Subject participation is inclusive of the Pre-screening, Screening, Treatment, Post-treatment, and Long-term Follow-up periods.

The Pre-screening period is up to 151 days (Day -180 to Day -29) and begins from the time the subject and/or their legally authorized representative sign the Pre-screening ICF/assent form to the time the Main Study ICF/assent form is signed. The Pre-screening period can start as early as the first dose of first-line systemic anti-cancer therapy.

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 and ends at time of randomization. The screening window may be extended up to 56 days by the sponsor, if a patient is recovering from toxicity related to first line systemic anti-cancer therapy, or completing local regional therapy, or baseline imaging needs adjudication to determine eligibility.

The Treatment period will begin on the day of randomization (Day 1), which is to be within 28 days after the last dose of first-line systemic anti-cancer therapy or the last day of local regional therapy, if applicable, and will continue until investigator-determined radiographic PD

6.3.1.2 Imaging at Screening

During the Screening period, and before randomization, imaging (images will include all organ systems that had disease present prior to start of first-line systemic anti-cancer therapy) will be performed, and all target and non-target lesions that were documented during Pre-screening will be assessed by the investigator using RECIST v1.1 to determine the subject's response to first-line systemic anti-cancer therapy. The images obtained at Screening will be compared with both images obtained at Pre-screening and images obtained before the start of first-line systemic anti-cancer therapy to ensure that no disease progression has occurred. Subjects who have a tumor response of SD 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. For individual subjects, the images obtained during the Screening period must have been collected using the same imaging method used for all images. Radiographic images at Screening (e.g., CT scan or MRI) will also be submitted to an IRC for storage and will be available for evaluation by a central reader, if requested by the sponsor. Details for the collection and evaluation of radiographic images are included in the Radiology Manual.

6.3.1.3 Imaging During Treatment to the Time of Disease Progression

Tumor imaging assessments will be performed and evaluated every 8 weeks after Day 1 until investigator-determined PD (using RECIST v1.1) is documented. Disease progression will be assessed by the investigator using RECIST v1.1. For each subject, the images obtained during the Treatment period must have been collected using the same imaging method for all images during the Pre-screening and Screening periods. Subjects who have a global deterioration of health status that is attributed to progressive disease and leads to discontinuation of study treatment, but who are unable to provide radiographic evidence of disease progression (symptomatic deterioration), will be considered as having PD at the time of documented global deterioration of health for the purpose of determining PFS. Radiographic images (e.g., CT scan or MRI) will also be submitted to an IRC for storage and will be available for evaluation by a central reader, if requested by the sponsor. Details for the collection and evaluation of radiographic images are included in the Radiology Manual.

6.3.2 Immune Response Assessments

Results for anti-NY-ESO-1 plasma antibody must be available for subject stratification at the time of randomization. In addition, at select US sites, pre- and post-treatment anti-NY-ESO-1 plasma antibodies may be used for exploratory analyses.

Pre- and post-treatment blood and tumor samples will be collected for exploratory analyses of potential biomarkers of CMB305 immunogenicity and clinical tumor response as shown in Table 3.

Circulating tumor genomics will be collected for exploratory analyses of potential immune response effect on tumor growth.

Table 3 At Select US Sites Only: Immune Response Assessments

Assessment	Subjects/Timepoint	Analysis
Presence of T cell immunity at baseline (peripheral blood)	Day 1 prior to dosing	NY-ESO-1-specific T cells are detected in PBMC by ELISPOT (ex vivo or following 7-day in vitro stimulation). The assay is performed in quadruplicate. Positive response is defined as follows: • ex vivo ELISPOT: no less than 15 IFNγ-secreting spots per well after background subtraction • in vitro stimulation ELISPOT: no less than 50 spots per well after background subtraction
Presence of antibody at baseline (peripheral blood)	Screening	NY-ESO-1 specific plasma antibodies that are detected by ELISA at a titer of ≥1:100
Induction of antibody on treatment (peripheral blood)	Day 92	• NY-ESO-1 specific plasma antibodies that are detected by ELISA at a ≥4-fold increase in titer at Day 92 or • Seroconversion of NY-ESO-1 specific plasma antibodies that are detected by ELISA at 92
Induction of T cells on treatment (peripheral blood)	Day 92 and only Day 365 for subjects who have not yet progressed	• Ratio of post-treatment to pre-treatment NY-ESO-1-specific T cell counts ≥2 or • Post-treatment positive ELISPOT from pre-treatment negative baseline
Intratumoral immune status at baseline and on treatment (tumor biopsy)	Fresh biopsy either at Prescreening or Screening, Day 92, Day 365, and at time of progression event will be encouraged	Ratio of post-treatment to pre-treatment NY-ESO-1-specific T cells within the tumor

ELISA = enzyme-linked immunosorbent assay; ELISPOT = enzyme-linked immunospot;
NY-ESO-1 = New York esophageal squamous cell carcinoma-1; PBMC = peripheral blood mononuclear cells

Many exploratory analyses for potential biomarkers are being investigated, but the predictive value of such tests is not yet known. The data collected from these exploratory tests will help to define a set of biomarkers that might be used in future studies to help define the ability of CMB305 to stimulate anti-tumor immune responses and to help stratify subjects who might respond to these treatments. Exploratory blood tests may include functional assays of cytolytic T cells or other immune cells directed against autologous tumor cells or surrogate target cells,

modifications of current assays to detect anti-tumor cellular immunity, detection and/or analyses of circulating tumor cells, or analyses of other (not yet undefined) tumor markers and immune function. Screening and post-treatment cancer biopsy tissue may be collected at select study sites and only if tumor sites are accessible. These tumor samples will be examined for evidence of anti-tumor cellular immunity (e.g., CD8 T cell or natural killer cell infiltration, tumor necrosis) by IHC and for evidence of immune suppression within the tumor microenvironment. Samples may also be sent for gene expression analysis, T cell receptor expression, fluorescence-activated cell sorting analysis, and isolation of tumor-infiltrating lymphocytes. Any blood or tumor samples will only be used to examine the subject's immune response, their cancer, or to help evaluate any potential toxicity arising in the study. The samples will not be examined for unrelated research or to examine unrelated genes or diseases.

The following immune monitoring may be conducted:

- Cellular immunogenicity by changes from baseline and over the course of the trial period in peripheral blood levels of NY-ESO-1 antigen specific T cells and T cell associated cytokine production
- Cellular immunogenicity by changes from baseline and over the course of the trial period in peripheral blood levels of overall T cell effector and memory populations
- Humoral immunogenicity as measured by changes from baseline and over the course of the trial period with anti-NY-ESO-1 antibodies and anti-LV antibodies

Details for sample handling and assay performance will be provided in the Laboratory Manual provided to study sites.

6.3.3 Tumor Biopsy

Biopsy samples will be collected as specified in the schedule of events (Table 1, Table 2) and in accordance with the site's standard operating procedures. Details of biopsy collection are included in the Laboratory Manual.

6.3.4 ECOG

ECOG scores will be obtained according to the schedule of events (Table 1, Table 2). The ECOG assessment tool is provided in Appendix 2.

6.3.5 QoL Assessment

Quality of life will be assessed using a paper form completed by the subject according to the schedule of events (Table 1, Table 2) using the EuroQol 5-Dimension 5 Level (EQ-5D-5L). for subject ≥18 years of age as shown in Appendix 3. or using the EuroQol 5-Dimension Youth (EQ-5D-Y) for subjects 12 to <18 years of age as shown in Appendix 4.

Table 4 Clinical Laboratory Tests (Central Laboratory)

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 T_3, T_4 to be evaluated)
Coagulation	Prothrombin time (PT); partial thromboplastin time (PTT); international normalized ratio (INR)
Urinalysis	Appearance; bilirubin; color; glucose; ketones; microscopic examination of sediment; nitrite; occult blood; pH; protein; specific gravity; urobilinogen
Viral tests	Hepatitis B (HepB), hepatitis C (HepC), or human immunodeficiency virus (HIV) infection

6.4.3.2 Sample Collection, Storage, and Shipping

Complete details for sample collection, storage, and shipping to the central laboratory are included in the Laboratory Manual.

6.4.4 Electrocardiogram

A standard 12-lead ECG will be obtained. Subjects should rest in the supine position before each 12-lead ECG recording is started. The ECGs should be reviewed, signed, and dated by a qualified health care practitioner and any clinically important finding recorded on the ECG report and on the appropriate eCRF. The investigator is responsible for providing the interpretation of all ECGs.

6.4.5 Concomitant Medication Use

Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study drug. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment or prophylaxis of an AE), the treatment must be recorded on the eCRF, including the reason for treatment, generic name of the drug, dosage, route, and date of administration. Restricted and prohibited concomitant medication use is presented in Section 5.8.

6.4.7.2 Adverse Event Reporting

All SAEs that are unexpected and considered possibly, probably, or definitely related to study drug by the investigator or sponsor will be reported to the Food and Drug Administration (FDA), applicable regulatory agencies, and IRB/IEC in accordance with the requirements in 21 Code of Federal Regulations (CFR) §312.32 and International Conference on Harmonization (ICH) guidelines.

At each study visit (including unscheduled visits), the investigator, or designee, will determine whether any AEs have occurred. Each AE will be reported in the subject's medical record and on the AE eCRF page and classified according to the criteria in Section 6.4.7.4, Section 6.4.7.6, and Section 6.4.7.7. If known, the diagnosis should be recorded, in preference to the listing of individual signs and symptoms. Any pre-existing conditions that are detected as part of the initial screening procedures will be reported in the medical history and not as an AE. However, pre-existing conditions that worsen after enrollment should be reported as an AE.

Adverse events will be reported to the FDA and applicable regulatory authorities in accordance with the requirements outlined in 21 CFR §312.32 and ICH guidelines. Progression of cancer is not considered an AE unless it is considered to be drug-related by the investigator. Deaths due to cancer progression will not be reported as expedited events. The investigator will continue to monitor the subject until any new, changed, or worsened AE resolves, returns to baseline, or until the investigator and IMDZ agree that follow-up is no longer necessary. AEs must be followed until resolution whenever possible.

6.4.7.3 Serious Adverse Event Reporting

If an SAE occurs, IMDZ will be notified within 24 hours of awareness of the event by the investigator. In particular, if the SAE is fatal or life-threatening, IMDZ must be notified immediately, irrespective of the extent of available AE information. In the rare event that the investigator or designee does not become aware of the occurrence of an SAE immediately, the investigator or designee must report the event within 24 hours of their awareness and document the time of when his/her first awareness occurred. For all SAEs, the investigator or designee is obligated to pursue and provide information to IMDZ in accordance with the time frames for reporting specified above. In addition, an investigator may be requested to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE case report form. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of causality.

New SAEs experienced by subjects during the Screening period (pre-study treatment) will be reported to IMDZ if the events are considered related to study procedures. New SAEs determined to be related to study tests or procedures (not including cancer-related events) and any hospitalizations determined to be related to study tests or procedures that are experienced by subjects from the time of signing the Main Study ICF/assent form until Day 1 (start of CMB305

treatment) will be noted on the SAE form and eCRF. From Day 1 until 30 days after administration of the last dose of the investigational product (i.e., CMB305), any new SAE will be noted on the SAE form and eCRF. After that point, any AE that comes to the attention of the site staff that may be causally related to study drug, i.e., CMB305, (i.e., there is a reasonable possibility that the event may have been caused by the drug) will be reported to IMDZ.

SAEs will be monitored until they have resolved, returned to baseline, or they are not clinically significant, stable, or do not require additional follow-up, as judged by the investigator and IMDZ.

STUDY CONTACT FOR REPORTING SERIOUS ADVERSE EVENTS	
Vendor:	Everest Clinical Research, Corp.
Telephone:	PPD (office) or PPD (mobile)
Email:	SAE forms must be completed electronically in the EDC clinical database. Back-up SAE report forms or supplemental information is to be emailed to: PPD

6.4.7.4 Medical Event of Interest Reporting

Selected non-serious AEs, as described in Section 6.4.7.5, are classified as MEOIs and must be recorded as such on the AE CRF and reported to the sponsor via electronic media or on the paper MEOI Report Form. MEOIs that are identified from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anti-cancer therapy, whichever is earlier, need to be reported to the sponsor within 24 hours of the event in the same manner as outlined for SAEs (see Section 6.4.7.3).

Subjects should be assessed for the occurrence of possible MEOIs before administration of each dose of study treatment. Laboratory results should be evaluated, and subjects should be asked about any signs and symptoms experienced that are suggestive of an immune-related event. If laboratory test results or symptoms indicate possible immune-related MEOIs, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then the MEOI will be considered to be immune-related.

6.4.7.5 Definitions of Adverse Event

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

treatment, or procedure whether or not considered possibly, probably, or definitely related to the medicinal product. Progression of cancer is not considered an AE unless it is considered to be drug-related by the investigator.

Treatment-Emergent Adverse Event (TEAE)—Any AE that occurs, or an existing condition that worsens in severity, after administration of the first dose of the study drug.

Medical Event of Interest (MEOI)—Selected non-serious AEs are classified as MEOIs. The following treatment-emergent immune-mediated event is an MEOI for CMB305:

- Pneumonitis

As NY-ESO-1 is only detected in certain testicular cells in healthy individuals (Gnjatic 2006), the following male genitourinary-related events are MEOIs for CMB305:

- Prostatic pain
- Groin pain
- Testicular pain
- Epididymo-orchitis

MEOIs for this study include the following:

- An overdose of the sponsor's investigational product that is not associated with clinical symptoms or abnormal laboratory results
- Results from protocol-specified or unscheduled laboratory results showing simultaneous:
    - Increased ALT and/or AST ≥3× ULN,
    - Increased serum total bilirubin ≥2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) and
    - No other reason can be found to explain the combination of increased aminotransferase enzymes and total bilirubin, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

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

During study conduct, additional new MEOIs may be identified by the Sponsor based on their clinical and laboratory features and understanding of underlying pathophysiology of the adverse events and will need to be reported as such. Such events may include dermatologic, endocrine, neurologic, gastrointestinal, respiratory and musculoskeletal toxicities, which are possibly

Table 6 Assessment of Relationship

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

AE = adverse event

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

6.4.7.8 Clinical Laboratory Adverse Events

Clinically significant laboratory test results, in the opinion of the investigator, will be considered AEs and will be reported as shown in Section 6.4.7.

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the local laboratory. In some cases, significant changes in laboratory values within the normal range will require similar judgment. An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- An action on the study drug is made as a result of the abnormality
- Intervention for management of the abnormality is required
- At the discretion of the investigator should the abnormality be deemed clinically significant

6.4.8 Pregnancy

Sexually-active men and FCBP must use a highly effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Before enrolling FCBP in this clinical trial, all FCBP must be advised of the importance of avoiding pregnancy during trial participation and for 30 days after the last dose of study drug administration and the potential risk factors for an unintentional pregnancy. Male subjects must be advised of the importance of their female partners avoiding pregnancy during the male subject's participation and for 3 months after the last dose of the study drug. All subjects (men and women) must sign an ICF documenting this discussion.

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

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

If following initiation of study dosing, it is subsequently discovered that a trial subject is pregnant or may have been pregnant within 1 month before or 4 months after, study regimens will be permanently discontinued, and the subject will be followed as possible by the investigator or designated health care professional to determine pregnancy outcomes for both mother and baby. If a male subject enrolled in study has a female sexual partner who becomes pregnant after initiation of the study, then the study subject should be asked by the investigator (or designated health care professional) for permission to approach his pregnant partner to follow-up to determine outcomes for both mother and baby.

6.4.9 HIV Screening Assessment

As part of study eligibility, subjects are required to have a negative HIV screening test at baseline. LV305 is an engineered lentivirus vector and is therefore derived from HIV. It is not known if treatment with LV305 will result in seroconversion of subjects to positive with HIV screening. Vectors derived from lentiviruses share some, but not all, of the proteins that are recognized in several screening blood tests for HIV. Secondary confirmatory assays such as Western Blot will demonstrate that the normal complement of HIV proteins is not present (unless, of course, the subject has developed true HIV infection). The informed consent document informs subjects regarding the possibility of positive HIV screening test after study treatment. Subjects enrolled in the study will be provided with a card from the study sponsor describing the possibility of a screening test becoming positive and the importance of confirmatory testing. In the event a study subject should have a screening HIV test performed and it returns a positive result, the site should inform and consult IMDZ for recommendations on the most appropriate confirmatory test to use.

3. Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness
4. Other

6.5.2 Removal from Study Drug

While subjects will be encouraged to continue participation in the study for safety and survival follow-up, subjects **MUST** be discontinued from receiving further study drug for the following reason:

- Progressive disease by RECIST v1.1 criteria
- Withdrawal of informed consent from study treatment
    - Subject will continue to be followed for imaging and quality-of-life assessment
- Any clinical AE that meets treatment discontinuation criteria in section 5.6 or any other reason that, in the opinion of the investigator, indicates that continued dosing on the study is not in the best interest of the subject
    - Subject will continue to be followed for imaging and quality-of-life assessment

Subjects will be permitted to continue study drug if the RECIST v1.1 criteria for PD are met provided they meet all the following criteria:

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

No unblinding will be permitted for subjects who continue study treatment beyond progression.

6.6 Appropriateness of Measurements

The measurements of efficacy and safety in this study are standard measurements widely used and generally recognized as reliable, accurate, and relevant. The safety measurements evaluated in this study are those used in most clinical studies, including the assessment of AEs.

7.0 PLANNED STATISTICAL METHODS

7.1 Determination of Sample Size

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.

7.2 Analysis Sets

For the purpose of statistical analysis, there are 3 analysis sets: Intent-to-Treat set (ITT), Efficacy Evaluable set (EE), and Safety 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.
- The EE set consists of all subjects without major protocol violations, who have received at least 1 dose of study drug, 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.
- 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. Efficacy analyses performed in the Safety set will be considered to be supportive.

7.3 Demographics and Baseline Characteristics

Subject disposition and characteristics including demographics, disease duration and stage at Screening, and relevant medical history will be summarized for the purpose of characterizing the subject population by treatment arm and establishing baseline comparability of the randomized treatment arms.

response assessments (except for subjects with symptomatic deterioration) prior to a visit with documented progression (or death) will be censored at the last visit where the subject was documented to be progression free. PFS, by investigator's assessment, will be the primary PFS analysis. PFS by independent radiological review will be the supportive analysis.

The null hypothesis of no difference in OS/PFS between CMB305 and placebo, will be tested using a stratified log-rank test stratified by: 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 OS/PFS on CMB305 is superior to that on placebo in subjects with synovial sarcoma if the 1-sided p value at the final analysis for the stratified log-rank test is less than the pre-specified alpha of 0.0125 as discussed in Section 7.10, Multiplicity. The associated HR and its 2-sided 97.5% and 95% CI will be provided using the stratified Cox proportional hazard model. The Kaplan-Meier curve will summarize OS/PFS graphically by treatment arm. Tabular summaries of the Kaplan-Meier curves, including the median, will be provided by treatment. The 1-year and 18-month OS/PFS rate will be provided by treatment. 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.

A pre-planned sensitivity analysis will be performed based on the number of cycles and type of prior therapy (neoadjuvant/adjuvant chemotherapy and surgery and/or radiotherapy).

7.7.2 Secondary Efficacy Analyses:

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 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.

7.7.2.1 Time to Next Treatment

Time to next treatment is defined as the time from randomization to start of post-study treatment anti-cancer therapy. Subjects who do not start post-study treatment anti-cancer therapy will be censored at their last known date of being alive. TTNT will be analyzed using the same methods described for OS/PFS. In the event that the percent of subjects with competing events in either arm exceeds 3%, the cumulative incidence estimates, and Gray's test will be the main TTNT comparison between the treatment arms.

Laboratory values measured by the central laboratory will be used in the analysis of laboratory toxicities and will be defined based on universal normal ranges and NCI-CTCAE, Version 4.03 or newer. The number and percentage of subjects will be summarized by grade using the most severe grade by treatment arm. Clinically significant changes in laboratory values will be summarized by treatment arm. Laboratory values will be listed, with grade 3 or 4 values flagged.

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.

7.9 Exploratory Analysis

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.

7.10 Multiplicity

The study is to be conducted with PFS and OS as 2 primary endpoints with the goal of a regulatory approval based on 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.

7.11 Data Monitoring Committee and Interim Analysis

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 this 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.

Treatment period:

The Treatment period will begin on the day of randomization (Day 1), which is to be within 28 days after the last dose of first-line systemic anti-cancer therapy or the last day of local regional therapy, if applicable, and will continue until investigator-determined progressive disease (PD) (using RECIST v1.1), unacceptable toxicity, or 1 year after the first dose, whichever occurs first.

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

- Arm A: Placebo
- Arm B: CMB305

An interactive response technology (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)

Subjects who are randomly allocated to the placebo arm will not be permitted to cross-over to the CMB305-containing treatment arm at any time before study closure.

Tumor imaging assessments will be performed every 8 weeks after Day 1 and radiographic evidence of disease progression will be determined by the investigator using RECIST v1.1. Subjects with a global deterioration of health status requiring discontinuation of study treatment but without objective evidence of disease progression (symptomatic deterioration) will be considered as having PD for the purpose of determining PFS. Radiographic images (e.g., computed tomography [CT] scan or magnetic resonance imaging [MRI]) will also be submitted to an independent review committee (IRC) for storage and will be available for evaluation by a central reader, if requested by the sponsor. Details for the collection and evaluation of radiographic images are included in the Radiology Manual provided to the study sites.

Tumor biopsy samples for NY-ESO-1 expression will be obtained from all subjects during the Pre-screening period (either archival tumor tissue or a fresh biopsy sample). All subjects will provide peripheral blood samples for anti-NY-ESO-1 antibody assay for stratification during screening.

Quality of life will be assessed up to 12 months from Day 1.

Safety will be monitored by evaluating the frequency and severity of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, immunogenicity, and persistence. Local laboratory test values will be used for treatment decisions and subject care; central laboratory test values will be used in the analysis of safety.

In addition, at only select US sites, the following will be collected:

Peripheral blood samples for the anti-NY-ESO-1 T cell and antibody assays will be obtained prior to start of study treatment from subjects on Day 1, Day 92, and Day 365 for subjects who have not had a progression event. A tumor biopsy will be obtained at screening, Day 92, and Day 365 for subjects who have not had a progression event. An additional tumor biopsy at time of progression event will be encouraged.

Post-treatment period (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.

Subjects will continue to undergo imaging until the time of disease progression. At the time of disease progression, subjects will enter the Long-term Follow-up period.

SAE	serious adverse event
SC	subcutaneous(ly)
SD	stable disease
SE	stable emulsion
SINV	Sindbis virus
SINVar1	Sindbis virus envelope glycoprotein
STS	soft tissue sarcoma
TEAE	treatment-emergent adverse event
TLR4	toll-like receptor 4
TTNT	time-to-next treatment
ULN	upper limit of normal
US	United States
vg	vector genome
WHO	World Health Organization

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

- Arm A: Placebo
- Arm B: CMB305

An interactive response technology (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)

Subjects who are randomly allocated to the placebo arm will not be permitted to cross-over to the CMB305-containing treatment arm at any time before study closure.

Tumor imaging assessments will be performed every 8 weeks after Day 1 and radiographic evidence of disease progression will be determined by the investigator using RECIST v1.1. Subjects with a global deterioration of health status requiring discontinuation of study treatment but without objective evidence of disease progression (symptomatic deterioration) will be considered as having PD for the purpose of determining PFS. Radiographic images (e.g., computed tomography [CT] scan or magnetic resonance imaging [MRI]) will also be submitted to an IRC for storage and will be available for evaluation by a central reader, if requested by the sponsor. Details for the collection and evaluation of radiographic images are included in the Radiology Manual provided to the study sites.

Tumor biopsy samples for NY-ESO-1 expression will be obtained from all subjects during the Pre-screening period as described in Section 3.1.1 (either archival tumor tissue or a fresh biopsy sample). All subjects will provide peripheral blood samples for anti-NY-ESO-1 antibody assay at the screening visit for stratification.

Quality of life will be assessed up to 12 months from Day 1.

Safety will be monitored by evaluating the frequency and severity of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, immunogenicity and persistence of LV305. Local laboratory test values will be used for treatment decisions and subject care; central laboratory test values will be used in the analysis of safety.

In addition, at only select US sites, the following will be collected:

Peripheral blood samples for the anti-NY-ESO-1 T cell and antibody assays will be obtained prior to start of study treatment from subjects on Day 1, Day 92, and Day 365 for subjects who have not had a progression event. A tumor biopsy will be obtained at screening, Day 92, and Day 365 for subjects who have not had a progression event. An additional tumor biopsy at time of progression event will be encouraged.

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

[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 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.

(using RECIST v1.1) is documented, the occurrence of unacceptable toxicity, or until 1 year after the first dose, whichever occurs first. All visits during the Treatment period will have a window of ±3 days from the day specified.

The Post-treatment period (for subjects who discontinue study treatment for reasons other than disease progression) will begin at the end of treatment and will continue until investigator-determined PD (using RECIST v1.1) is documented. All visits during the Post-treatment period will have a window of ±7 days from the day specified.

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. All visits during the Long-term Follow-up period will have a window of ±14 days from the day specified.

4.0 STUDY POPULATION SELECTION

4.1 Study Population

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

4.2 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the study.

1. Have documented histologic diagnosis of synovial sarcoma (may be confirmed by the presence of t(X;18) (p11:q11) translocation or B cell lymphoma 6 corepressor [BCOR] rearrangement) and have disease that is unresectable locally-advanced or metastatic prior to the start of first-line systemic anti-cancer therapy. Unresectable is defined as having evidence of positive surgical margins after resection of primary disease or a documented surgical consultation with assessment of an inability of resection to provide clear margins.
2. Have IHC test results from tumor biopsy for NY-ESO-1 that are positive (≥1% expression).
3. At the time of Pre-screening, subjects must be receiving a first-line anthracycline or ifosfamide-containing systemic anti-cancer therapy regimen (single agent ifosfamide, single agent anthracycline, combination anthracycline plus ifosfamide, or combination anthracycline plus olaratumab). Subjects must have received at least 4 cycles but no more than 8 cycles of therapy (or no more than 180 days of systemic anti-cancer therapy). Subjects who have received local regional therapy (surgical resection, radiotherapy, radiofrequency ablation, or cryotherapy) are eligible if they meet the following:
    a. Subjects whose disease converted to operable after completion of first-line chemotherapy are eligible, if local regional therapy (surgical resection, radiotherapy, radiofrequency ablation or cryotherapy) is completed within the

6.4 Safety Assessments

The investigator is responsible for the appropriate medical care and safety of subjects who have entered this study. The investigator must notify the sponsor within 24 hours if any of the following events occurs:

- Any grade 3 or higher event, regardless of relationship to the study drug(s)
- Any event meeting the criteria for an SAE
- Any medical event of interest (MEOI) (see Section 6.4.7.5)

Safety assessments will include solicited and unsolicited symptoms, physical examination findings, vital signs, documentation of AEs, ECGs and/or echocardiogram as applicable, clinical laboratory evaluations, deviations or discontinuations attributed to AEs, concomitant medication use, and LV305 persistence.

6.4.1 Physical Examination

A physical examination will be performed at Screening and 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. At subsequent visits, limited, symptom-directed physical examinations should be performed.

Measurements of weight and height will be recorded only at screening and weight at every visit.

6.4.2 Vital Signs

Vital sign measurements will include systolic/diastolic blood pressure, respiratory rate, heart rate, and body temperature. 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. Vital signs should be performed before invasive procedures (e.g., blood sample collection).

6.4.3 Clinical Laboratory Tests

6.4.3.1 Laboratory Parameters

Central laboratory parameters to be analyzed are shown in Table 4. Screening laboratory measurements will be used to determine study eligibility. Central laboratory measurements will be used for safety analyses and for other exploratory data analyses. Data on local laboratory tests may be collected for subjects experiencing adverse events upon sponsor notification. Sites will collect and analyze blood and urine samples at local laboratories based on their routine practice.

The use of concomitant medications will be recorded from Day 1 through the end of the Treatment period or until the time of disease progression. Details of concomitant medication use should include the name, dose, route of administration, and indication.

6.4.6 LV305 Persistence

Peripheral blood will be collected at Screening and at the following timepoints after administration of the first dose of study drug on Day 1: no sooner than Day 92 (3 months) up to 4 months; from 6 months up to 9 months; and from 1 year up to 15 months; and then yearly at no sooner than every 12 months but not more than 15 months until 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.

6.4.7 Adverse Events Assessments

All subjects who receive at least 1 study injection or another study-related procedure will be considered evaluable for safety. This includes any untoward signs (including abnormal laboratory findings) or symptoms experienced by the subject from the time of enrollment until 30 days post administration of the last dose of the study drug (i.e., CMB305). Safety will be evaluated for all treated subjects using the NCI-CTCAE v.4.03 or newer. Safety assessments will be based on medical review of both solicited and spontaneously reported AEs, including symptoms, physical examination findings, vital signs, laboratory findings, ECGs, and treatment discontinuations due to AEs. The nature, severity, and frequency of AEs will be monitored on an ongoing basis for risk assessment and to determine if risk management interventions are warranted (e.g., expedited notification of safety findings to investigators, IRBs/IECs, or regulators; update of Investigator's Brochure and ICF risks and re-consenting study subjects; revision of safety monitoring procedures; revision of eligibility criteria or other study procedures).

6.4.7.1 Adverse Event Collection Period

All enrolled subjects will have periodic assessment of clinical and laboratory AEs. All AEs, SAEs, and MEOIs will be collected until at least 30 days after administration of the last dose of the study drug (i.e., CMB305). MEOIs, immune-mediated events and secondary malignancies (regardless of causality) to be reported through 90 days following last IP dose/cessation of treatment or 30 days after initiation of new anti-cancer therapy, whichever is earlier, need to be reported to the Sponsor within 24 hours of event in the same manner as outlined for SAEs. All SAEs and new malignancies that come to the attention of the site staff and are considered at least possibly related to CMB305 will be collected until the time of last subject contact. AEs are to be reported 30 days after last dose of study drug if possibly related to CMB305/blinded IP, unless they fall in category above.

immune-mediated and possibly related to the study drug mechanism of action. Such adverse events may be delayed and wide ranging in terms of organs affected and severity.

Unexpected Adverse Event—An AE is "unexpected" when its nature (specificity), severity, or frequency are not consistent with the known or foreseeable risk of AE associated with the research procedures described in the protocol, Main Study ICF/assent form, or the Investigator Brochure.

Serious Adverse Event (SAE)—Any AE that results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization

  Note: Hospitalizations not to be reported as SAEs include admissions for planned medical/surgical procedure (such as scheduled tumor excision or debulking surgery) or routine health assessment requiring admission for baseline/trending of health status documentation (e.g., routine colonoscopy) or admission for social purposes such as lack of housing, economic inadequacy, caregiver respite, or family circumstances.

- A persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is a medically important condition that is judged by a health care professional as serious

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

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

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

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

There are special circumstances in which an SAE reporting form is used to communicate important clinical trial safety observations that may not constitute an SAE.

6.4.10 Immune-mediated Events

While available data do not provide evidence of a causal relationship between CMB305 and the occurrence of immune-related events, a potential for such events exists because of the mechanism of action of CMB305. Investigators should promptly identify signs and symptoms of AEs representing an immunologic etiology and provide appropriate treatment. If an MEOI that is considered grade 2 or higher (with the exception of alopecia or vitiligo) occurs, subsequent doses of CMB305 should be withheld. CMB305 dosing should resume only after consultation with the sponsor.

The occurrence of any immune-mediated event will be evaluated by the data monitoring committee (DMC).

The immune-mediated event of pneumonitis will be captured as an MEOI; procedures for reporting MEOIs are provided in Section 6.4.7.4.

6.5 Removal of Subjects from the Trial or Study Drug

Unless consent is withdrawn and the subject is unwilling to continue with safety follow-up, the subject is lost to follow-up, or the study is terminated, all efforts should be made to continue tumor and quality of life assessments as well as safety monitoring of all subjects.

Subjects who withdraw prior to the end of the study should be followed for new AEs for at least until 30 days after their last dose of study drug, i.e., CMB305. If the subject withdraws prematurely and is unwilling to continue safety follow-up, any subsequent SAE that may be causally related to study drug (i.e., CMB305) that comes to the attention of the site staff should be reported to IMDZ.

Information for long-term survival status should be obtained by any means, which includes, but is not limited to, public records where allowed by 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.

6.5.1 Removal from Trial

While subjects will be encouraged to continue participation in the study for safety follow-up, subjects **MUST** be discontinued from the study for the following reasons:

1. Pregnancy within 1 month before or 4 months after study regimen administration (NOTE: All FCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant [e.g., missed or late menstrual period] at any time during study participation.)
2. Termination of the study for safety

7.4 Primary Endpoints

- PFS, defined as the time from randomization to the investigator-determined (using RECIST v1.1) date of disease progression or death
- OS, as the time from randomization to the date of death

7.5 Secondary Endpoints

- TTNT
- DMFS
- ORR, defined by RECIST v1.1
- Safety and tolerability
- QoL, using the EQ-5D-5L for subjects ≥18 years of age or using the EQ-5D-Y for subjects 12 to <18 years of age

7.6 Exploratory Assessments or Analyses

- Intratumoral and peripheral blood anti-NY-ESO-1 immune changes

7.7 Efficacy Analysis

7.7.1 Primary Efficacy Analyses:

The 2 primary efficacy endpoints of PFS and OS will be compared between CMB305 and placebo. Overall survival is defined as the time from randomization to the date of death.

Progression-free survival 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. Radiographic images will be collected and assessed using RECIST v1.1 until the time the subject begins a new line of treatment.

For the purpose of PFS analysis, any one of the following events, whichever occurs first, will be used:

- Disease progression per RECIST v1.1 (See Appendix 1 Table 7 [Eisenhauer 2009])
- 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 (See Appendix 1 Table 8)

Otherwise, subjects who do not have disease progression or have not died will be censored at the date when the last tumor imaging assessment determines a lack of progression. If a subject begins a new anti-cancer therapy or has radiotherapy, surgery, or other local regional therapy at a lesion site prior to documented progression, the subject will be censored at the last assessment where the subject was documented as progression free prior to the intervention. For subjects with NED at study entry, the appearance of a new malignant lesion as per RECIST v1.1 is defined as an event of progression for the purpose of PFS analysis. Subjects with 2 or more missing

7.7.2.2 Distant Metastasis-Free Survival

Distant metastasis-free survival is defined as the time from randomization to evidence of a new distant metastasis not documented at time of randomization. DMFS will be analyzed using the same methods described for OS/PFS. In the event that the percent of subjects with competing events in either arm exceeds 3%, the cumulative incidence estimates, and Gray's test will be the main DMFS comparison between the treatment arms.

7.7.2.3 Other Secondary Efficacy Endpoints

ORR defined by RECIST v1.1 will be summarized by the number and percent of subjects who achieve a CR or PR based on the investigator's assessment. ORR will be compared between treatment arms using a logistic regression.

QoL (EQ-5D-5L or EQ-5D-Y) scores will be compared between the treatment arms using a mixed model.

7.8 Safety Analysis

Safety will be assessed primarily based on reported AEs. A 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). Medical events of interest, immune-mediated events, and AEs that occur more than 30 days after the last dose, and that are deemed as related to the study drug, will be included as TEAEs. 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. All AEs will be coded using the Medical Dictionary for Regulatory Affairs® (MedDRA v20.0 or newer). TEAEs will be tabulated by system organ class, preferred term, by treatment, and will be further categorized by NCI-CTCAE (v4.03 or newer) grade, and by relationship to the study drug. Clinically significant laboratory abnormalities, as measured by either the local or central laboratory, will be reported as AEs. The incidence for each AE will be provided as the total number of subjects that experience the AE, as well as the percentage of the population that this represents. If an AE is reported more than once during treatment for a given subject, the worst grade of severity and the most conservative relationship will be presented in the summary tables.

AEs will also be listed for individual subjects, along with information regarding onset, duration, grade, relationship to the study drug, and outcome. AEs that lead to withdrawal from the study treatment will be listed and summarized. Tabulations and listings of SAEs and deaths also will be generated.

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.

8.0 ADMINISTRATIVE CONSIDERATIONS

8.1 List of Personnel and Organizations Responsible for Conduct of the Study

A list of personnel and organizations responsible for the conduct of the study will be provided to the study sites as part of the Investigator Study File (or equivalent). This list will be updated by the IMDZ or its authorized representatives and provided to study sites on as-needed basis.

8.2 Trial Sponsor:

Immune Design Corp. (IMDZ)
1616 Eastlake Ave. E, Suite 310
Seattle, WA 98102 USA

8.3 Sponsor's Medical Monitor:

PPD

Immune Design Corp. (IMDZ)
601 Gateway Blvd., Suite 250
South San Francisco, CA 94080 USA
Office: PPD
Email: PPD

8.4 Clinical Trial Agreement

This study will be conducted under a Clinical Trial Agreement between IMDZ (or its authorized representatives) and the respective institutions representing the study sites. Any financial support given to the study sites will be detailed in the Clinical Trial Agreement. The Clinical Trial Agreement, which must be signed before the start of any study related procedures, will clearly delineate the responsibilities and obligations of the investigator and the sponsor (or its authorized representatives), and will form the contractual basis upon which the study will be conducted.

8.5 Financial Disclosure by the Investigator

Prior to study initiation, the investigator and any subinvestigator(s) directly involved in the treatment or evaluation of study subjects at each study site will disclose to IMDZ (or its authorized representatives) any relevant financial or proprietary interests in either the study product or the sponsor company. The appropriate disclosure form(s) will be provided by the sponsor (or its authorized representatives) for this purpose. Any relevant updates to the financial disclosure information that occur during the conduct of the study, or during one year after completion of the study, will be provided by the investigator and subinvestigator(s) to the sponsor (or its authorized representatives). All financial disclosure information provided by the investigator and subinvestigator(s) will be submitted to appropriate competent authorities according to the applicable regulatory requirements.