Study Title: A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T cells in subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma

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Adaptimmune LLC

EFFICACY SUPPLEMENT, STATISTICAL ANALYSIS PLAN

Protocol Number ADP-0044-002

A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T cells in subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma
(SPEARHEAD 1 STUDY)

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Version (Final)

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VERSION HISTORY			
Version	**Version Date**	**Summary of Additional Analysis for Efficacy Supplement**	**Rationale**
1.0	09 Feb 2023	1. Update to include summary of BOR and ORR for ITT population. 2. Update to include summary of concordance between BOR per Independent Reviewer and BOR per Investigator using RECIST v1.1. 3. Update to include summary of BOR by subgroup. 4. Update to include summary of viable transduced dose cells.	1. To provide the efficacy assessment of the primary endpoint in the ITT population. 2. To assist in the interpretation and the robustness of the BOR analysis. 3. To have consistent summary with integrated summary of efficacy. 4. Exploratory analysis of dose considering cell viability.

Table of Contents

List of Abbreviations and Definition of Terms

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Aminotransferase
BMI	Body Mass Index
BOR	Best Overall Response
CARTOX	CAR T Cell Therapy Toxicity Test
CDISC	Clinical Data Interchange Standards Consortium
CDx	Companion Diagnostic
CMC	Chemistry, Manufacturing and Controls
CI	Confidence Interval
CR	Complete Response
CRP	C-reactive protein
CRS	Cytokine Release Syndrome
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria for Adverse Events
DoR	Duration of Response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EQ-5D-3L	EuroQOL Group EQ-5D 3 Level Version
FDA	Food and Drug Administration
ICE	Immune Effector Cell-Associated Encephalopathy
ICF	Informed Consent Form

Abbreviation	Description
INR	International Normalized Ratio
ITT	Intent-to-Treat
IVD	In vitro diagnostic
KM	Kaplan-Meier
LTFU	Long-Term Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MRCLS	Myxoid/Round Cell Liposarcoma
NE	Not Evaluable
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
PT	Preferred Term
RCL	Replication Competent Lentivirus
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
TCR	T Cell Receptors
TEAE	Treatment-emergent adverse event
TTR	Time to Response

Abbreviation	Description
ULN	Upper Limit of Normal
WHO	World Health Organization

1 Introduction

This document provides a description of statistical methods and procedures to be implemented for the analysis of data in relation to efficacy and safety analyses for Study ADP-0044-002, based on the study protocol version amendment 3 and the electronic Case Report Form (eCRF).

Any deviation from the final version of this Statistical Analysis Plan (SAP) will be supported by sound statistical rationale and will be documented in the final Clinical Study Report (CSR).

A separate analysis plan for the secondary objective related to the development of the validated Companion Diagnostic (CDx) is provided in a separate document. A separate analysis plan for biomarkers will be developed and is outside of the scope of this document.

2 Objectives

2.1 Primary Objective

- To evaluate the efficacy of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS

2.2 Secondary Objectives

- To evaluate the safety and tolerability of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS
- To evaluate the efficacy of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS
- Development and validation of an in vitro diagnostic (IVD) assay for the screening of tumor antigen expression for regulatory approval
- Characterize the in vivo cellular pharmacokinetics (PK) profile of ADP-A2M4 cells

2.3 Exploratory Objectives

- [redacted]
- [redacted]
- [redacted]

3 Study Overview

3.1 Study Design

Please refer to Section 4 of the study protocol for details of the study design.

3.2 Treatments

3.2.1 Premedication

Please refer to Section 6 of the study protocol for details on leukapheresis and lymphodepleting chemotherapy.

3.2.2 T Cell Infusion

Please refer to Section 6.3 of the study protocol for details.

3.3 Determination of Sample Size

A sample size of 45 subjects in Cohort 1 will provide at least 90% power to reject the null hypothesis if the true ORR is at least 40%. The sample size was determined based on the following statistical design and assumptions:

- The assessment for efficacy will be based on the mITT population using confirmed ORR via RECIST v1.1 per independent review in Cohort 1;
- The two-sided type I error (α) for this test will be no more than 0.05;
- The type II error (β) will not exceed 0.1;
- Exact Binomial method will be used to test the hypothesis;
- Cohorts 1 and 2 are independent.

The hypothesis of interest for the primary endpoint is:

(Null Hypothesis) H0: $p \leq p0$, vs. (Alternate Hypothesis) H1: $p > p0$, where p0 (historical control rate) = 0.18.

Based on above assumptions, the TCR ORR (i.e., p1) is set at 0.4. The two-sided type I error (α) for this test will be no more than 0.05 and the type II error (β) will not exceed 0.1. Exact Binomial methods will be used to test the hypothesis.

An additional 45 subjects are planned to be enrolled in Cohort 2 to supplement Cohort 1 with additional safety and efficacy data based on clinical judgement. No formal hypothesis testing is planned for either Cohort 2 or across cohorts.

See Section 9.2 of the protocol for additional information.

4 Study Endpoints and Covariates

4.1 Study Endpoints

Definitions and methods of summary will be detailed in section 10.9 and section 10.10.

4.1.1 Primary Endpoints

The primary endpoint is the Overall Response Rate (ORR) in Cohort 1. The ORR will be based on confirmed (tumor) responses per RECIST v1.1 by independent review.

- As a secondary endpoint, ORR will also be assessed across Cohorts (overall).

4.1.2 Secondary Endpoints

All secondary endpoints are defined for Cohort 1 and across cohorts.

For Cohort 1 and across Cohorts (overall):	• **Adverse Events (AEs)** AEs, including Serious Adverse Events (SAEs); incidence, severity and duration of the AEs of special interest are secondary endpoints. AE will be coded by MedDRA v23.0. • **Incidence, severity and duration of the AEs of special interest.** • **Replication Competent Lentivirus (RCL)** • **T cell Clonality and Insertional oncogenesis (IO)** • **Time to Response (TTR)** • **Duration of Response (DoR)** • **Best Overall Response (BOR)** • **Progression Free Survival (PFS)** • **Overall Survival (OS)** • **Persistence** Peak persistence and other relevant pharmacokinetic (PK) parameters of ADP-A2M4 cells.
Across cohorts (overall)	• **Overall Response Rate (ORR) per RECIST v1.1 by independent review across Cohorts(overall)**

	• **Retention of additional tumor tissue during Pre-screening to enable development and validation of the MAGE-A4 antigen expression companion diagnostic assay**

4.1.3 Exploratory Endpoints

- [redacted]
- [redacted]
- [redacted]

5 Hypothesis and/or Estimations

The hypothesis of interest for the ORR in Cohort 1 is; (Null Hypothesis) H_0: $p \leq p_0$, vs. (Alternate Hypothesis) H_1: $p > p_0$, where p_0 (historical control rate) = 0.18.

No hypothesis testing is planned for the secondary endpoints.

6 Definitions

6.1 General Definitions

6.1.1 Baseline Definition

Unless specified otherwise, baseline is defined as the last non-missing assessment (including unscheduled assessments) prior to lymphodepleting chemotherapy. Detailed baseline visits are given in Table 1 below.

Table 1. Baseline Visits for Primary and Secondary Efficacy and Safety Endpoints

Assessment/Test	Visit
Target and Non-target Lesions	Baseline 1-5 days prior to lymphodepleting chemotherapy (Visit 4)
Hematology, Chemistry, CRP	Baseline 1-5 days prior to lymphodepleting chemotherapy (Visit 4)
Vital Signs, Physical Exam, ECOG	Baseline 1-5 days prior to lymphodepleting chemotherapy (Visit 4)
Electrocardiogram	Screening (Visit 1)
Cytokines	Baseline 1-5 days prior to lymphodepleting chemotherapy (Visit 4) (first run of baseline serum

	sample should be used in case of multiple runs of the baseline)

Note, if baseline values are missing, most recent pre-baseline value (including unscheduled visits) will be used.

6.1.2 Other Definition

Nominal study day is relative to T cell infusion. Day 1 and Study Day are defined in Table 2 below.

Table 2 Definition of Study Day 1 and Study Day

Day 1	The first day of the initial T cell infusion in the study
Study Day	(Date of Interest - Date of first T-cell infusion) + 1 If Date of Interest is >= first T-cell infusion date
	Date of Interest - Date of first T-cell infusion If Date of Interest is < first T-cell infusion date

6.2 Definition for Safety Endpoints

6.2.1 AEs

Please refer to Section 8.5 of the protocol for relevant information.

7 Analysis Population

A by-subject listing of analysis population details will be provided. This listing will be presented by cohort and by tumor type, and will include subject identifier, inclusion/exclusion flag for each population, and reason for exclusion from each population.

7.1 Intent-to-Treat Population

This is the population of all subjects who were enrolled in the trial. The ITT population will be used to assess the safety of the end-to-end autologous T cell therapy procedure. The ITT population may also be used for important efficacy summary as data permits.

7.2 Modified ITT (mITT) Population

This is the population of all ITT subjects who received T cell infusion. The mITT population is the primary analysis population for safety and efficacy evaluations following T cell infusion.

8 Interim Analysis and Data Review

8.1 Interim Analysis

There is no interim analysis planned.

8.2 Data Review

Please refer to Data Safety Monitoring Board (DSMB) charter for details on the specific data displays. Unless noted otherwise, all relevant definitions, derivations and conventions from this document will apply for displays specified in the DSMB charter.

9 General Analysis Conventions

There are two analyses for each endpoint: Cohort 1 (primary) and overall (across cohorts). For the primary analysis (Cohort 1), please refer to Section 5.5 of the protocol for the clinical follow-up.

Data collected in this study will be analyzed using summary tables, figures/plots or subject data listings.

Unscheduled assessments (laboratory data, scans, ECG, vital signs, etc. associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not summaries. If there are more than one laboratory value is available for a given visit, the worst laboratory value will be used in summaries and all observations will be presented in listings, unless otherwise stated.

Continuous variables will be summarized using descriptive statistics (Number of subjects, Mean, Median, Standard deviation, Minimum and Maximum). Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, mean, lower quartile, minimum, standard deviation, and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The standard deviation will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic. Confidence intervals will be presented to one more decimal place than the raw data. If the confidence intervals are calculated for proportions, then they will be presented to three decimal places.

Categorical variables will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Adverse events, medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0 or higher. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version (2020) or higher.

All tables, listings, and figures will be programmed using SAS Version 9.4 or higher.

9.1 Study Periods

Please refer to Section 8.5 of protocol for collection of AE / SAE information through the study.

For the purposes of reporting, adverse events will be summarized using two main time periods in the interventional phase. The periods will start as indicated below and end at subject's end of intervention phase.

- From the time of signing the treatment ICF
- From start of lymphodepleting chemotherapy, defined as starting on the first day of lymphodepleting chemotherapy.

AEs will be included in these periods if:

- They are ongoing events (i.e., there is no AE end date), in the corresponding period
- The AE end date falls in the corresponding period

For subjects who receive the T cell therapy, AEs deemed to be LTFU AEs will be summarized and listed. (Note, for programming purposes, these AEs are listed as preferred terms in a separate document and may involve other preferred terms not currently included in the LTFU eCRF.)

Pre-screening period SAEs will be listed.

9.2 Visit Windows

Study visits are expected to occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. No imputation of data will be performed for missed assessments unless otherwise noted. In data listings, the relative study day of all dates will be presented.

Note: for time-to-event analyses, evaluations will be based on the actual date of the event rather than on the visit of the event.

10 Statistical Methods of Analysis

10.1 Handling of Dropouts or Missing Data

Missing data will not be imputed unless otherwise indicated.

In general, imputed partial dates will not be used to derive study day, duration (e.g., duration of adverse events), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date in the overall survival analysis dataset.

Imputed dates will not be displayed in listings unless otherwise stated.

The partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation. The flag variable can contain the values: blank, 'D', 'M', 'Y'.

- blank: indicates that no imputation was done
- D='Day': indicates that the day portion of the date is imputed
- M='Month': indicates that the month and day portions of the date are imputed
- Y='Year': indicates that the entire date (year, month, and day) is imputed

Imputing partial AE, medical history, initial diagnosis partial dates, and prior/concomitant medication start dates:

a) If the year is unknown, the date will not be imputed and will be assigned a missing value.
b) If only year is present, and month and day are unknown, then:
    1. If the year matches the first dose date of lymphodepleting chemotherapy:
        - If the stop date is available and complete, and is on or after the first lymphodepleting chemotherapy date, then impute to the month and day of the first lymphodepleting chemotherapy date.
        - If the stop date is available and complete, and is before the first lymphodepleting chemotherapy date, then impute to the first day of the month of the stop date.
        - If the stop date is missing (and unable to be imputed) or no stop date is applicable, then impute to the month and day of the first lymphodepleting chemotherapy date.
    2. Otherwise, assign ‘January 01’.
c) If month and year are present and the day is unknown, then:
    1. If the month and year match the first lymphodepleting chemotherapy date, then impute to the day of the first lymphodepleting chemotherapy date.
    2. Otherwise, assign ‘01’ of the month.

Imputing partial AE, medical history, and prior/concomitant medication stop dates:

a) If the year is unknown, the date will not be imputed and will be assigned a missing value.
b) If the month is unknown, then assign 'December 31'.
c) If the day is unknown, then impute to the last day of the month.

Note: After imputation, if the imputed date is later than the date of death or the date that the subject ends the study, then the date of death or date of end of the study will be used, whichever is earlier. If AE is ongoing but the subject discontinues the study, then the stop date will be resolved to the date that the subject discontinues the study.

If a period determination cannot be made for an adverse event, it will be attributed to the post-lymphodepletion period.

For cytokine parameters with character values, following guidelines will apply:

- Characters such as "Fail QC" "Fail Std" "CV>25%" "TNP" "DNR" "CV>30%" "std" "std Fail" "<##.#" or ">##.#" will set to missing (i.e., ".").

For persistence, the values of expansion < xx should be mapped to 1 on the applicable outputs.

10.2 Pooling of Centers in Multi-Center Studies

Data will not be summarized by study center.

10.3 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons or multiplicity are planned.

10.4 Examination of Subgroups

Efficacy and safety summaries will be displayed across both synovial sarcoma and MRCLS tumor types (overall) and by tumor type. ORR and BOR will also be summarized by subgroups in table 3 in section 10.9.2.

10.5 Subject Disposition

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion. Summaries of subject disposition in the ITT and mITT population in Cohort 1 and Overall (across cohorts), presented by tumor type and overall will be provided as follows:

- Number and percentage of subjects in the analysis populations
- Number and percentage of subjects who completed leukapheresis and/or lymphodepleting chemotherapy
- Number and percentage of subjects who are on going in Interventional Phase.
- Number and percentage of subjects who completed/discontinued the Interventional Phase
- Number and percentage of subjects in LTFU phase.

- Number and percentage of subjects who withdrew early from the interventional phase (including reasons for early withdrawal)
- Number and percentage of subjects who withdrew early from the study (including reasons for early withdrawal)
- Number and percentage completed the study

By-subject listings of infusion dates, and withdrawal details (including reason for discontinuation and days on study) will also be provided.

10.6 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized and listed for subjects in the ITT and mITT population in Cohort 1 and Overall (across cohorts) for each tumor type and overall:

- Age at time of informed consent (in years, as a continuous variable)
- Age categorization (<65, >= 65 years)
- Sex (Male, Female)
- Race (White, Black/African American, Asian, American Indian/Alaska Native, Hawaiian Native/Other Pacific Islander)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown, Not Reported)
- Weight at baseline (in kilograms)
- Height at baseline (in centimeters)
- BMI at screening (in kg/m^2) calculated using weight and height at screening
- Geographical Region (North America, Europe, UK)
- Primary Tumor Type (Myxoid/Round Cell Liposarcoma, Synovial Sarcoma)
- Histological Grade
- Current Cancer Stage
- Time since initial diagnosis to enrollment
- Time from initial diagnosis to T cell infusion
- Prior Lines of Systemic Therapy (as a continuous variable)
- Prior Lines of Systemic Therapy categorization (0, 1, 2, 3, 4+)
- Bridging therapy (as a continuous variable)
- Bridging therapy (Yes, No)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance

Since age is part of the inclusion criteria, age will be reported as the number of complete years at the date of informed consent.

Additionally, MAGE-A4 expression at screening is collected in Clinical LIMS database and will be summarized for subjects in the ITT and mITT populations in Cohort 1 and Overall (across cohorts) for each tumor type and overall across tumor type. Expression will be summarized by P Score and H Score, each calculated as below:

P score is defined as:

% 2+ tumor staining intensity + % 3+ tumor staining intensity

H score is defined as:

% 1+ tumor staining intensity + 2 x % 2+ tumor staining intensity + 3 x % 3+ tumor staining intensity

A by-subject listing will also be provided for the ITT population.

In case of multiple records, the following record selection criteria will be applied:

a. Select the record with latest analysis date in Clinical LIMS data.
b. If there are duplicates after applying step a then select the record with maximum 'HE Estimated nr of cancer cells' in Clinical LIMS data.
c. If one record has a value '100-500' and another record has a value '>500' then select the record with value '>500'
d. If there are still duplicates, then select the one with highest H Score/ P Score.

10.7 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher.

The number and percentage of subjects with each medical history condition collected on the eCRF will be summarized for the ITT population and the mITT population in Cohort 1 and Overall (across cohorts) for each tumor type and overall.

A by-subject listing of all medical history terms will also be created.

10.8 Prior Cancer Therapy

Prior systemic therapy, radiotherapy, and surgery history will be displayed for the ITT, mITT population. The following variables will be displayed:

- Number of lines of prior systemic therapy
- Prior systemic therapy (yes/no)
- Type of systemic therapy
- Prior systemic therapy regimens
- Best response to last systemic therapy
- Prior radiotherapy (yes/no)

- Anatomical site of radiotherapy
- Prior cancer-related surgery (yes/no)
- Anatomical site of cancer-related surgery
- Site of prior cancer-related surgery

Additionally, systemic therapy, radiotherapy and surgery history from screening to leukapheresis, and from leukapheresis to start of lymphodepletion (i.e., bridging therapy) will be listed by subject in a data listing.

10.9 Efficacy Analysis

Efficacy analyses will be summarized for mITT population in Cohort 1 and Overall (across cohorts) by tumor type and overall. The primary and secondary efficacy variable analyses will be conducted based on independent review (per RECIST v1.1). The following will be considered for sensitivity analyses:

- RECIST v1.1

Additional sensitivity analyses for the efficacy variables may include the ITT population, if different from the mITT population.

10.9.1 Overall Response Rate (ORR)

The primary endpoint is the Overall Response Rate (ORR) in Cohort 1, defined as the proportion of subjects with a confirmed Complete Response (CR) or a confirmed Partial Response (PR) relative to the total number of subjects in the mITT population. The ORR will be based on confirmed (tumor) responses per RECIST v1.1 by independent review.

- As a secondary endpoint, ORR will also be assessed across Cohorts (overall).
- Sensitivity analyses of ORR may be provided based on confirmed responses per RECIST v1.1, and on investigator assessment of overall response (per RECIST v1.1). For details, please refer to section 10.9.7.

The number and proportion of subjects achieving confirmed CR or PR will be summarized and presented by tumor type and overall for the mITT population and ITT population in Cohort 1 and Overall (across cohorts). ORR will be summarized using a two-sided exact Clopper-Pearson (exact Binomial) 95% confidence interval (CI).

- If data permits, as a sensitivity analysis, two-sided 95% confidence interval using the Wilson method may also be provided. For details, please refer to section 10.9.7.

Maximal change in target lesions from baseline will be shown in a waterfall plot by each tumor type and overall. Change in target lesions from baseline over time by patient will be shown in a spider plot.

10.9.2 Best Overall Response (BOR)

The best response recorded from T cell infusion until disease progression/recurrence. Response categories from best to worst are: confirmed CR, confirmed PR, Stable Disease (SD), Progressive Disease (PD) and Not Evaluable (NE) per RECIST v1.1.

BOR will be summarized by the number and percentage of subjects with each category of best overall response. Categories will be confirmed CR, confirmed PR, SD, PD, and NE.

To confirm CR or PR, changes in tumor measurements must be confirmed by repeat assessments that should be no less than 4 weeks (28 days) after the criteria for response are first met, excluding the day of the initial assessment of CR or PR. In case of SD, it must have occurred at least 4 weeks post infusion (on or after 28 days) from baseline; otherwise, BOR will depend on subsequent assessments. BOR will be presented as PD, regardless of duration.

To take into account potential pseudoprogression, no tumor assessments prior to the 29 day window from baseline will be considered for BOR determination, unless there is unequivocal progression of existing non-target lesions and/or the appearance of new malignant lesions. Please refer to the Section 8.3.1 of the protocol for additional information.

The overall visit response will be derived programmatically in accordance with RECIST v1.1 criteria. Measurements collected on the eCRFs for target, non-target, and new lesions will be used for the derivation of overall response for each visit and across all visits to determine BOR.

In the absence of unequivocal progression of existing non-target lesions and/or the appearance of new malignant lesions:

- Overall response for any tumor assessment prior to 29 day window will be presented.
- If a subject only has tumor assessments prior to 29 day window as of data cut date, then BOR=NE

Summaries BOR by investigator and BOR by independent assessment will be examined for subgroups specified in Table 3 below. The following subgroups analyses will be performed for ORR and BOR. These analyses will be summarized by frequency counts and percentages. A by-subject listing will also be provided.

Table 3: Subgroups

Subgroup	**Subgroup Definition (cut-offs)**
Age	< 40 years; ≥ 40 years
Gender	Female; Male
Prior systemic lines of Therapy	≤ 2 lines; ≥ 3 lines
Geographical region	North America/Europe

H Score	< 200; ≥ 200
Baseline sum of diameter	SLD < 100 mm; SLD ≥ 100 mm
Bridging therapy	Yes; No
Transduced cell dose	< 7B; ≥ 7B
CRS Any Grade	Yes; No
Response to Treatment*	Responders (Confirmed CR and PR as BOR per RECIST V1.1); Non-responders

10.9.3 Time to Response (TTR)

Time to response (CR or PR) is defined as the interval between the date of first T-cell infusion and the earliest date of first documented confirmed CR or confirmed PR.

- TTR (in weeks)= [date of initial confirmed CR or PR – date of T-cell infusion+1]/7

TTR (in weeks) will be summarized as a continuous response for all subjects with a confirmed CR/PR. A by-subject listing of TTR will also be provided.

10.9.4 Duration of Response (DoR)

DoR is measured from the time criteria are first met for CR/PR (whichever is first recorded) until the first date of progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). This will only apply to subjects with confirmed CR or confirmed PR and will be calculated as: (first event date – first OR date + 1)/7.

DoR (in weeks) will be summarized and displayed graphically using KM methodology to estimate the 25th, 50th (median), 75th percentiles, Min and Max. This analysis, however, will only apply to subjects that have achieved confirmed response.

A swim lane plot will be created indicating subject's BOR, duration of response, PD, and death.

A by-subject listing will also be provided.

Censoring will occur as follows:

- If there are no adequate tumor assessments after the subject achieved confirmed response, DoR will be censored and have a duration set to 1.
- If a subject is known to be alive and progression-free, DoR will be censored on the day of the last adequate tumor assessment.
- Note per Section 6.5.1 of the protocol, use of active curative anticancer therapy post T cell infusion (i.e. prior to disease progression) will also be considered as meeting the PD criterion. If a subject is given subsequent curative anti-tumor curative anticancer therapies and curative anti-cancer surgeries other than the study treatment, not including approved palliative radiation and diagnostic procedures such as surgical biopsies prior to PD or death, DoR will be censored on

the date of the last progression-free tumor assessment prior to the start date of the anti-tumor treatment.

- If a subject discontinues the interventional phase of the study prior to PD, DoR will be censored on the date of last adequate progression-free tumor assessment.
- If a subject misses 2 or more consecutive post-baseline tumor assessments and the following assessment is a PD, or if a subject misses 2 or more consecutive post-baseline tumor assessments and then dies, DoR will be censored on the date of the last adequate tumor assessment.

Sensitivity Analyses on DoR may be performed:

Sensitivity Analysis #1 will also consider death to be an event. If death occurs before PD is documented, the date of death will be used for the DoR event calculation.

10.9.5 Progression Free Survival (PFS)

Progression-Free Survival (PFS) is defined as the time from the T cell infusion to the date of the first documentation of PD or death due to any cause, whichever occurs first. PFS (in weeks) will be calculated as: (first event date – first T cell infusion date + 1) / 7.

PFS data will also be listed by subject; reason for censoring will be included in listing.

The details regarding the handling of missing assessment and censoring for primary PFS analysis are presented as follows:

- If a subject has an inadequate baseline scan, PFS will be censored and have a duration set to 1.
- If there are no adequate post baseline tumor assessments after T cell infusion or date of death recorded, PFS will be censored and have a duration set to 1.
- If a subject is known to be alive and progression-free, PFS will be censored on the day of the last adequate tumor assessment.
- Note per Section 6.5.1 of the protocol, use of active curative anticancer therapy post T cell infusion (i.e. prior to disease progression) will also be considered as meeting the PD criterion. If a subject is given subsequent curative anti-tumor curative anticancer therapies and curative anti-cancer surgeries other than the study treatment, not including approved palliative radiation and diagnostic procedures such as surgical biopsies prior to PD or death, PFS will be censored on the date of the last progression-free tumor assessment prior to the start date of the anti-tumor treatment.
- If a subject discontinues the interventional phase prior to PD, PFS will be censored on the date of the last adequate tumor assessment.

- If a subject misses 2 or more consecutive post-baseline tumor assessments and the following assessment is a PD, or if a subject misses 2 or more consecutive post-baseline tumor assessments and then dies, PFS will be censored on the date of the last adequate tumor assessment.

When determining PFS, the recorded date of progression (defined as first time at which progression can be declared) will be used. For progression due to the presence of a new lesion, the date of progression is the first date that the new lesion was observed. If multiple assessments based on the sum of target lesion measurements are done at different times, the date of progression is the date of the first observation or radiological assessment of target lesions that shows a predefined increase in the sum of the target lesion measurements.

PFS will be summarized and displayed graphically using KM methodology to estimate the 25th, 50th (median), 75th percentiles, Min and Max. These summaries will include 6, 12, 18, and 24-weeks survival probabilities along with corresponding 95% CIs by tumor type and overall, as well as the proportion of censored observations.

Given the expected size of Cohort 1 (45 subjects) and Overall (90 subjects), the expected (half-)widths of two-sided 95% confidence intervals for PFS are displayed in Table 4. The expected CI width is shown for various assumed true median PFS and censoring rate values. For example, if the true median PFS is 4.6 months (that is, if the median PFS is similar to that of pazopanib; see Section 2.2.3 of the protocol) and there is no censoring, the expected width of the 95% CI for PFS in Cohort 1 is ±1.90 months, or 3.79 months total. If 10% of subjects are censored, the confidence interval is expected to be wider.

Table 4 Expected PFS Confidence Interval Widths

True Median PFS	Censoring Rate	Cohort 1	Overall
*4.6 months	0%	±1.90	±1.37
	10%	±2.01	±1.39
6 months	0%	±2.47	±1.79
	10%	±2.62	±1.82
8 months	0%	±3.30	±2.38
	10%	±3.49	±2.42

Additional sensitivity analyses of PFS may be performed as follows:

Sensitivity Analyses on PFS

Sensitivity Analysis #1 will be conducted to assess the impact of missed or NE tumor assessments. This analysis will backdate any PD events that occur immediately after missing or NE assessments. If the PD occurs immediately after missed or NE assessment (or series of missed or NE assessments), the PD date will be the date of the first missed or NE assessment preceding the PD. Death after missed visits will be considered as censored at the date of last adequate assessment prior to missing visits.

Sensitivity Analysis #2 will consider discontinuation from the interventional phase for clinical progression will be considered as progressed at date of discontinuation from the interventional phase.

10.9.6 Overall Survival (OS)

OS is defined as the time from the date of first T cell infusion to the date of death (due to any reason). OS in weeks will be calculated as: (death date – first T cell infusion date + 1) /7. The details regarding the handling of missing assessment and censoring for OS analysis are presented as follows:

- If there is no confirmation of death, OS will be censored on the date the subject is last known to be alive, or the data cutoff date, or the end of study date, whichever is earlier.

OS will be summarized by cohort using KM method displaying 25th, 50th (median), and 75th percentiles with associated 2 sided 95% CIs, as well as the proportion of censored observations. Subjects who remain alive or who are lost to follow-up will be censored at the date of last contact. A KM plot will be provided.

OS may be assessed at fixed time points such as 1 year and 2 years. OS data will also be listed by subject; reason for censoring will be included in listing.

10.9.7 Other Efficacy Analysis

Sensitivity analysis of ORR and discordance analysis for BOR, DoR, PFS may be provided as data permits.

10.9.7.1 Sensitivity Analysis of ORR

Sensitivity analyses of ORR will be based on confirmed responses per RECIST v1.1.

As a sensitivity analysis, two-sided 95% confidence interval using the Wilson method may also be provided.

As a sensitivity analysis for DoR, TTR and PFS, determination of progression (via RECIST v1.1) using lesion assessments may also be provided.

10.9.7.2 Discordance analysis for DoR, PFS

Independent Assessment vs Investigator Assessment

A summary of the Independent assessment versus investigator assessment will be provided including numbers of concordant and discordant assessments as well as the number of cases where DOR event

was assessed at different timepoints based on independent assessments and investigator assessments. Same summary will be applied to PFS.

Table 5 outlines the possible outcomes by investigator assessment and independent assessment (Amit et al. 2011).

Table 5. Possible Outcomes for Investigator assessment vs Independent assessment per RECIST v1.1

		Independent assessment	
Investigator assessment		**Event**	**No Event**
	Event	a = a1 + a2 + a3	b
	No Event	c	d

a1: number of agreements on timing and occurrence of event.

a2: number of times agreement on event but investigator declares event later than independent reviewers.

a3: number of times agreement on event but investigator declares event earlier than independent reviewers.

N= a+b+c+d.

The timing agreement of event is defined as a window of ± 7 days

The following measure of discordance will be calculated:

- Total Event Discrepancy Rate: (b+c) / N
- Early Discrepancy Rate (EDR): (a3+b) / (a+b)
- Late Discrepancy Rate (LDR): (a2+c) / (a2+a3+b+c)
- Overall Discrepancy Rate: (a2+a3+b+c) / N

The EDR represents the positive predictive value of investigator assessment and quantifies the frequency with which the investigator declares DOR event earlier than independent reviewers as a proportion of the total number of investigator assessed events.

The LDR quantifies the frequency with which the investigator declares DOR event later than independent reviewers as a proportion of the total number of discrepancies.

10.9.7.3 Other exploratory endpoints analysis

The pharmacokinetic (PK) profile will be described by summaries of peak expansion (i.e., maximum persistence) and time to peak expansion by responder status and overall. Peak expansion will also be summarized by use of Anti-IL6 therapy, and by use of (systemic) corticosteroids during the intervention phase. Persistence data will also be displayed by subject listings and line plots.

[redacted]

10.10 Safety Analysis

Some of the safety analyses may not be performed as part of the efficacy supplement.

The safety assessments include study drug exposure, adverse events, vital signs, clinical laboratory parameters, and electrocardiogram (ECG) measurements. All safety summaries and analyses will be based upon the mITT population in Cohort 1 and Overall (across cohorts) and for each tumor type. Safety summaries may also be reported for the ITT population.

All safety data will be included in data listings.

10.10.1 Study Drug Exposure

T cell dose is based on the total number of transduced cells and will be reported as stated in the protocol in units of 10^9. The total number of transduced cells, transduction efficiency (i.e., percent of cells transduced), and total cell dose (in billions) will be summarized for the mITT population in Cohort 1 and Overall (across cohorts) by tumor type and overall using descriptive statistics.

All dose administration data including Cyclophosphamide, Fludarabine, Mesna, G-CSF and T cell infusion will be presented by subject in data listings.

New calculated viable transduced cell doses will be an exploratory analysis and will be summarized using the same summary method as T cell dose, the calculated dose will be provided from CMC.

10.10.2 Adverse Events

Adverse events (AE) will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher. Adverse events will be graded according to the NCI CTCAE v 5.0.

A treatment-emergent adverse event (TEAE) in the interventional phase is defined as an AE (identified by PT) that begins or is on-going after the first day of lymphodepleting chemotherapy has been administered until either discontinuation from the interventional phase or 30 days after T cell infusion, which ever date is later. Treatment-related TEAEs are those with reasonable causality to a study drug marked as "definitely related", "probably related", or "possibly related" on the eCRF. TEAEs with an outcome of death are those with a grade of 5 or an outcome of "fatal."

An AE in the long-term follow-up (LTFU) period is defined as an AE that starts after discontinuation from the interventional period or 30 days after T cell infusion, which-ever is later, until discontinuation from the long-term follow-up period. If an AE or AE from the interventional period is ongoing at the start of the long-term follow-up period, it will not be summarized as an AE in the long-term follow-up period. LTFU AE will be collected in a separate LTFU AE eCRF page and will not be programmatically derived.

10.10.2.1 Overview of Adverse Events

Summary tables will be presented for AE and TEAEs by tumor type and overall. An overall presentation of AE information will include the following:

- Number and percentage of subjects with at least one AE
- Number and percentage of subjects with at least one TEAE
- Number and percentage of subjects with at least one treatment-related TEAE
    - Number and percentage of subjects with a TEAE related to: Cyclophosphamide, Fludarabine, T cell infusion
- Number and percentage of subjects with at least one TEAE of Grade 3 or higher
- Number and percentage of subjects with at least one treatment-related TEAE of Grade 3 or higher
    - Number and percentage of subjects with a TEAE of Grade 3 or higher related to: Cyclophosphamide, Fludarabine, T cell infusion
- Number and percentage of subjects with at least one serious TEAE
- Number and percentage of subjects with at least one treatment-related serious TEAE
- Number and percentage of subjects with at least one TEAE leading to death

10.10.2.2 Adverse Events

TEAE information will also be presented by NCI CTCAE severity grade and by relationship to study treatment. If a subject had more than one occurrence of a TEAE, the most severe grade will be used in the summary tables.

The following summaries will be provided:

- Number and percentage of subjects for each AE, categorized by PT, all grade and Grades 3 or higher in the ITT population and the mITT population
- Number and percentage of subjects for each TEAE, categorized by PT, and SOC, PT, by all grades and Grades 3 or higher
- Number and percentage of subjects for each TEAE of Grade 3 or higher, categorized by SOC and PT, all grade and Grades 3 or higher
- Number and percentage of subjects for each TEAE, categorized by SOC, PT, and maximum CTCAE grade
- Number and percentage of subjects for each TEAE, categorized by PT and SOC, PT, and relationship to T cell infusion, all grade and Grades 3 or higher
- Number and percentage of subjects for each treatment-related TEAE, categorized by SOC and PT, all grade and Grades 3 or higher
- Number and percentage of subjects for each treatment-related TEAE, categorized by SOC, PT, and maximum CTCAE grade

A summary and listing of long-term follow-up AEs will also be provided. Please refer to Table 6 for summaries by reporting periods.

Counts will be by subject, not by event, and subjects are only counted once within each SOC or PT. For tables categorized by maximum CTCAE grade, subjects with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.

A by-subject listing of all AEs (including non-treatment-emergent events) will be provided. This listing will be presented by treatment arm and will include: subject identifier, age, gender, race, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, duration, CTCAE grade, seriousness, and relatedness. Additionally, by-subject listings for subjects experiencing cytokine release syndrome (CRS), persistence (copies / microgame of DNA) of MAGE-A4c1032T and replication-competent lentivirus (RCL) over time will be provided.

For missing or partially missing dates, imputation will be done according to Section 10.1. In general, however, adverse events will be assumed to be treatment-emergent unless there is clear evidence

(through comparison of partial dates) to suggest that the adverse event started prior to the date of first dose study therapy.

Additional, significant AE summaries that will be provided are:

- Number and percentage of subjects with serious TEAEs
- Number and percentage of subjects with treatment-related serious TEAEs
- Number and percentage of subjects with fatal TEAEs

For subjects with data, LTFU AE will be summarized and listed as described above. Additionally, AEs that occur prior to the first day of lymphodepleting chemotherapy will be summarized. If an AE starts prior to the first day of lymphodepleting chemotherapy but continues into the interventional phase, this AE will be summarized in both reporting periods.

Table 6: Summary of AEs by Reporting Period

	AEs (from ICF up to first day of LD)	Interventional Period TEAEs- First Infusion	LTFU Period
AEs by PT	X	X	X
T Cell Related AEs by PT		X	
Serious AEs by PT		X	
T Cell Related Serious AEs by PT		X	
Fatal AEs by PT		X	
AEs by SOC and PT		X	
Serious AEs by SOC and PT		X	
T Cell Related AEs by SOC and PT		X	
Fatal AEs by SOC and PT		X	

AEs by SOC and PT and Maximum Toxicity Grade		X	X
T Cell Related AEs by SOC and PT and Maximum Toxicity Grade		X	
Lymphodepletion Related AEs by SOC and PT and Maximum Toxicity Grade		X	

Prolonged Cytopenia

Prolonged Cytopenia is defined as Grade 3 or higher Anemia, Thrombocytopenia, Neutropenia or WBC decreased (Leukopenia). The severity is assessed using CTCAE v 5.0 criteria Grade 3 or higher the following summaries are to be produced:

- Incidence of Anemia: Hgb < 80 g/L, Thrombocytopenia: Platelets < 50 10^9/L, Neutropenia: ANC < 1.0 10^9/L), WBC decreased (Leukopenia): WBC < 2.0 10^9/L

Listing of Lab data for Hemoglobin (g/L), Platelets (10^9/L), ANC (10^9/L) and WBC (10^9/L) between and inclusive of Week 4 and Week 12 will be provided. Data from all scheduled and unscheduled visits included between Week 4 and Week 12 will be mapped to Week 4, Week 8 and Week 12 based on the following reporting window:

- Visit windowing for Week 4 is based on worst value from Day 24 to Day 41 post T-cell infusion inclusive.
- Visit windowing for Week 8 is based on worst value from Day 42 to Day 69 post T-cell infusion inclusive.
- Visit windowing for Week 12 is based on worst value from Day 70 to Day 98 post T-cell infusion inclusive.

If there are more than one value at the same visit, the worst laboratory value will be displayed. If there are more than one record with the same worst laboratory value, only the first one would be selected.

A table to summarize the proportion of patients who have cytopenia at week 4, 8, 12 will be provided. Duration of prolonged cytopenia in weeks is calculated as (Date of visit -date of T-cell infusion+1)/7. A by-subject listing will also be provided.

Cytokine Release Syndrome (CRS)

Time to first cytokine release syndrome (CRS) will be summarized by means, standard deviation, median, min and max.

- Time to first CRS (in days) = [date of first occurrence of CRS – date of T-cell infusion + 1]

Time to resolution of cytokine release syndrome (CRS) will be summarized by means, standard deviation, median, min and max.

- If a subject has only one occurrence of Cytokine Release Syndrome, then Time to resolution of CRS (in days) = [Stop date of CRS – Start date of CRS + 1]
- If a subject has multiple occurrences of Cytokine Release Syndrome, then Time to resolution of CRS (in days) is the number of days from the first onset of CRS syndrome to the last stop date of CRS, with the non-event date in between subtracted
  [stop date of last CRS – Start date of first CRS +1] – number of non-event days in between

The number and percent of subjects with CRS will be summarized by worst CRS toxicity grade. Additionally, Tocilizumab/Siltuximab use will be summarized overall and by CRS toxicity grade. If a subject has multiple occurrences of CRS and Tocilizumab/Siltuximab was administered for all occurrences, then only the worst will be presented in the table.

If a subject has two occurrences of CRS with grades 1 and 2 and Tocilizumab/Siltuximab administered for CRS with only Grade 1 then CRS with Grade 1 will be presented in the table.

On-study deaths will be summarized by reporting number and percentage of subjects on study who died and the number and percentage of subjects who are alive at last contact. Reason for death will be summarized. Number of days since T cell infusion will be reported in the category of death less than 30 days since T cell infusion, and death greater than or equal to 30 days since T cell infusion.

A by-subject listing of death will be provided.

Additionally, CARTOX-10 assessment results will be listed by subject at baseline (the assessment taken on the same day as, but prior to T cell infusion), and each scheduled post-baseline visits for the mITT population in Cohort 1 and Overall (across cohorts).

The three categories of CARTOX-10 scores are:

- Mild Impairment – total reported CARTOX-10 score of 7-9
- Moderate Impairment – total reported CARTOX-10 score of 3-6
- Severe Impairment – total reported CARTOX-10 score of 0-2

The Immune Effector Cell-Associated Encephalopathy (ICE) neurological assessment results will be listed by subject at T cell infusion and each scheduled post-infusion visits for the mITT population in Cohort 1 and Overall (across cohorts).

10.10.3 Clinical Laboratory Data

The list of all clinical laboratory tests is provided in Section 10.3 of the protocol.

Local laboratories will be used for laboratory safety evaluations in this study. Laboratory normal ranges will be provided by the local laboratory. For parameters where an NCI CTCAE v.5.0 scale exists, laboratory results will be graded according to the NCI CTCAE v.5.0 severity grade. For parameters for where an NCI CTCAE v.5.0 scale does not exist, an indicator of whether the value is below, within, or above the normal range will represent severity instead.

All laboratory values will be reported in SI units.

Summaries for each laboratory parameter will be presented by tumor type and visit. For by-visit summaries, the first non-missing assessment (including repeat assessments) recorded at each visit will be used. This will only apply to scheduled visits and unscheduled visits will not be summarized. Optional laboratory parameters will not be summarized by tumor type, only listed.

For laboratory values reported as a character value, such as <40, will be transformed into numerical values for summary reasons by following the specified guidelines. If a laboratory value is reported using the less than symbol, '<', 0.10 will be subtracted from the original numeric value. If a laboratory value is reported using the greater than symbol, '>', 0.10 will be added to the original numeric value.

Shifts in grade from baseline to the maximum shift (across all visits) will be summarized by tumor type and overall for Cohort 1 and Overall (across cohorts).

A by-subject listing of all laboratory data, with abnormal values flagged, will be provided by tumor type. This listing will include subject identifier, age, gender, race, and visit, as well as laboratory reference ranges for each parameter.

The by subject graph for Hematology parameters (PLT, HGB, ANC, ALC, WBC) over time will be provided. The graph will be generated for all visits until end of the interventional phase using the worst values in the visit window.

To assess Hy's Law, the number and percentage of subjects with potentially clinically significant post-baseline elevations in hepatic parameters shown in Table 7 below will be summarized by treatment. A listing of the subjects with potentially clinically significant post-baseline hepatic elevations will be provided. The listing will contain all a subject's values for parameters meeting the criteria.

Table 7. Potential Clinically Significant Elevations in Hepatic Parameters

ALT, AST and BIL Elevations	(>=3xULN AST and/or ALT) and >=2xULN BIL)
	(>=3xULN AST and/or ALT) and >=1.5xULN BIL)
ALT Elevations	>=20xULN
	>=10xULN
	>=5xULN
	>=3xULN
BIL Elevations	>=2xULN
	>=1.5xULN

10.10.4 Vital Signs

Vital signs data will include systolic blood pressure, diastolic blood pressure, pulse rate, temperature, respiration rate. Depending on the size and scope of changes, results will be summarized at baseline and post-baseline visit, and change from baseline using descriptive statistics (N (overall, and missing), mean, median, standard deviation, and minimum and maximum values). Vital signs will be listed by subject.

10.10.5 Electrocardiograms

A 12-lead ECG will be performed in accordance with the schedule of assessments as specified in Table 1 of the study protocol. This assessment will include result findings categorized as normal; abnormal, not clinically significant; abnormal, clinically significant; or unevaluable. The following ECG parameters will be recorded: RR-interval (msec), QRS-interval (msec), PR-interval (msec), QT-interval (msec), QTc-interval (msec), QT-interval corrected using the Frederica correction formula (QTcF) (msec).

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values will be presented by tumor type and overall in Cohort 1 and Overall (across cohorts).

All ECG parameters will be listed by subject for each tumor type and time point.

LVEF (%) will be listed by subject for each tumor type and timepoint.

10.10.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG performance status results will be summarized at each scheduled visit and as proportion of subjects with each score for each tumor type and overall in Cohort 1 and Overall (across cohorts). ECOG performance status will be listed by subject.

10.10.7 Prior and Concomitant Medications

All medications will be collected from the time the subject signs the informed consent form and throughout the subject's participation in the interventional phase. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version (2020).

Medications will be assigned to a time period (prior and/or concomitant) as follows:

- If both the start and stop date exist and are before the lymphodepleting chemotherapy, the medication will be counted as prior.
- If the start date is on or after lymphodepleting chemotherapy, the medication will be counted as concomitant.
- If the start date is before the lymphodepleting chemotherapy and the stop date is after the lymphodepleting chemotherapy or the medication is continuing, the medication will be counted as prior and concomitant.
- If the start date is missing and the stop date is before lymphodepleting chemotherapy, the medication will be counted as prior.
- If the start date is missing and the stop date is after lymphodepleting chemotherapy or the medication is continuing, the medication will be counted as concomitant.
- If the start and stop dates are missing and the subject get lymphodepletion the medication will be counted as concomitant, otherwise the medication will be counted as prior.

Summaries showing number of subjects and percentage taking each medication categorized by the WHO-DD Anatomical Therapeutic Chemical 3rd level (ATC-3) will be provided for each medication preferred term by tumor type and overall in the mITT population in Cohort 1 and Overall (across cohorts). This will be done separately for prior and for concomitant medications.

A by-subject listing of all prior and concomitant medication data will also be provided.

Bridging therapy will also be listed.

11 References

1. Eisenhauer EA, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1) 2009; Eur J Ca 45:228-247.
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4. a meta-analysis. 2011.