9. STATISTICAL ANALYSIS PLAN

Statistical Analysis Plan

A Phase 2, Multicenter Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-144) for Treatment of Patients with Metastatic Melanoma

SAP Version:	Version 3.0
Protocol Version	C-144-01 Version 9.0, 22 Oct 2019
NCT	NCT02360579
EudraCT Number	2017-000760-15

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND TERMS

Term	Definition
AE	Adverse Event
BMI	Body mass index
BOR	Best overall response
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
DTIC	Dacarbazine
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOA	End of Assessment
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EOT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
HLGT	High-level group term
HLT	High-level term
HRQoL	Health-related quality of life
ICF	Informed consent form
ICU	Intensive care unit
IL-2	interleukin-2
IRC	Independent Review Committee
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LLT	Low-level term
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NE	Not evaluable

Term	Definition
NMA-LD	non-myeloablative lymphodepletion
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PR	Partial response
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System (SAS®)
SD	Stable disease
SI Units	International System of Units
SOC	System organ class
SOD	Sum of diameters
TEAE	Treatment-emergent adverse event
TH	Tumor harvested
TIL	Tumor infiltrating lymphocyte
TPS	Tumor Proportion Score
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a comprehensive and detailed description of methods of the data analyses outlined in C-144-01 protocol version 9 (dated October 22, 2019), and also to pre-specify the statistical approaches to the analysis of study data prior to the database lock. This SAP will be finalized and signed prior to the clinical database lock for the primary analysis. All statistical analyses detailed in this SAP will be conducted using Statistical Analysis System (SAS®) Version 9.4 or higher.

Results obtained from the analyses described in this document will provide the basis of the Clinical Study Report (CSR) for this study. Analysis sets, and methods specified in this document take precedence over those described in the protocol should there be any difference due to timing of finalizing each document.

2 DESCRIPTION OF THE STUDY

This is a prospective, interventional multicenter study evaluating patients who receive adoptive cell therapy via infusion of LN-144 (autologous tumor infiltrating lymphocytes [TIL]). Patients will receive a nonmyeloablative lymphodepletion (NMA-LD) preconditioning regimen, then a single infusion of LN-144, followed by the administration of a regimen of interleukin-2 (IL-2). This clinical trial consists of four cohorts, which enroll similar patient populations with unresectable or metastatic melanoma:

- Cohort 1: to receive Gen 1 LN-144, non-cryopreserved TIL product
- Cohort 2: to receive Gen 2 LN-144, cryopreserved TIL product
- Cohort 3: Patients from Cohorts 1, 2 or 4, after having participated in the study and received LN-144, may rescreen for a second administration of LN-144, cryopreserved TIL product
- Cohort 4: to receive Gen 2 LN-144, cryopreserved TIL product.

Overall duration of study is approximately 5 years comprising the following periods:

Screening: Up to 28 days from signing the informed consent form (ICF).

Enrollment and Tumor Resection: Upon tumor resection for TIL generation.

Treatment Period: NMA-LD preconditioning regimen (up to 7 days) and LN-144 infusion (1 day, Day 0) followed by IL-2 administration (up to Day 4), continuing to Day 28. Patients will need to

return for safety assessment visits on Day 14 and Day 28 (Day 28 corresponds with the end of treatment [EOT] visit).

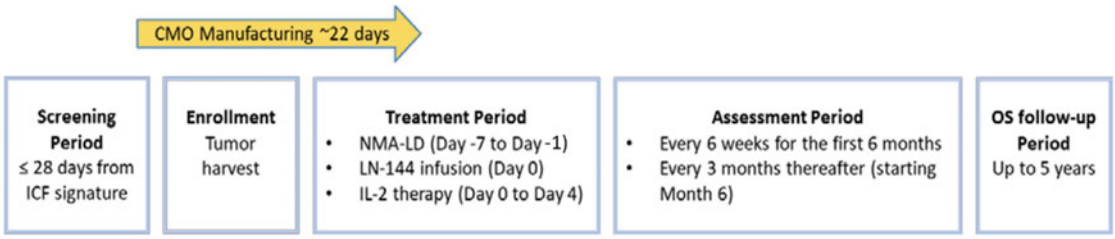
Assessment Period: Following the EOT visit, efficacy (i.e., tumor response) assessments will be performed at Week 6 (Day 42) post-LN-144 infusion and then occur every 6 weeks until Month 6 (Week 24). Patients will continue to be evaluated for response every 3 months (12 weeks) starting from Month 6 up to 5 years or until:

- Disease progression
- Start of a new anticancer therapy

At that time, the End of Assessment (EOA) visit will be completed.

Overall Survival Follow-up Period: Begins after completion of the last study assessment (i.e., EOA) and will continue for up to 5 years from enrollment or until discontinuation from the study; with telephone contact every 3 months to obtain survival status and subsequent anticancer therapy information. Patients who had tumor resection but did not receive LN-144 for any reason will perform an EOA visit and transition directly into the OS Follow-up Period.

Figure 1 Study Flowchart



Note: CMO = contract manufacturing organization; ICF = informed consent form; IL-2 = interleukin-2; NMA-LD = nonmyeloablative lymphodepletion; OS = overall survival.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

To evaluate the efficacy of LN-144 in patients with unresectable or metastatic melanoma using the objective response rate (ORR), as assessed by the independent review committee (IRC) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

3.1.2 Secondary Objectives

- To evaluate the efficacy endpoints of duration of response (DOR), disease control rate (DCR), and progression free survival (PFS), as assessed by the IRC per RECIST v1.1
- To further evaluate efficacy of LN-144 in patients with unresectable or metastatic melanoma by assessing ORR, DOR, DCR, and PFS, as assessed by the Investigator per RECIST v1.1
- To evaluate overall survival (OS)
- To characterize the safety profile of LN-144 in patients with unresectable or metastatic melanoma

3.1.3 Exploratory Objectives

- To explore the persistence of LN-144 and potential immune correlates of response, outcome, and toxicity of the treatment
- To explore efficacy based on immune-related RECIST (irRECIST) criteria (Bohnsack 2014) as assessed by the investigator
- To assess health-related quality of life (HRQoL)

3.2 Study Endpoints

3.2.1 Primary Endpoints

- ORR, as assessed by the IRC per RECIST v1.1

3.2.2 Secondary Endpoints

- DOR, DCR, and PFS per RECIST v1.1, as assessed by the IRC
- ORR, DOR, DCR and PFS per RECIST v1.1 as assessed by the investigator
- OS
- Incidence, severity, seriousness, relationship to study treatment, and characteristics of treatment-emergent adverse events (TEAEs), including AEs leading to early discontinuation from treatment or withdrawal from the Assessment Period, and AEs resulting in deaths.

3.2.3 Exploratory Endpoints

- TIL persistence in the peripheral blood and immune correlates with respect to response, outcome, and/or toxicity of the treatment will be determined by immunological and molecular

assays

- ORR, DOR, DCR, and PFS using irRECIST as assessed by the Investigator
- Patient-reported outcomes for HRQoL based on the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire – Core 30 Instrument (EORTC QLQ-C30)

4 GENERAL METHODOLOGY AND CONVENTIONS

4.1 Analysis Sets

Three analysis sets are defined for the analysis and presentation of the data. The Full Analysis Set (FAS) will be the primary set for the analysis of efficacy data. The Safety Analysis Set will be the primary set for safety data. Additional analysis for the primary efficacy endpoint, AEs, and SAEs will be conducted using the Tumor Harvested (TH) Set.

The TH Set (also termed Enrolled Set) is defined as all tumor-resected patients for production of LN-144, regardless of whether they have received LN-144 or not (per FDA's Response to Sponsor's Question 11 in the memorandum dated October 5, 2018 [CRMTS #11302]).

The Safety Analysis Set is defined as patients who have received any LN-144 infusion.

The FAS is defined as patients who have received LN-144 that meets the final manufacturing product specifications (per FDA's Response to Sponsor's Question 4 in the memorandum dated June 24, 2019 [IND 16819 CRMTS #11766]).

4.2 Sample Size Determination

Cohort 1: Infused 23 patients using the non-cryopreserved autologous TIL product manufacturing process. Enrollment into this cohort was stopped to focus on the Gen-2 cryopreserved autologous TIL product.
Cohort 2: Approximately 60 patients are planned to be infused in Cohort 2. Sixty patients will allow estimation of ORR using the maximum half width of the two-sided 95% Clopper-Pearson Confidence Interval (CI) of less than 13.2% when ORR is expected to range from 20–50%.
Cohort 3: This cohort is expected to infuse approximately 10 patients from Cohorts 1, 2, or 4 who have elected to undergo a second LN-144 treatment.
Cohort 4: Approximately 75 patients are planned to be infused and receive cryopreserved LN-144. A sample size of 75 patients in the FAS will provide more than 90% power to demonstrate statistical

significance to H_0: ORR ≤ 10% at a two-sided overall significance level of 0.05 using the exact test assuming the true response rate for LN-144 therapy in this study population is 25%.

4.3 Hypothesis Testing and Multiplicity Adjustment

At the time of primary analysis, the hypothesis testing of the primary efficacy endpoint, ORR as assessed by the IRC per RECIST v1.1, will be performed in Cohort 4 for the FAS as following:

- Hypothesis for Cohort 4: H_{01}: ORR≤ 10% vs. H_{a1}: ORR>10%

The null hypothesis H_{01} will be tested at significance level of 5% (two-sided). The hypothesis will be rejected if the lower bound of the two-sided 95% Clopper-Pearson CI for the primary efficacy endpoint in Cohort 4 FAS is greater than 10%. The study is considered to have met its primary objective if the null hypothesis H_{01} is rejected.

If the null hypothesis for Cohort 4 (H_{01}) is rejected, a second hypothesis testing of the primary efficacy endpoint will be performed based on the combined Cohorts 2 and 4 data. The same enrollment criteria, the same cryopreserved TIL manufacturing process, and the same treatment regimen between Cohort 2 and Cohort 4 support pooling of the data.

- Hypothesis for combined Cohorts 2 and 4: H_{02}: ORR≤ 10% vs. H_{a2}: ORR>10%

Similarly, H_{02} will be tested at significance level of 5% (two-sided). The hypothesis will be rejected if the lower bound of the two-sided 95% Clopper-Pearson CI for the primary efficacy endpoint in combined Cohorts 2 and 4 FAS is greater than 10%.

The null hypothesis for combined Cohorts 2 and 4 (H_{02}) will only be tested after the null hypothesis for Cohort 4 (H_{01}) is rejected. This fixed sequence testing procedure is used to ensure strong control of the family-wise error rate at a two-sided significance level of 5%. The statistical hypothesis for the primary efficacy endpoint will be tested only once at the primary statistical analysis. The primary efficacy endpoint might be summarized descriptively based on a different data cut after the primary statistical analysis but not for statistical hypothesis testing.

4.4 Justification of Null Hypothesis

As cited in the National Comprehensive Cancer Network guideline for metastatic melanoma, only dacarbazine (DTIC) is an approved therapy for the metastatic melanoma patient population.

Response rates to chemotherapy, including DTIC, in recent Phase 3 melanoma trials ranged from 4–10% (studies comparing chemotherapy with pembrolizumab or nivolumab in patients who were refractory to ipilimumab) (Hamid 2017; Weber 2015; KEYTRUDA USPI; OPDIVO USPI). Patients in the active control arms of these studies, which supported the original approvals of pembrolizumab and nivolumab, received investigator choice chemotherapy (ICC). Patients in both studies must have had progression after anti-CTLA-4 treatment, such as ipilimumab, and patients with a BRAF V600 mutation-positive tumor mutation must have had progression on anti-CTLA-4 treatment and a BRAF inhibitor. Patients had not received prior anti-PD-1, making this patient population somewhat healthier than the patients enrolled in C-144-01.

At median follow-up of 28 months in the KEYNOTE-002 study of pembrolizumab, the median DOR to chemotherapy was 6.8 months (range 2.8-11.3) (Hamid 2017); the median DOR to chemotherapy in the CheckMate 037 study of nivolumab was 3.5 months (range 1.3+ to 3.5) (Weber 2015). Data on activity of chemotherapy, and DTIC specifically, in melanoma patients after failure of anti-PD1 are limited, and median DOR for chemotherapy administered post-PD-1 has not been reported in literature. A retrospective analysis of patients who had received immune checkpoint inhibitor (CPI, including anti-CTLA4, anti-PD1 or combinations) prior to chemotherapy (various monotherapy agents and combinations) reported an ORR of 12.4%, across all CPIs and chemotherapy agents. In patients who had received anti-PD1, ORR was 11%, and ORR for DTIC, the only approved chemotherapy agent in the administered therapies, was 10% (Goldinger 2018).

A historical control ORR of 10% for advanced melanoma was also used for the single arm study Keynote-001 (Kang 2017), which enrolled ipilimumab-naïve patients, and for the randomized study Checkmate-037, after it discontinued the control arm (i.e., Investigators' choice) due to a high dropout rate.

In summary, ORR for DTIC in patients post-PD-1 is expected at best to reach 4-10% with a median DOR of 3.5 to maximumly 6.8 months, which were based on a patient population in earlier line than the patients enrolled C-144-01. Taken together these data support a null hypothesis of 10%.

4.5 Timing of Analysis

The primary analysis and statistical hypothesis testing of primary efficacy endpoint will be performed after all confirmed responders, as assessed by IRC per RECIST v1.1, have had at least 6 months follow up from their initial response (per FDA's Response to Sponsor's Question 6 in the

memorandum dated October 29, 2020 [CRMTS #12796]), or the timing as per the agreement with health authority.

The final analysis will be performed after all patients have been infused and their overall survival has been followed to maturity, or until at least 70% of patients have died, in order to characterize the effects on long term outcome data for DOR, PFS, and OS.

4.6 General Convention

The statistical analyses of efficacy and safety data will be performed by cohort and for Cohorts 2 and 4 combined, unless otherwise specified. The data from Cohort 4 provide primary evidence of effectiveness and safety of cryopreserved TIL product. The data from Cohort 2 and Cohorts 2 and 4 combined will provide supportive information for cryopreserved TIL product. A separate data analysis from Cohort 1 will evaluate non-cryopreserved TIL product.

Cohort 3 data for those patients who had a second course of LN-144 treatment will be presented separately. All reporting of Cohort 3 data will be descriptive, using summary tables and listings. No statistical hypothesis testing will be performed. Due to small number of patients, the tabular format will be limited to demographics and baseline disease characteristics, ORR as assessed by Investigator. TEAE analysis will be provided as well.

Patients who did not receive LN-144 treatment following the initial screening with or without initial tumor harvest (due to screen failure, manufacturing failure or other reasons) may be re-screened and may receive LN-144 if they meet eligibility criteria at the second screening. These patients will be included in the analysis sets of the cohort corresponding to the cohort in which they received LN-144 treatment.

Continuous data will be summarized as the number of patients with non-missing data (N), mean, standard deviation, median, minimum, and maximum values. Categorical data will be summarized as counts and their related percentages, where applicable. Estimation of CIs will use the Clopper-Pearson exact method with a two-sided 95% criterion unless otherwise specified. The formula to estimate “duration” in days is provided for relevant endpoints below and will be converted to months divided by 30.4375, when applicable.

5 PATIENT CHARACTERISTICS AND TREATMENT EXPOSURE

5.1 Patient Disposition

The patient disposition will be summarized using frequency and percentage for each of the categories listed below:

- All screened patients and the reason for not enrolling
- TH Set (Enrolled Set) and the associated reason for patients who did not receive LN-144
- Safety Analysis Set and the associated reason for patients who were excluded from FAS
- FAS and the associated reason for patients who discontinued from assessment period or from study, respectively

A summary of patients enrolled by site and geographic region will be provided.

5.2 Protocol Deviations

The protocol deviations are identified and assessed by Sponsor clinical research associate or designee following company standard operational procedure. Patients with important protocol deviations will be summarized by categories of deviations for the FAS as well as Safety Analysis Set. All protocol deviations will be listed.
All deviations related to COVID-19 will be documented. Impact of such protocol deviations, e.g., missing protocol-specified information, will be assessed and sensitivity analyses will be performed as appropriate. These additional analyses are described in Section 8.1.

5.3 Demographics and Baseline Disease Characteristics

5.3.1 Demographics

The following variables will be summarized descriptively for FAS, Safety Analysis Set, and TH set: age, age categories (<40, ≥40 to <65, and ≥65), gender, race, ethnicity, weight, body mass index (BMI), geographic region (United States, Europe), and country.

5.3.2 Baseline Disease Characteristics

The following disease baseline characteristics will be summarized for FAS, Safety Analysis Set, and TH set when applicable: baseline lactate dehydrogenase (LDH), number and type of prior systemic anti-cancer therapies, percent of patients with progressive disease (PD) for at least one prior anti-PD-1/anti-PD-L1 therapy, percent of patients with PD for at least one prior anti-CTL4

therapy for patients who received prior anti-CTLA4, percent of patients with PD for the last prior therapy before study entry, primary refractory to anti-PD-1/anti-PD-L1 (defined as patients who had best response of progressive disease to prior anti-PD-1/anti-PD-L1; the initial anti-PD-1/anti-PD-L1 with documented response is considered if multiple anti-PD-1/anti-PD-L1 therapies are received), time from last prior therapy to tumor harvest (months), time on first prior anti-PD-1/anti-PD-L1, cumulative time on anti-PD-1/anti-PD-L1 antibody if a patient received more than one round of anti-PD-1/anti-PD-L1 therapy, time on prior anti-CTLA-4 antibody, Time on combination of anti-PD-1 and anti-CTLA-4, number of patients with baseline liver and/or brain lesions, number of patients with mucosal melanoma, PD-L1 status (Tumor Proportion Score [TPS]), summary statistics of baseline target lesion sum of diameters (SOD), number of baseline target and non-target lesions, resected tumor anatomic site, screening and baseline Eastern Cooperative Oncology Group (ECOG) performance status, and BRAF mutation status.

Continuous variables will be summarized descriptively by number of patients, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients in each category. Individual patient listings will be provided to support the summary tables.

5.4 Medical History

A summary of medical history will be presented by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher for the Safety Analysis Set. A patient data listing of medical and surgical history will also be provided.

5.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Global B3 March 2021 or higher. Prior medications are defined as any medications that are stopped before the first dose of NMA-LD, not including prior anti-cancer systemic therapy. Concomitant medications are defined as medications that are either initiated before and continued after the first dose of NMA-LD or initiated after the first dose of NMA-LD through 30 days post LN-144 infusion, not including study regimen. The number and percentage of patients who take prior medications and concomitant medications will be summarized for the Safety Analysis Set.

New anti-cancer therapy received after LN-144 infusion will be summarized for the Safety Analysis Set. Time to new anti-cancer therapy will also be analyzed for the FAS using Kaplan-Meier (KM) method. Time to new anti-cancer therapy is defined as the time (in months) from the date of LN-144 infusion to start of new anti-cancer therapy. Patients not receiving new anti-cancer therapy at the time of data cut will have their event times censored on the last date of their known survival status or date of death for patients who have died. The median with its 95% CI and anti-cancer therapy free rate at appropriate time points (e.g. Months 6, 9, 12, and 18) will be obtained using the KM method.

All medications recorded on the case report form (CRF) will be listed.

5.6 Treatment Exposure

Study treatment and extent of exposure summaries will be provided for the patients in the Safety Analysis Set as well as patients in FAS. The total cells infused and relative infusion for LN-144 will be calculated and summarized descriptively. The relative infusion for LN-144 is calculated as the actual infused viable cells divided by the total manufactured and released viable cells.

The exposure to the NMA-LD regimen (cyclophosphamide and fludarabine) and IL-2 will be summarized based on number of patients who received the agent, total number of infusions received, total cumulative dose, relative dose intensity of protocol planned dose. Relative dose intensity is defined as the actual dose intensity divided by the planned dose intensity where dose intensity refers to the accumulative dose of above-described agents divided by the corresponding protocol planned number of doses (i.e. 2 doses for cyclophosphamide, 5 doses for fludarabine, and up to a maximum of 6 doses for IL-2).

6 EFFICACY ANALYSIS

Efficacy analysis will be performed for patients in the FAS. Additional analysis for the primary efficacy endpoint will be performed based on TH set.

6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is ORR as assessed by the IRC using RECIST v1.1, which will be analyzed in FAS. It is derived as the number of patients who have the best overall response (BOR) of complete response (CR) or partial response (PR) as assessed by IRC divided by the number of patients in the FAS x 100%. In order for the BOR to be categorized as CR or PR, a confirmatory

evaluation is required 4 weeks or more apart after the first CR or PR. To determine BOR, all tumor response assessments up to the first PD per RECIST v1.1 should be considered. Any further tumor response assessments after the first PD or after the start of a new anti-cancer therapy are not considered. Patients without any baseline or any post-baseline measurements are considered non-evaluable (NE).

ORR is expressed as a binomial proportion and will be summarized as a point estimate and its two-sided 95% confidence interval based on the Clopper Pearson exact method.

As a sensitivity analysis, ORR as assessed by the IRC using RECIST v1.1 will also be estimated for patients in the TH set.

The concordance rate between the IRC review and investigator assessment for response will be summarized along with the Cohen's kappa statistic for the FAS. The concordance rate of response will be computed as the frequency with which IRC and Investigator agree on classification of a patient as responder/non-responder as a proportion of the total number of patients in the FAS.

6.2 Secondary Efficacy Endpoints

ORR as assessed by Investigator per RECIST v1.1 will be analyzed for FAS patients in the same fashion as assessed by IRC per RECIST v1.1. ORR is expressed as a binomial proportion and will be summarized using a point estimate and its two-sided 95% CIs based on the Clopper-Pearson exact method. Derivation of confirmed BOR based on two consecutive tumor assessment visits 4 weeks or more apart per RECIST v1.1 is provided in Table 1.

As a sensitivity analysis, ORR by Investigator per RECIST v1.1 will also be estimated among patients in the TH set.

Table 1 - General Rule to Derive BOR as Assessed by Investigator based on RECIST v1.1

Overall Response first timepoint	Overall response subsequent timepoint	BOR per RECIST v1.1
CR	CR	CR
CR	PR	SD, PD or PR [a]

CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR [b]	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
SD	CR [b]	SD
SD	PR [b]	SD
SD	SD	SD
SD	PD	SD provided minimum criteria for SD duration met, otherwise PD
SD	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE
PD		PD

Note: BOR = best overall response. CR = complete response. PR = partial response. SD = stable disease. PD = progressive disease. NE = not evaluable. The minimum criteria for SD duration is defined as 4 weeks from LN-144 infusion for cohort 4, and 6 weeks from LN-144 infusion for Cohort 2.

[a] If a CR is met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[b] Subsequent assessments should be conducted to confirm the CR/PR of that specific time point.

DOR, DCR, and PFS will be analyzed per RECIST v1.1 as assessed by IRC and by investigator, respectively. For time-to-event endpoints such as DOR, PFS, OS, the KM product limit method will be used to estimate the survivorship function. Median time to event and two-sided 95% CI based on log-log transformation will be obtained. The event-free rates for appropriate time points including Months 6, 9, 12, 18, and 24 will also be provided for PFS and OS depending on the maturity of study data at the time of analysis.

DOR is defined as the time (in months) from the time point at which the initial measurement criteria per RECIST v1.1 are met for a CR or PR, whichever response is observed first, until the first date that PD is objectively documented, or the patient expires. Patients not experiencing PD or who have not died prior to the time of data cut will have their event times censored at the last adequate tumor assessment. For patients who received new anticancer therapies, DOR will be censored at the date of last tumor response assessment prior to the start of new anticancer therapies. Patients with PD or death immediately after two or more consecutive missing tumor assessment visits, the DOR will be censored at the last adequate tumor assessment prior to the missing tumor assessments.

DOR (day) = Date of PFS event (PD or death) or censoring – Date of first response + 1

The median DOR and its 95% CI will be obtained using the KM method for patients achieving a response (CR or PR).

DCR is defined as the proportion of patients who have the BOR of CR or PR, stable disease (SD), or non-CR/non-PD, where non-CR/non-PD is only for patients without target lesions. DCR is expressed as a binomial proportion and will be summarized using a point estimate and its two-sided 95% CIs based on the Clopper-Pearson exact method.

PFS is defined as the time (in months) from the date of LN-144 infusion to PD or death due to any cause, whichever occurs earlier. Patients not experiencing PD or not having died at the time of the data cut will have their event times censored at the last adequate tumor assessment. The PFS censoring rules and definition of progression date follow the Food and Drug Administration (FDA) "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018)". For patients who received new anti-cancer therapy, the PFS will be censored at the date of last tumor response assessment prior to the start of new anticancer therapies. Patients with PD or death immediately after two or more consecutive missing tumor assessment visits, the PFS will be censored at the last adequate tumor assessment prior to the missing tumor assessments.

PFS (day) = Date of PFS event (PD or death) or censoring – Date of LN-144 infusion + 1

An additional analysis of PFS will be performed following definition per European Medicines Agency (EMA) guideline (Guideline on the evaluation of anticancer medicinal products in man, 2017). The approach is similar as described above, except that missing assessments or initiation of new anticancer therapy will not result in censoring for PFS.

The median PFS with its 95% CIs and PFS at appropriate time points (e.g. Months 6, 9, 12, and 18) will be obtained using the KM method.

OS is defined as the time (in months) from the date of LN-144 infusion to death due to any cause. Patients not having died at the time of data cut will have their event times censored on the last date of their known survival status. The date of last known alive will be derived as the latest among dosing records, safety and any other assessment dates indicating that a patient is alive. The median OS with its 95% CI and OS at appropriate time points (e.g. Months 6, 9, 12, and 18) will be obtained using the KM method.

OS (day) = Date of death or Last known alive – Date of LN-144 infusion + 1

6.3 Exploratory Efficacy Endpoints

6.3.1 ORR, DOR, DCR, and PFS as assessed by investigator per irRECIST

Tumor response is also assessed per irRECIST by Investigator for Cohort 4 patients. The efficacy tumor response endpoint of ORR, DOR, DCR, and PFS as assessed per irRECIST by the Investigator will be explored for Cohort 4 FAS patients. The tumor response will be determined using RECIST v1.1 with a modification to require confirmation of PD per irRECIST performed at least 4 weeks after the first PD assessment. Tumor response assessment may be continued at the investigator's discretion if the PD is not confirmed due to pseudo-progression. The confirmatory tumor assessment following the initial PD will be based on Total Measured Tumor Burden (TMTB), non-target lesions, and new non-measured lesions. The BOR will be determined using tumor assessment data entered in the sponsor clinical database following the irRECIST criteria, including any tumor response assessments after the first unconfirmed PD due to pseudo-progression. Any further tumor response assessments after the start of a new anti-cancer therapy are not considered. Derivation of confirmed BOR based on two consecutive tumor assessment visits per irRECIST is provided in Section 9.3. In the absence of irRECIST assessment, the response assessment per RECIST v1.1 will be used.

ORR, DOR, DCR and PFS per irRECIST will be analyzed in the same manner as described for assessments per RECIST v1.1. ORR and DCR per irRECIST are expressed as a binomial proportion and will be summarized using a point estimate and its two-sided 95% CIs based on the Clopper-Pearson exact method. DOR is defined as the time from the first CR or PR to the date of first documentation of confirmed PD per irRECIST or death, whichever occurs earlier. PFS is

defined as the time from the date of LN-144 infusion to the date of first documentation of confirmed PD per irRECIST or death, whichever occurs earlier.

6.3.2 Health-Related Quality of Life (HRQoL)

Patient-reported outcomes for HRQoL will be assessed using the EORTC QLQ-C30 v3.0 instrument and analyzed per the published evaluation manual. The EORTC QLQ-C30 is composed of multi-item scales and single-item measures. It includes five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/vomiting, and pain), a global health status/HRQoL scale, and six single items (dyspnea, insomnia, appetite, constipation, diarrhea, financial difficulties). Each scale and single-item measures range in score from 0 to 100, with a higher score on functional scale indicating better function and a higher score on symptom scale indicating worse symptoms. Baseline scores, post-baseline scores and change from baseline will be descriptively tabulated (number, mean, standard deviation, median, min, max) at each time point.

6.4 Assessing Study Center Effect

This study is a multicenter, international study. Due to the expected small number of patients per study center, the assessment of treatment effect by study center is not meaningful. Therefore, the study centers will be pooled by geographic regions (United States and Europe) and subgroup analysis by geographic region will be assessed for the primary efficacy endpoint (Section 6.5) as well as TEAE (Section 7.1.2).

6.5 Subgroup Analysis of Efficacy Endpoint

Subgroup analysis of ORR and DCR by IRC will be performed in the following critical demographic and baseline disease characteristics for the FAS. Other subgroup analyses may be performed if deemed necessary.

- Age category (< 65 years and ≥ 65 years)
- Gender (male, female)
- Number of prior lines of therapy (1 to 3 vs ≥ 4)
- Prior anti-CTLA4 therapy use (yes, no)
- BRAF mutation status (BRAF V600E or V600K mutated, others including BRAF wild type, other mutation or unknown)

- Geographic region (United States, Europe)
- ECOG performance status at baseline (0, ≥1)
- Tumor PD-L1 expression (TPS ≥5%, TPS <5%; TPS ≥1%, TPS <1%)
- LDH value at baseline (≤ ULN, > ULN; ≤ ULN, 1-2xULN, >2xULN)
- Primary refractory to anti-PD-1/anti-PD-L1 (yes, no)
- Contract Manufacturing Organization (WuXi, Lonza, and Moffitt)
- Baseline target lesion SOD (<70, ≥70 mm; < median vs ≥ median)
- Number of baseline target and non-target lesions (≤ 3, >3)
- Patients with baseline liver lesion
- Patients with baseline brain and/or liver lesion
- Time from stop of anti-PD-1/PD-L1 to TIL infusion (≤ median vs > median)
- Cumulative time on prior anti-PD-1/PD-L1 (≤ median vs > median)
- Mucosal melanoma (yes, no)

6.6 Other Planned Efficacy Analyses

The following analyses may be performed for FAS patients unless otherwise specified.

- Time to first response, time to best response, and number of patients with deepened response over time (ie. SD improved to confirmed PR or PR improved to confirmed CR) will be calculated and summarized descriptively based on patients with a confirmed PR or CR as assessed by IRC and by investigators.
- The response rates for appropriate time points including Months 6 and 12 will be calculated for IRC assessments and summarized descriptively.
- The infused LN-144 dose relationship with clinical efficacy as assessed by IRC will be evaluated using visual displays as formal tests of hypotheses or quantitative evaluation are not amenable given the patient-specific, autologous nature of LN-144 product. Boxplot will be used to illustrate dose distributions by disease control status, and scatter plots will be used to show distributions of dose versus best change from baseline in target lesion SOD.

7 SAFETY ANALYSIS

Safety analysis will be performed for patients in the Safety Analysis Set. Additional analysis for AEs and SAEs will be conducted using the TH set. The assessment of safety data will be descriptive and based on the summarization of adverse events, vital signs, and clinical laboratory tests.

7.1 Adverse Events

Adverse event will be coded using the MedDRA version 24.0 or higher. SOC, high-level group term (HLGT), high-level term (HLT), PT, and lower-level term (LLT) will be provided in the AE dataset. The severity of each adverse event will be graded by the Investigator using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, unless otherwise specified in the protocol.

Related AEs are based on 3 out of the 5 categories of causal relationship to study drug reported by investigators: “Definite”, “Probably”, and “Possible”. The causal relationships of “Not Likely” and “Not Related” will categorize AEs as “unrelated”. Adverse events will be identified and captured as SAEs if they meet the definition for SAE.

7.1.1 Analysis Periods for Adverse Events

Four analysis periods are defined below for AE analyses. The focus of the AE summarization will be based on the TEAEs.

Tumor-Harvest AEs include AEs that occur after Tumor Harvest and before the start of NMA-LD. For patients who didn’t receive NMA-LD, AEs up to 30 days from tumor harvest will be included.

AEs during NMA-LD period include AEs that occur from the start of NMA-LD and before the start of LN-144 infusion. For patients who didn’t receive LN-144 infusion, AEs up to 30 days from the last dose of NMA-LD will be included.

TEAEs include AEs that occur from the start of LN-144 infusion and up to 30 days after LN-144 infusion.

Post treatment-emergent AEs include AEs that occur from 30 days post LN-144 infusion and up to 6 months after LN-144 infusion or up to the start of a new anti-cancer therapy, whichever occurs first.

7.1.2 Summary of Adverse Event

Tabular summaries including numbers and percentages of patients with the following AEs will be presented by SOC and PT (Table 2). In addition, AE summaries will be presented by PT only for TEAEs, TEAEs related to LN-144, and Treatment-emergent SAEs.

For AE summaries by PT, cytopenia AEs will be grouped based on PTs and presented as leukopenia (including white blood cell count decreased and leukopenia), lymphopenia (including lymphocyte count decreased and lymphopenia), neutropenia (including neutrophil count decreased and neutropenia), and thrombocytopenia (including platelet count decreased and thrombocytopenia). These grouped cytopenia PTs belong to different SOCs: Blood and lymphatic system disorders or Investigations. For AE summaries by SOC and PT, for analysis purpose, they will be summarized under SOC of Blood and lymphatic system disorders.

All grade AEs, Grade 3/4 AEs and Grade 5 AEs will be presented in separate columns. The most severe grade will be used for those AEs that occur more than once for a given PT in an individual patient.

Table 2 – Summary of AE analyses

Summary	**Population**
Tumor-Harvest AEs	TH set
AEs during NMA-LD period	Patients who received NMA-LD
TEAEs	Safety Analysis Set
Post treatment-emergent AEs	Safety Analysis Set
TEAEs related to LN-144	Safety Analysis Set
TEAEs leading to LN-144 discontinuation	Safety Analysis Set
Tumor-Harvest SAEs	TH set
SAEs during NMA-LD period	Patients who received NMA-LD
Treatment-emergent SAEs	Safety Analysis Set
Post treatment-emergent SAEs	Safety Analysis Set
Treatment-emergent SAEs related to LN-144	Safety Analysis Set

Deaths that occur after tumor harvest prior to receiving LN-144 infusion	TH set
Deaths that occur after LN-144 infusion	Safety Analysis Set

Note: AE = adverse event. TEAE = treatment-emergent adverse event. SAE = serious adverse event. TH = tumor harvested. NMA-LD = non-myeloablative lymphodepletion.

In addition to the summaries described above, a histogram plot of AE onset frequency over time will be provided with different colors for different toxicity grades. All occurrences will be counted if a patient experience the same AE, but multiple records are reported on the CRF due to toxicity grade increase. If multiple records are reported on the CRF due to toxicity grade decrease when the event is resolving, it will be counted once with the highest grade displayed on the histogram plot.

Subgroup analysis of TEAE will be performed on the following demographic and baseline disease characteristics for the Safety Analysis Set.

- Age category (< 65 years and ≥ 65 years)
- Gender (male, female)
- Geographic region (United States, Europe)
- ECOG performance status at baseline (0, ≥1)
- LDH value at baseline (≤ ULN, > ULN)
- Baseline target lesion SOD (<70 vs ≥70 mm)
- Contract Manufacturing Organization (WuXi, Lonza, and Moffitt).

Patient data listings for the corresponding AE and death summary will also be provided.

7.1.3 Other Planned AE Analyses

The following analyses may be performed for Safety Analysis Set patients unless otherwise specified.

The infused LN-144 dose relationship with clinical safety will be evaluated using tabulation of TEAE, and TE-SAE by infused LN-144 dose group (at or below vs above the median of the infused LN-144 dose).

7.2 Laboratory Evaluations

Local laboratories are used for all laboratory assessments in this study. All laboratory values will be converted to and reported in the SI units and classified as normal, low, or high according to the

reference ranges provided by local laboratories. All laboratory data will be listed with a variable indicating whether the event is treatment emergent. Descriptive statistics for laboratory parameters will be summarized for Safety Analysis Set.

7.2.1 Analysis Periods for Laboratory Abnormalities

Three analysis periods are defined below for the laboratory abnormality analysis. All laboratory data will be listed. The focus of the laboratory data summarization will be based on the treatment-emergent laboratory abnormalities.

The **NMA-LD Period** includes the laboratory results that are collected after the start of NMA-LD and before the start of LN-144 infusion.

The **treatment-emergent Period** includes the laboratory results that are collected from LN-144 infusion and through 30 days post LN-144 infusion.
The **post treatment-emergent Period** includes the laboratory results that are collected 30 days after LN-144 infusion through the end of assessment period or until the start of a new anti-cancer therapy, whichever occurs first.

7.2.2 Graded Laboratory Results

Applicable hematology and clinical chemistry laboratory data will be graded according to NCI-CTCAE, Version 4.03 severity grade. Grade 0 includes all non-missing values that do not meet criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels; analyses for each direction (i.e., increased, decreased) will be presented separately.

The baseline CTCAE severity grade, and the maximum grade during each analysis period will be summarized using number and percentage of patients in each category. Patients will be categorized according to the most severe abnormality grade.

Number and percentage of patients with Grade 3 or 4 laboratory toxicity will be summarized for baseline, and each post-baseline visit.

Shift tables will be presented by showing the change in CTCAE severity grade from baseline to each analysis period. For parameters for which a CTCAE severity scale does not exist, shift tables will be presented showing change in results from the baseline value (low, normal, and high) to post-baseline value (low, normal, and high) in each analysis period. Summary of laboratory abnormalities will also be provided for worsening ≥ 2 grades from baseline to each analysis period (ie. shift from baseline

Grade 0 to post-baseline Grade 2, 3 or 4, from baseline Grade 1 to post-baseline Grade 3 or 4, or from baseline Grade 2 to post-baseline Grade 4), as well as for worsening from baseline Grade 0-2 to post-baseline Grade 3-4 summary.

7.2.3 Numeric Laboratory Results

Summaries of numeric laboratory data will be based on observed data and will be reported using SI units. Baseline, measurements after baseline, and changes from baseline at each post-treatment visit will be summarized using descriptive statistics for each laboratory parameter. The by visit plot for mean ± standard error of the mean will be provided for parameters of hemoglobin, neutrophils, leukocyte, platelets, and lymphocytes for baseline and each post-baseline visit.

7.3 Vital Signs

Descriptive statistics for vital signs parameters (i.e., body weight, heart rate, respirations, blood pressure, and temperature) and changes from baseline will be presented by visit for the Safety Analysis Set.

8 OTHER PLANNED ANALYSES

8.1 Impact of COVID-19 Pandemic

The protocol deviations and missing data related to COVID-19 will be identified and documented. Additionally, the following analyses will be performed to assess the impact of COVID-19 pandemic (FDA guidance on Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, June 2020):

- Listing of patients with at least one missing radiological response assessment including COVID-19 related missingness
- Number and percentage of patients with missing radiological response assessment due to any reasons including COVID-19, and the impact on response and DOR. The following are considered as missing pattern scenarios that may have had an impact on an individual's response or DOR:
    - For non-responders, if a missed visit occurs next to single PR visit (eg, by-visit overall response as PR-Missed) or if there are 2 or more consecutive missed visits (eg, SD-Missed-Missed), missed visit(s) may have impact on response

  - For responders, if a missed visit occurs at last visit (eg, PR-PR-PR-Missed) or the missed visit is followed by PD (eg, PR-PR-Missed-Missed-PD), then missed visit(s) may have impact on DOR
  - Other missing pattern is considered not having impact response or DOR
- Number and percentage of patients with radiological response assessment performed at outside facility due to COVID-19
- Number and percentage of patients who discontinued response assessment or discontinued study due to COVID-19

All patients in Cohorts 2 and 4 were enrolled and received LN-144 infusion on or before January 15, 2020 and the last date for TEAE reporting was 14 February 2020; these dates are considered to be before the pandemic onset or during the initial phase of the pandemic. Therefore, the patient enrollment, study population characteristics, study treatment, and TEAE assessments and results are considered to not be substantially impacted by the COVID-19 pandemic.

8.2 Hospital Resource Utilization

A summary of hospital resource utilization will be provided for Cohort 4 FAS (as hospitalization CRF was only added in Cohort 4 database) to summarize all inpatient stays before the earliest date of initial PD, new anti-cancer therapy, and data cutoff date. The summary will include number of total hospitalization days and index hospitalization days. Index hospitalization is defined as the hospitalization stay involving study regimen administration starting from admission until discharge. Hospitalization days and number of patients will also be summarized by unit and by reason.

9 DEFINITONS AND DATA HANDLING CONVENTIONS

9.1 Definitions and Computations

The study day is the day relative to the LN-144 infusion. It will be calculated from the date of LN-144 infusion and derived as: assessment date - LN-144 infusion date. Study Day 0 is defined as the day of LN-144 infusion.

For tumor assessments per RECIST v1.1, baseline value will be based on imaging data from the scheduled baseline visit (Day -21 to Day -10).

Patients with baseline liver and/or brain lesion, referred to as presence of liver and/or brain metastasis, are defined if patients have liver and/or brain lesions identified based on imaging data from the screening visit or baseline visit.

For all other assessments, baseline value will be defined as the last non-missing value on or before the first dose of NMA-LD. For patients who had tumor resected but did not receive NMA-LD, baseline value will be defined as the assessment from the scheduled baseline visit. If baseline visit is not performed, screening assessment will be used unless screening value is summarized separately.

For time-to-event efficacy endpoint, the interval is calculated as:

- Time to event (in days) = event date/censoring date - start date + 1, or
- Time to event (in months) = (event date/censoring date - start date + 1)/30.4375, or
- Time to event (in years) = (event date/censoring date - start date + 1)/365.25

Calculation of follow-up time for time-to-event endpoints (e.g, OS, DOR) will be performed using the reverse KM method.

9.2 Missing Data Handling

General handling rule for missing response assessment data

For the derivation of BOR, patients without any baseline or any post-baseline measurements are considered not evaluable (NE). For the BOR to be categorized as CR or PR, a confirmatory evaluation is required 4 weeks or more apart after the first CR or PR.

The censoring rules and the definition of progression date for PFS and DOR follow FDA's guidance documents, ie, Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018). For patients with PD or death after single missing tumor assessment visit, the PFS or DOR are considered as having an event at date of progression assessment or death. For patients with PD or death after two or more consecutive missing tumor assessment visits, the PFS or DOR are censored at the last adequate tumor assessment prior to the missing tumor assessments. The missing response assessments will be ignored if the subsequent assessment shows no progression.

General imputation rules for missing or partial dates

For missing or partial start and end dates for AEs, a conservative approach shall be taken for performing the relevant analyses. If the available information of a date is not enough to judge whether an event occurred on or after initiation of the study treatment, it will be taken as a treatment-

emergent event. In case of completely missing, AE start date will not be imputed, and the AE will be treated as treatment emergent. If partial AE start date is in the same year or same year and month as LN-144 infusion date, then AE start date will be imputed as LN-144 infusion date.

Otherwise, the following general imputation rule is applied for partial start and end dates of AEs. The general rule below may also be applied for partial dates of prior/concomitant medications, or subsequent anti-cancer therapy for analysis purpose.

- If only day is missing, then the 15th of that month will be used.
- If only year is present, then June 30th will be used.

If an imputed start date is after the end date, the end date will be used. If an imputed end date is before the start date, the start date will be used. If an imputed end date is after the death date, the death date will be used.

Other missing data handling

Missing height will be imputed using average heights among patients of the same sex in TH set.

9.3 Derivation of Best Overall Response per irRECIST

Table 3 - General Rule to Derive BOR as Assessed by Investigator per irRECIST

Overall Response first timepoint	Overall response subsequent timepoint	BOR per irRECIST
CR	CR	CR
CR	PR	SD, PD or PR [a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR [b]	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD

PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
SD	CR [b]	SD
SD	PR [b]	SD
SD	SD	SD
SD	PD	SD provided minimum criteria for SD duration met, otherwise PD
SD	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE
PD		PD [c]
PD	irCR [b]	SD provided minimum criteria for SD duration met, otherwise PD
PD	irPR [b]	SD provided minimum criteria for SD duration met, otherwise PD
PD	irSD	SD provided minimum criteria for SD duration met, otherwise PD
PD	irPD	PD
PD	NE	PD

Note: BOR = best overall response. CR = complete response. PR = partial response. SD = stable disease. PD = progressive disease. NE = not evaluable. The minimum criteria for SD duration is defined as 4 weeks from LN-144 infusion for cohort 4.

[a] If a CR is met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[b] Subsequent assessments should be conducted to confirm the CR/PR of that specific time point.

[c] PD by RECIST v1.1 will become PD by irRECIST in the absence of a confirmation assessment.

9.4 Imputation Rules for Laboratory Values Reported with Symbols

Laboratory values that are reported with "<" or "≤" in the database will be imputed by the numeric values x 0.99, and laboratory values that are reported with ">" or "≥" in the database will be imputed by the numeric values x 1.01 for reporting purposes. The original laboratory value will be listed.

9.5 Visit Window

For summarizing data by visit, all scheduled and unscheduled assessments will be assigned to analysis visits according to a visit window schema. Visit windows for laboratory, vital signs and other assessments are defined as shown in Table 4 unless noted otherwise. If more than 1 assessment is within a given visit window, the assessment closest to the target date will be used. If 2 assessments

are equally close to the target day, the earlier assessment will be used. By visit analysis will not be conducted after Month 24 due to expected small sample size.

Table 4 - Visit Windows for laboratory and vital sign Assessments

Nominal Visit	Target Study Day	Start (Study Day)	End (Study Day)
Day -7	-7	-7	-7
Day -6	-6	-6	-6
Day -5	-5	-5	-5
Day -4	-4	-4	-4
Day -3	-3	-3	-3
Day -2	-2	-2	-2
Day -1	-1	-1	-1
Day 0	0	0	0
Day 1	1	1	1
Day 2	2	2	2
Day 3	3	3	3
Day 4	4	4	5
Day 14	14	6	20
Day 28	28	21	34
Week 6	42	35	63
Week 12	84	64	105
Week 18	126	106	155
Month 6	183	156	229
Month 9	274	230	320
Month 12	365	321	410
Month 15	456	411	502
Month 18	548	503	594
Month 21	639	595	685
Month 24	730	686	775

10 CHANGES TO THE STATISTICAL ANALYSES SPECIFIED IN THE PROTOCOL

- FAS definition is further clarified as "patients who have received LN-144 that meets the final manufacturing product specifications"

  Justification: to ensure that efficacy analyses will be performed on patients who received LN-144 that meets product specifications to align with FDA's Response to Sponsor's Question 4 in the memorandum dated June 24, 2019 [CRMTS #11766].
- Safety Analysis Set is added for safety analyses, defined as "patients who have received any LN-144 infusion".

  Justification: to ensure that safety analyses will be performed on all patients who received any LN-144 infusion irrespective of meeting final product specifications.
- An additional hypothesis testing will be performed on combined Cohorts 2 and 4 data after the null hypothesis of primary endpoint based on Cohort 4 is rejected

  Justification: Given the same enrollment criteria, the same cryopreserved TIL manufacturing process, and the same treatment regimen between Cohort 2 and Cohort 4, data from combined two cohorts with larger sample size provide additional evidence to evaluate the primary efficacy endpoint in unresectable or metastatic melanoma patient population in addition to data from Cohort 4. The family-wise error rate at a two-sided significance level of 5% is controlled since null hypothesis for combined Cohorts 2 and 4 will only be tested after null hypothesis for Cohort 4 is rejected.

11 REFERENCE

- Bohnsack O, Ludajic K, Hoos A. Adaptation of the Immune-related Response Criteria: irRECIST. ESMO; 2014.
- EMA Guideline on the evaluation of anticancer medicinal products in man, September 2017. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf
- FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, December 2018. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf
- FDA guidance on Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, June 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statistical-considerations-clinical-trials-during-covid-19-public-health-emergency-guidance-industry
- Goldinger SM, Lo S, Hassel JC, et al. The utility of chemotherapy after immunotherapy failure in metastatic melanoma: A multicenter case series. Journal of Clinical Oncology. 2018;36(15_suppl):e21588-e21588.

- Hamid O, Puzanov I, Dummer R, Schachter J, Daud A, Schadendorf D, et al. Final Analysis of a Randomised Trial Comparing Pembrolizumab Versus Investigator-Choice Chemotherapy for Ipilimumab-Refractory Advanced Melanoma. Eur J Cancer. 2017 Nov; 86:37-45.2017
- Kang SP, Gergich K, Lubiniecki GM, et al. Pembrolizumab KEYNOTE-001: an adaptive study leading to accelerated approval for two indications and a companion diagnostic. Ann Oncol. 2017;28(6):1388-1398.
- KEYTRUDA® (pembrolizumab), United States Prescribing Information, Merck Sharpe & Dohme Corp., 2020
- OPDIVO (nivolumab), United States Prescribing Information, Bristol-Myers Squibb Company, 2020.
- QOL Unit, EORTC Data Center. EORTC QLQ-C30 Scoring Manual. EORTC 2001 3rd edition
- Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab Versus Chemotherapy in Patients With Advanced Melanoma Who Progressed After anti-CTLA-4 Treatment (CheckMate 037): A Randomised, Controlled, Open-Label, Phase 3 Trial. Lancet Oncol. 2015 Apr;16(4):375-84.

12 APPENDIX

Table 5 - Summary of changes from SAP v2.0 to SAP v3.0

Change	Rationale
Section 4.1 Analysis Set Section 5 Patient Characteristics and Treatment Exposure Section 7 Safety Analysis	Safety Analysis Set is added to ensure that safety analyses will be performed on all patients who received any LN-144 infusion irrespective of meeting final product specifications.

Signature Manifest

Document Number: SAP-0001 **Revision:** 03

Title: A Phase 2, Multicenter Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN 144) for Treatment of Patients with Metastatic Melanoma

Effective Date: 13 Sep 2021

All dates and times are in Pacific.

SAP-0001 C-144-01 Statistical Analysis Plan v3.0

Originator Approval

Name/Signature	Title	Date	Meaning/Reason
PPD	PPD	13 Sep 2021, 10:56:07 AM	Approved

Functional Approval

Name/Signature	Title	Date	Meaning/Reason
PPD	PPD	13 Sep 2021, 11:10:49 AM	Approved
PPD	PPD	13 Sep 2021, 01:58:15 PM	Approved

Quality Approval

Name/Signature	Title	Date	Meaning/Reason
PPD	PPD	13 Sep 2021, 01:59:19 PM	Approved

Quick Approval

Approve Now

Name/Signature	Title	Date	Meaning/Reason
PPD	PPD	13 Sep 2021, 02:07:39 PM	Approved