16.1.9. Documentation of Statistical Methods

Statistical Analysis Plan

A Phase 2 Study of Intratumoral Injection of LTX-315 in Combination with Pembrolizumab in Patients with Percutaneously Accessible Lesions with Advanced Melanoma Refractory to PD-1/PD-L1 Inhibitor Therapy

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Information described herein is confidential and may be disclosed only with the express written permission of the sponsor.

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Reviewers

The following reviews of the Statistical Analysis Plan (SAP) were conducted:

Name and Title	Role	Version Last Reviewed	Company / Organization
[redacted]			

Glossary of Abbreviations

Abbreviation	Term
ADA	Antidrug antibody assessments
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity
CBR	Clinical benefit rate
CI	Confidence Interval
C_{max}	Maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for AEs
DBP	Diastolic blood pressure
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FDA	Food and Drug Administration
GGT	Gamma-Glutamyl Transferase
iBOR	Immune best overall response
ICI	Immune checkpoint inhibitor
iCPD	Immune confirmed progressive disease
iCR	Immune complete response
iORR	Immune objective response rate
iPD	Immune progressive disease
iPR	Immune partial response
iRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
iTPD	Immune therapy progressive disease
ITT	Intention-to-treat
iUPD	Immune unconfirmed progressive disease
LKAD	Last known alive date
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for AEs
NE	Not evaluable
ORR	Objective response rate
PCI	Potentially Clinically Important
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred Term

Abbreviation	Term
QTcF	Fridericia corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious AE
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SD	Stable disease
SI	International System of Units
SOC	System Organ Class
$t_{1/2}$	Apparent plasma terminal elimination half-life
TEAE	Treatment Emergent AEs
TFLs	Tables, Figures and Listings
TTR	Time to response
WHO DD	World Health Organization Drug Dictionary

Statistical Analysis Plan Amendment

This is the amendment to the final v1.0 SAP issued on 21FEB2023. Typographical changes have been revised. Major changes to the planned analyses are discussed in Section 7. This amendment was finalized prior to database hard-lock.

1. Source Documents

The SAP was written based on the following documentation:

Document	Date	Version
Protocol	4th December 2023	6.0
Electronic case report form (eCRF)	30th August 2024	7.0

2. Protocol Details

2.1. Overall Study Design

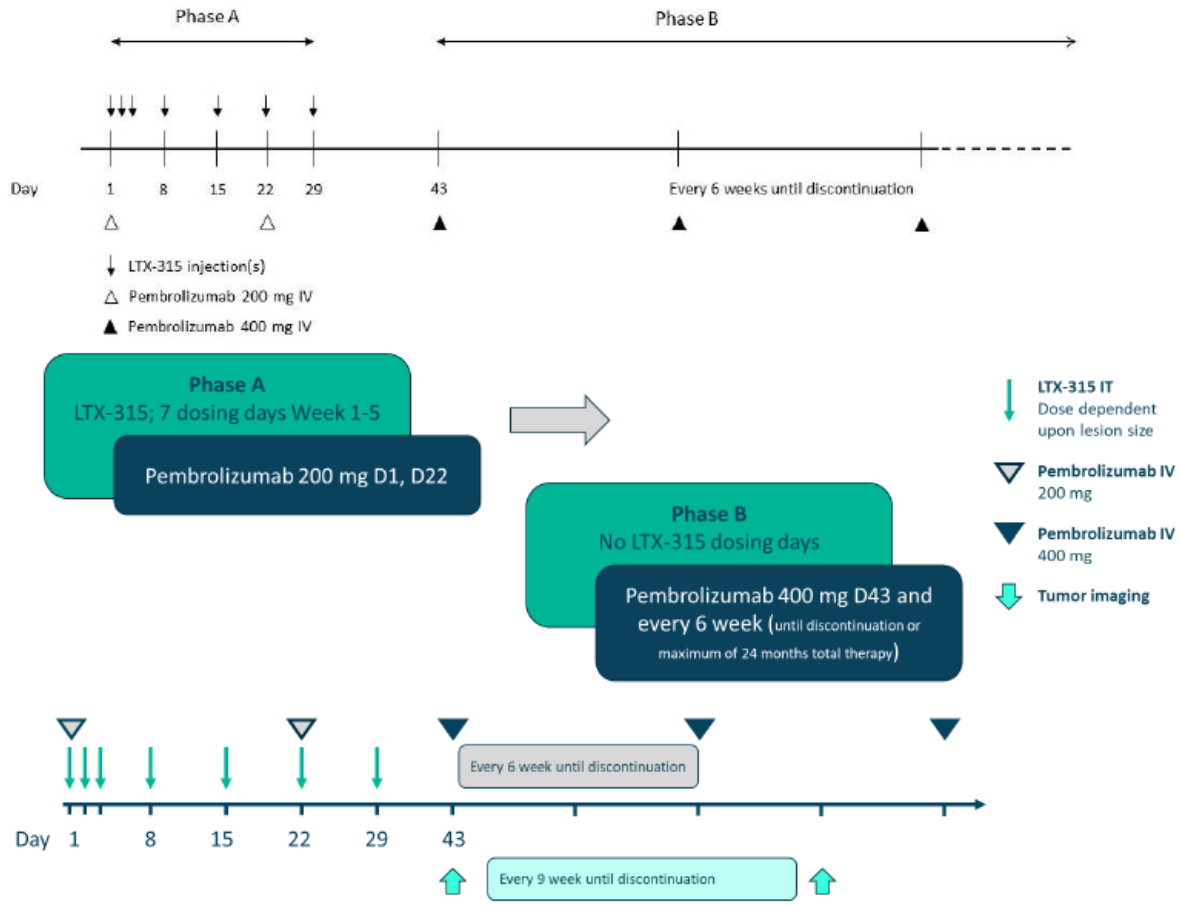
This study is a Phase 2, open-label, single-arm study in patients with advanced metastatic melanoma accessible for injection (cutaneous, subcutaneous, lymph node, or intramuscular tumors) and who have either exhausted treatment options or are not eligible for, suitable for, or willing to undergo such treatments. Patients will be recruited, as follows:

- Patients with unresectable Stage III B, C, D and Stage IVm1a, m1b metastatic melanoma, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, who have received an approved anti-programmed death-protein (PD-1)/anti-programmed death-ligand 1 (PD-L1) therapy and who have progressed on or after prior anti-PD-1 or anti-PD-L1 therapy, alone or in combination with systemic therapy.

Patients must have a minimum of 2 tumors. All patients will have at least 1 lesion with a mean longest perpendicular diameter ≤ 3 cm available for injection with LTX-315, and at least 1 additional measurable per Response Evaluation Criteria in Solid Tumors (RECIST) (non-injected) lesion; the additional lesion may be located in any place and must be a measurable target lesion with a longest diameter ≥ 1.0 cm (or ≥ 1.5cm short diameter if target lesion is a lymph node) according to RECIST version 1.1. Any lesion classed as target for RECIST should not be biopsied and should not be injected with LTX-315.

Treatment will be administered in 2 phases, as depicted in Figure 1.

Figure 1 Study Schematic



Abbreviations: D = day; IT=intra tumoral; IV = intravenous.

Patients will be discontinued from the study when they experience disease progression, unacceptable toxicity, or withdraw for another reason such as investigator's decision or withdrawal of consent, whichever comes first. In the case of disease progression, patients should remain on treatment until a confirmatory scan has been performed (4-6 weeks after initial disease progression scan), unless continued treatment is not considered acceptable by the Investigator. After a screening period of up to 28 days, eligible patients will arrive at the clinical site on the first day of dosing to confirm eligibility, complete pre-dose baseline assessments, and receive the first dose of study treatment and premedication.

Phase A

On Day 1, following administration of premedication, LTX-315 will be injected into the lesion(s) and patients will receive an IV infusion of 200 mg pembrolizumab. The tumor(s) for injection will be selected based on the investigator's clinical judgment; tumors located close to airways will not be selected. Additional LTX-315 intratumoral injections will be given on

Days 2, 3, 8, 15, 22, and 29, with a second dose of 200 mg pembrolizumab being given on Day 22. Multiple injections of LTX-315 may be needed per day; the number of injections per lesion per dosing day depends on lesion size.

Phase B
In Phase B, pembrolizumab will be administered as 400 mg IV infusion, with the first 400 mg dose given on Day 43 and further doses given every 6 weeks until discontinuation from the study or for a maximum of 24 months' total therapy, whichever comes first.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of this study is:

- To evaluate preliminary antitumor activity of LTX-315 in combination with pembrolizumab in the treatment of advanced melanoma in patients who have failed or are refractory to anti-PD-1/anti- PD-L1 therapy.

2.2.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of LTX-315 in combination with pembrolizumab in patients with advanced melanoma who have failed or are refractory to anti-PD-1/PD-L1 therapy.
- To explore pharmacokinetics (PK) of LTX-315 in plasma following intratumoral injection in 20 patients with advanced melanoma who have failed or are refractory to anti-PD-1/PD-L1 therapy.

2.2.3. Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate preliminary anti-tumor activity of LTX-315 in combination with pembrolizumab in the treatment of advanced melanoma in patients who have failed or are refractory to anti-PD-1/PD-L1 therapy.
- To evaluate the immune response in injected and non-injected lesions.
- To perform biomarker analyses in all patients.

2.3. Sample Size and Power

A sample size of 20 patients provides approximately 84% power to detect a response rate of 20% for the combination treatment (LTX-315 plus pembrolizumab) assuming

pembrolizumab alone would deliver a response rate of 5% or less in this population utilizing a 1-sided test with an alpha spend of 0.1. No estimation for dropouts was included due to this being a study in an advanced cancer population where patients are expected to continue on therapy until progression.

2.4. Primary Efficacy Endpoints

The primary efficacy endpoints are:

- Objective response rate (ORR), defined as the proportion of patients who achieved partial response (PR) and/or complete response (CR) per local investigator assessment using RECIST version 1.1.
- Clinical benefit rate (CBR), defined as the proportion of patients who respond to treatment, estimated as the proportion of patients who achieve stable disease (SD), PR, or CR per local investigator assessment using RECIST version 1.1.
- Overall survival (OS), evaluated as time from baseline until death.

2.5. Secondary Endpoints

The secondary safety and tolerability endpoints are:

- Incidence and severity of adverse events (AEs) (including physical examination findings) related to LTX-315 or to the combination of LTX-315 and pembrolizumab from baseline to end of treatment.
- Incidence of clinical laboratory abnormalities based on clinical chemistry, hematology, urinalysis, and coagulation test results.
- Change from baseline in vital signs measurements (pulse rate, body temperature, respiration rate).
- Change from baseline in blood pressure measurements.
- Change from baseline in 12-lead electrocardiogram (ECG) parameters, including Fridericia's corrected QT interval (QTcF).
- Incidence of LTX-315 injection site assessment findings (injection site pain, swelling, and redness).

The secondary PK endpoints of LTX-315 in plasma are:

- Area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$).
- Maximum observed plasma concentration (C_{max}).
- Apparent plasma terminal elimination half-life ($t_{1/2}$).

Plasma PK parameters of LTX-315 will be calculated using standard non-compartmental methods for 20 patients enrolled. PK analyses will not be performed in patients enrolled into the Expansion cohort.

Renal function will be documented at baseline and at subsequent timepoints for each patient enrolled in the study. The effect of renal impairment on the PK of LTX-315 may be evaluated via population PK modeling and will be reported separately.

2.6. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- ORR, defined as the proportion of patients who achieved PR and/or CR per local investigator assessment using immune-related Response Evaluation Criteria in Solid Tumors (iRECIST).
- CBR, defined as the proportion of patients who respond to treatment, estimated as the proportion of patients who achieve SD, PR, or CR per local investigator assessment using iRECIST.
- Regression of injected tumor lesion as assessed by caliper measurement or ultrasound.
- Progression free survival (PFS), evaluated as time from baseline until objective tumor progression or death, whichever comes first, up to 90 days after end of treatment per local investigator assessment using RECIST v1.1 and iRECIST.
- Duration of response (DoR), defined as the interval between the date of the first observation of tumor response (CR or PR) and the first date that progressive disease (PD) is objectively documented per local investigator assessment using RECIST v1.1 and iRECIST.
- Time to response (TTR), defined as the time between the first intratumoral injection and the first observation of tumor response (CR or PR) per local investigator assessment using RECIST v1.1 and iRECIST.
- To evaluate biomarkers of immune response in injected and non-injected lesions at cellular and molecular levels
- To evaluate efficacy based on specific biomarkers (such as PD-1/PD-L1 with different immunohistochemistry cut-off values) in tumor tissue, and/or additional biomarkers to be defined in the future.

3. Estimand(s)

Not required for this study.

4. Analysis Populations

In accordance with ICH E3 and E9[1], the following analysis sets will be used for the analyses. If populations are identical, analyses will not be duplicated.

4.1. Safety (Intention-to-treat [ITT]) Population

All patients who receive at least 1 injection of LTX-315 and/or 1 infusion of pembrolizumab and have at least 1 post-dosing safety evaluation. Post-dosing safety evaluation is defined as an on-treatment safety assessment consisting of laboratory tests, vital signs, ECGs, Physical examinations, blood pressure monitoring, body weight, and injection site assessments.

For analysis purposes, the ITT Population is defined equivalent to the Safety Population and will be referred to as Safety Population. The Safety Population will be used for summaries and analysis of demographics, disposition, baseline characteristics, study drug exposure and the secondary safety and tolerability endpoints.

4.2. Efficacy Population

The efficacy population will consist of all patients who received at least 5 out of the 7 injection days of LTX-315 (or fewer, if injections were stopped early due to complete necrosis of the injected lesion), at least 1 infusion of pembrolizumab, and have at least 1 post-dosing efficacy evaluation. Post-dosing efficacy evaluation is defined as an on-treatment tumor assessment, scheduled 43 days' post first dose of LTX-315.

The efficacy population will be used for summaries and analysis of the primary and exploratory efficacy endpoints.

4.3. Pharmacokinetics Population

The PK population will include all patients who received at least 1 injection of LTX-315 and have evaluable PK data.

5. Data Handling

5.1. Time Points and Visit Windows

5.1.1. General Definitions

All assessment days will be related to the first day of first dose of study drug

Day 1 is defined as first dose of treatment (either LTX-315 or pembrolizumab). Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1. Day 0 is not defined.

The date of the first dose of treatment for each patient will be taken from the LTX-315 administration eCRF page for LTX-315 and pembrolizumab administration page for pembrolizumab. If the dates in both of these eCRF pages are missing, alternatively the Day 1 date in date of visit eCRF page will be used.

The date of the last dose of treatment for each patient will be taken from the same eCRF pages as first dose of treatment.

5.1.2. Screening Period

For all patients, the screening period (up to 28 days) is defined as the period from informed consent to the first dose of treatment. For some variables, data from more than one assessment within the screening period can be collected prior to the first dose of treatment.

In general, the latest screening data will be considered for patients that are rescreened.

In general, the baseline value for a variable is therefore defined as the last non-missing value collected before the first dose of treatment.

Screening procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing the informed consent form may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the scheduled of assessments in the study protocol.

Assessments carried out on day of first dose of treatment are considered to have taken place before the first dose of treatment, if the corresponding times or timepoints have not been recorded.

5.1.3. Treatment Period

Data collected at Day 1 will be assigned to the treatment period unless the time (HH:MM) of data collection and time (HH:MM) of first dose of treatment are both recorded and the data collection time is before the time of first dose of treatment. In this case, the assessment will be assigned to the screening period. If the time (HH:MM) of data collection is not recorded but the protocol and / or eCRF includes an instruction to the effect that all Day 1 assessments

are to be performed prior to the first dose of treatment, the data collected at Day 1 will be assigned to the screening period. However, adverse events and medications starting on Day 1, will be assigned to the treatment period.

The treatment period is defined as the period from the date / time of the first dose of treatment up to and including the date / time of the last dose of treatment.

The treatment period will also be split into Phase A and Phase B. Phase A portion of the treatment period is defined as the period from the date / time of the first dose of treatment up to date / time of third dose of pembrolizumab administration (scheduled on Day 43). Phase B portion of the treatment period is defined as the period from the third dose of pembrolizumab until end of treatment visit.

5.1.4. Visit Windows

All data will be analyzed using nominal study visit as defined in the Study Schedule and eCRF. No visit windows will be applied for summary and analysis.

5.2. Handling of Dropouts, Missing Data, and Outliers

5.2.1. Handling of Missing Efficacy Data

Patients with missing data for time-to-event analysis will be censored as per description in Section 6.6.

Death date for time-to-event analysis will be imputed according to the following rules:

- If partial date has day and month missing, then the date will not be imputed.
- If partial date has missing day only, then the first day of the month will be assigned to the missing day.
- If the imputed first day of the month is before the treatment start date, then the date will be imputed as the treatment start date.

For tumor sizes that are too small to measure and placed in the form of "< xxx" the value "xxx" will be instead used in analysis.

5.2.2. Handling of Missing Safety Data

Missing mean ECG values are collected as -99 and will be reported as missing for analysis.

AE imputations for missing severity or relationship are given in Section 6.7.2. Unknown or partial medication and AE date imputations are given below and to be used only for the assessment of prior / concomitant status for medications and treatment-emergent status for AEs.

5.2.3. Handling of Partial and Missing Dates for Adverse Events, Prior / Concomitant Medications

Missing or Partial AE and Prior / Concomitant Medication Start Dates

Missing and / or incomplete dates for medications and AEs are imputed in a manner resulting in the earliest onset or the longest duration during the Treatment Period, whilst ensuring that the start date does not occur after the stop date. The stop date will not be imputed if the medication or AE is "Ongoing". Technically, this will be done as follows:

For a missing / incomplete start date the earliest date of the following will be imputed:

- The later date of: the earliest possible start date, and the date of first dose of treatment.
- The latest possible start date.
- The latest possible stop date.

For a missing / incomplete stop date the later date of the following will be imputed:

- The earlier date of the latest possible stop date and the date of last dose of treatment.
- The earliest possible stop date.
- The earliest possible start date.

Here, the earliest possible date is defined as:

- The date itself, if available.
- The date of the first day of the month, if month and year are available but the day is missing.
- The date of the first day of the year, if year is available but day and month are missing.
- The date of informed consent, if the date is completely missing.

The latest possible date is defined as:

- The date itself if available.
- The date of the last day of the month, if month and year are available but the day is missing.
- The date of the last day of the year, if year is available but day and month are missing.
- The last known date on the study for the patient plus one year, if the date is completely missing.

6. Statistical Methods

6.1. General Principles

All data processing, summarization and analyses will be performed using Fortrea's Statistical Analysis System (SAS) Environment / Version 9.4 (or later) of the SAS® statistical software package.

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation, median, minimum (min), maximum (max), for those patients with data.

All summary statistics will be rounded (using the SAS® function ROUND) and presented to the decimal place accuracy described in the mock shells.

For qualitative variables, the number (n) and percentage (%) of patients with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Number of patients in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in TFLs mock shell(s).

Laboratory test results will be received from the central and local laboratories, and the results will be provided in standard internal units. For the TFLs, the results will be summarized or presented in International System of Units (SI) units. Refer to Appendix of the TLFs mock shells for the SI unit corresponding to each laboratory test.

Refer to Appendix of the TLF shells for the precision level in which each laboratory test is reported by the central laboratories.

Specifications for table, figures and data listing formats can be found in the TFL shells specifications for this study. Please refer to "2. General Format Guidelines" section within TFL shells for more details on presentation of results.

6.2. Patient Disposition and Data Sets Analyzed

Patient disposition will be summarized, where appropriate, for all patients screened. The following information will be reported:

- Number of patients for the following categories:
  - Screened,
    - Discontinued during screening period,
    - Completed screening but not treated.
- Number and percentage of patients (based on the number of patients treated) for the following categories:
  - Treated,
    - Ongoing in treatment period,

        - Discontinued treatment period,
        - Completed treatment period
    - Entered into follow-up period,
        - Discontinued during follow-up period,
        - Completed follow-up period.
    - Completed the study,
    - Ongoing in the study,
    - Discontinued the study,
        - Reasons for study discontinuation.
    - Study duration (3 months, 6 months etc.)
- Number and percentage of patients (based on the Safety Population) included in, and excluded from, each study population together with the reasons for exclusion from the analysis population;
- Number and percentage of patients (based on the Safety Population) who met / did not meet all eligibility criteria, together with the criteria not met;
- Number and percentage of patients (based on the Safety Population) who failed screening prior to treatment (Note: This includes rescreened patients who were treated, and patients treated by mistake) including the primary reason for screen failure;

Study duration will be calculated as follows,

$$\frac{\text{Date of last visit} - \text{start date of treatment} + 1}{30.4375}$$

A patient will be regarded as having completed the study if the status recorded on the End of Study eCRF form is answered as 'Yes'. A patient will be considered as having discontinued the study if the status is answered as 'No'. Otherwise, the patient will be considered as ongoing study.

A listing of all patients with their study completion status, including the respective reasons for study discontinuation will be presented for all patients screened.

A listing of all screen failed patients with their reasons for screen failure will be presented for all patients screened. A separate listing of patients who failed at least one inclusion / exclusion criteria including a text description of the criterion failed will be presented for all patients screened.

A listing of all patients excluded from at least one analysis population will be presented for the Safety Population.

6.3. Protocol Deviations

A listing of all patients with one or more important protocol deviations will be presented for the Safety Population. In addition, a listing of the patients with a Coronavirus Disease of 2019 (COVID-19) important protocol deviation will be provided for the Safety Population.

6.4. Demographic and Other Baseline Characteristics

6.4.1. Demographic Characteristics

Demographic characteristics will be summarized for the Safety Population as described below. All missing data will be presented as part of a missing category, if appropriate. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)
- Height (cm) at baseline
- Weight (kg) at baseline
- Body mass index (kg/m^2) at baseline
- Body Temperature (Degrees Celsius) at baseline
- Respiration Rate (breaths per minute) at baseline
- Systolic Blood Pressure (SBP [mmHg]) at baseline
- Diastolic Blood Pressure (DBP [mmHg]) at baseline
- Pulse Rate (beats per minute [bpm]) at baseline

Total counts and percentages of patients will be presented for the categorical variables of:

- Age group (years):
  - ≤ 65
  - > 65
- Sex
- Race
- Ethnicity

Demographic characteristics will be listed for the Safety Population.

6.4.2. Baseline Characteristics

Baseline characteristics will be summarized for the Safety Population as described below. All missing data will be presented as part of a missing category, if appropriate.

Standard descriptive statistics will be presented for the continuous variables of:

- Time from initial diagnosis to first study treatment (months)

Total counts and percentages of patients will be presented for the categorical variables of:

- Prior Lines of Therapy
- Melanoma Histological Sub-Types
- Histological Diagnosis
- Stage at Initial Diagnosis
- Stage at Screening Visit
- Metastatic Disease Sites (Abdominal, Bone, CNS/Brain, Liver, Lung, Lymph Nodes, Other)
- BRAF Mutation Present
- Eastern Cooperative Oncology Group (ECOG) Performance Status at baseline

Prior lines of therapy include the following: Chemotherapy, Concurrent Radiotherapy, Hormonal Therapy, Immunotherapy, Monoclonal Therapy and Other.

No formal tests of statistical significance will be performed on the demographic and baseline characteristics data.

Baseline characteristics will be listed for the Safety Population.

6.4.3. Medical and Surgical History

Medical and surgical history is defined as any condition, with the exception of the study indication, that the patient may have had prior to enrollment in the study, including any chronic conditions diagnosed prior to entry in the study.

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [version 25.1 or a later version if updated during the study] and will be presented by System Organ Class (SOC) and Preferred Term (PT) and total. The SOCs and PTs are to be sorted by descending order of SOCs and PTs in the total column.

Medical history and surgical records will be summarized for the Safety Population as follows:

- The number and percentage of patients with at least one medical and surgical history record will be presented.
- The number and percentage of patients with at least one medical and surgical history record within each primary SOC and PT will be presented. The summary will be sorted using descending order of overall numerical counts for SOC and PT. Where terms tie, these will be sorted alphabetically.

Medical and surgical history records will be listed by site and patient and within-patient by medical and surgical history start date for the Safety Population.

6.4.4. Prior and Concomitant Medications

All medications will be coded using the WHO Drug Global Dictionary, Format B3 [Version SEP2022 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken within 28 days prior to screening with a stop date prior to the start of the Treatment Period.
- Concomitant medications are those with a start date on or after the start of the Treatment Period, or those with a start date before the start of the Treatment Period and either a stop date on or the start of the Treatment Period, or are ongoing at the end of the study.

See Section 5.2.3 for imputation of missing or partial dates for medication.

Prior and concomitant medications will be summarized separately for the Safety Population as follows:

- The number and percentage of patients with at least one prior / concomitant medication will be presented.
- The number and percentage of patients with at least one prior / concomitant medication within each Anatomical Group (ATC Level 1), Therapeutic Subgroup (ATC Level 2), and preferred term will be presented. The summary will be sorted using numerical counts by descending order of Anatomical Group, then descending order of Therapeutic Subgroup, then descending order of preferred term in the total column. Where groups or terms tie these will be sorted alphabetically.

Prior medications and concomitant medications will be listed separately for the Safety Population. In the listings the relative start and stop day of prior / concomitant medication use will be calculated relative to the first dose date of any study treatment and will be presented for those patients who received at least one dose of treatment. If the concomitant medication is “Ongoing” it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

6.4.5. Prior Anticancer Therapy

Prior anticancer therapy will be summarized separately for the Safety Population. Total counts and percentages of patients will be presented for the following categories:

- Agent type by regimen
- Regimen by reason for discontinuation

6.5. Measurements of Treatment Compliance

Compliance not applicable. Treatment exposure given in Section 6.7.1.

6.6. Efficacy

Ultrasound data collected for endpoints using RECIST v1.1 or iRECIST will be deemed as not evaluable for analysis. Therefore, if an endpoint uses continuous data from RECIST endpoints, the data will be missing; and the data will be considered not evaluable (NE) and re-derived for endpoints using objective response. If an assessment considers the change from baseline, and the baseline is collected via ultrasound, then all visits post-baseline are considered not evaluable.

A visit is considered ultrasound-affected if any non-injected lesion is assessed using ultrasound at that visit. Injected lesions are defined as those with documented exposure to LTX-315 on the LTX-315 Administration Details CRF page. For an ultrasound-affected visit the overall visit response is re-derived by:

1. Setting the affected lesion type (Target Lesion, Non-Target Lesion, or New Lesion) to NE or No as appropriate.
2. Apply the timepoint response criteria as per RECIST v1.1 (Table 1)[2] or iRECIST (Table 2)[3]
3. Ensure previous PD or iCPD response are considered when assigning the re-derived overall response.

6.6.1. Primary Efficacy Analysis

6.6.1.1. Objective Response Rate per RECIST v1.1

Objective response rate (ORR), as determined by RECIST v1.1[2], assessed by local investigator, is defined as the proportion of patients in the efficacy population who have best overall tumor response of CR or PR during the course of the study. Patients whose best overall tumor response is CR or PR will be considered as responders while other patients will be considered as non-responders.

Best overall tumor response is defined as the best visit response per RECIST v1.1 (ordered CR, PR, SD, PD, NE) over all post-treatment assessments on or prior to first progression or any new systemic anticancer therapy, subject to the following additional rules:

- Time point responses of CR require confirmation by a consecutive CR at least 4 weeks later, with no intervening assessment of PR, SD or PD.
- Time point responses of PR require confirmation by a subsequent PR or CR at least 4 weeks later with no intervening SD or PD.
- Time point assessments of SD must occur at least 5 weeks following first treatment. A time point assessment of SD occurring prior to 5 weeks will be classified as NE for purposes of calculating BOR.
- Unconfirmed assessments of CR or PR, if meeting the timing requirements for SD, will be classified as SD.
- If the requirements of CR, PR, SD or PD are not met, the BOR is NE.

ORR will be calculated with 80% and 90% exact confidence intervals (CIs).

The number and percentage of patients with each type of response [CR, PR, SD, PD, NE] as outlined in RECIST v1.1, will be summarized for best overall response.

RECIST v1.1 response assessments over time will be summarized by visit.

BOR and response assessments over time will be listed.

Unscheduled assessments will be utilized in the determination of an ORR responder/non-responder.

A swimmer plot will be generated for response over time showing time on and off treatment for RECIST v1.1.

6.6.1.2. Clinical Benefit Rate per RECIST v1.1

Clinical benefit rate (CBR) is defined as the proportion of patients who have a best overall response of SD, PR or CR per local investigator assessment using RECIST version 1.1.

CBR will be calculated with 80% and 90% exact confidence intervals (CIs).

6.6.1.3. Overall Survival

Overall survival is defined as the time from first treatment start date until death (weeks).

OS will be summarized descriptively. The product limit estimates of the survival distribution function using Kaplan-Meier will be presented with: N, total events, total censored, time to event (median, 25th and 75th percentile), range (with and without censoring), probability of event-free survival at pre-specified weeks, such as 9, 18, 27 etc. weeks.

Kaplan-Meier curve will also be generated.

The censoring rules are provided in Table 1.

Table 1 Overall Survival Censoring Rules

Situation	End Date	Outcome	Reason for censoring
Death	Date of death	Event [a]	Not applicable
Patient did not have a death event	Date of last visit	Censored	Patient did not have a death event.

OS = (End Date – treatment start date+1)/7;

a The earliest end date in the table is used in calculating the OS

6.6.2. Subgroup Analysis

Not applicable.

6.6.3. Exploratory Analysis

6.6.3.1. Objective Response Rate per iRECIST

The exact confidence interval analysis for RECIST v1.1 in Section 6.6.1.1 will be repeated using iRECIST[3]. Immune objective response rate (iORR) as determined by iRECIST, is defined as the proportion of patients in the analysis population who have immune best overall response (iBOR) of immune complete response (iCR) or immune partial response (iPR) during the course of the study. The iCR or iPR must be confirmed by a second assessment of iCR/iPR at least 4 weeks apart. iORR analysis method is identical to ORR. Unconfirmed progression will be reported as immune unconfirmed progressive disease (iUPD) and confirmed progression will be reported as immune confirmed progressive disease (iCPD). If the latest occurrence of iUPD was not confirmed, then the reason for non-confirmation will also be summarized and listed.

6.6.3.2. Clinical Benefit Rate per iRECIST

Clinical benefit rate will be analyzed in an approach analogous with Section 6.6.1.2 utilizing the categories described in Section 6.6.3.1.

6.6.3.3. Regression of RECIST v1.1 Target (Non-Injected) Lesions

The sum of RECIST v1.1 target lesions (I.e., non-injected lesons) will be summarized by visit with the percentage change from baseline for the efficacy population. Data on individual RECIST v1.1 target lesions will also be listed.

Baseline is the last non-missing values collected before the first dose of treatment. Size of non-injected lesions will be determined from the longest diameter (mm). Non-injected lesions that are lymph nodes will be determined from the short axis (mm). Only lesions measured at baseline are included in the sum, I.e., new lesions are not included.

Waterfall plots will be generated displaying best percentage change in RECIST v1.1 target lesions from baseline with the best overall tumor response.

A spider plot will be generated displaying percentage change in RECIST v1.1 target lesions over time with the best overall tumor response.

6.6.3.4. Progression-Free Survival per RECIST v1.1 and iRECIST

Progression-free survival is defined as time from treatment start date until PD for RECIST v1.1, or immune progressive disease (iPD) for iRECIST, or death (Weeks), whichever comes first, up to 90 days after the end of treatment. The date of iPD is the date of iUPD when confirmation occurs. For iUPD (without subsequent iSD, iPR, or iCR), the iPD will be the first date of the most recent iUPD chain in the following scenarios: if the patient stops protocol treatment because they were not judged to be clinically stable, or no further response assessments are done (because of patient refusal, protocol noncompliance, or patient death); the next timepoint responses are all iUPD, and iCPD never occurs; or the patient dies from their cancer, whichever occurs first. Details of censoring have been provided in Table 2.

Table 2 Progression-Free Survival and Duration of Response Censoring Rules

Situation	End Date	Outcome	Reason for censoring	Applicable analysis
(i)PD (Within 90 days of end of treatment)	Date of first (i)PD	Event [a]	Not applicable	PFS and DoR
Death (Within 90 days of end of treatment) without radiological (i)PD assessment before death	Date of death	Event [a]	Not applicable	PFS and DoR
Patient discontinued from study due to a reason other than PD or death	Date of last adequate radiological assessment	Censored	Patient discontinued from study due to a reason other than PD or death	PFS and DoR
Patient discontinued from study due to PD, but no documented date of (i)PD	Date of last adequate radiological assessment before discontinuation	Censored	Patient discontinued from study due to PD, but no documented date of (i)PD	PFS and DoR
Patient completed or is still on study at the time of data cutoff without (i)PD	Date of last adequate radiological assessment before data cutoff	Censored	Patient completed study or is still on study without (i)PD	PFS and DoR
New anticancer treatment started prior to radiological (i)PD or death	Date of last adequate radiological assessment before starting new systemic anticancer treatment	Censored	New systemic anticancer treatment started	PFS and DoR
Death more than 90 days after end of treatment	Date of last adequate radiological assessment	Censored	Patient died more than 90 days after end of treatment	PFS and DoR

Situation	End Date	Outcome	Reason for censoring	Applicable analysis
(i)PD more than 90 days after end of treatment	Date of last adequate radiological assessment	Censored	Patient had (i)PD more than 90 days after end of treatment	PFS and DoR
No evaluable post baseline radiological assessments	Treatment start date	Censored	Patient has no evaluable post baseline radiological assessments	PFS and DoR

PFS (End Date – treatment start date+1)/7; or DoR =(End Date – first tumor response date+1)/7

a The earliest end date in the table is used in calculating the PFS or DoR

PFS will be summarized descriptively, separately for RECIST v1.1 and iRECIST. The product limit estimates of the survival distribution function using Kaplan-Meier will be presented with: N, total events, total censored, time to event (median, 25th and 75th percentile), range (with and without censoring), probability of event-free survival at pre-specified weeks, such as 9, 18, 27, etc. weeks.

Kaplan-Meier curves will be generated, separately for RECIST v1.1 and iRECIST.

6.6.3.5. Duration of Response per -RECIST v1.1 and iRECIST

Duration of response (DoR) is defined as the interval between the date of the first observation of tumor response ([i]CR or [i]PR, whichever status is recorded first) and the first date that (i)PD is documented. This is applicable only for those who responded prior to (i)PD. Determination of (i)PD and the analysis will follow Section 6.6.3.4 and the censoring rules are included in Table 2.

6.6.3.6. Time to Response per RECIST v1.1 and iRECIST

Time to response (TTR) is defined as the time from first intratumoral injection and the first observation of tumor response ([i]CR or [i]PR, whichever status is recorded first). The analysis to be done will follow the method described in Section 6.6.3.4. The censoring rules are provided in Table 3

Table 3 Time to Response Censoring Rules

Situation	End Date	Outcome	Reason for censoring
(i)CR or (i)PR	Date of first event ([i]CR or [i]PR)	Event [a]	Not applicable
Patient does not have (i)CR or (i)PR	Date of last adequate radiological assessment	Censored	Patient does not have (i)CR or (i)PR
New anticancer treatment started prior to (i)CR or (i)PR	Date of last adequate radiological assessment before starting new	Censored	New systemic anticancer treatment started

Situation	End Date	Outcome	Reason for censoring
	systemic anticancer treatment		
No evaluable post baseline radiological assessments	Treatment start date	Censored	Patient has no evaluable post baseline radiological assessments

TTR = (End Date – first intratumoral injection +1)/7;

a The earliest end date in the table is used in calculating the TTR

6.6.3.7. Biomarkers of Immune Response in Injected and Non-Injected Lesions

Not applicable. Biomarkers of immune response in injected and non-injected lesions will be reported separately.

6.7. Safety

6.7.1. Extent of Exposure

Exposure of LTX-315 will be categorized into dosing days in categories from 1 to 7.

Duration of exposure for pembrolizumab (weeks) =

([date of last dose of pembrolizumab – date of first dose pembrolizumab] + 1) / 7

The duration of exposure for pembrolizumab will be categorized as:

- less than 7 weeks
- ≥ 7 weeks to < 13 weeks
- ≥ 13 weeks to < 19 weeks
- ≥ 19 weeks to < 25 weeks
- ≥ 25 weeks to < 31 weeks
- ≥ 31 weeks to < 37 weeks
- ≥ 37 weeks to < 43 weeks
- ≥ 43 weeks to < 49 weeks
- ≥ 49 weeks

Exposure will be summarized in two ways for the Safety Population

- Descriptive statistics will be presented for dosing days/duration of exposure.
- Number and percentage of patients within each of the exposure categories will be presented.

Total number of LTX-315 injections per visit will be categorized as: 1, 2, 3 and >=4. All LTX-315 injections across entire study will also be presented. Pembrolizumab infusions will also be categorized as: 1, 2, 3, 4, 5, 6, 7, 8, 9 and >=10. Treatment exposure will be

summarized by visit for LTX-315, and total for pembrolizumab using the same approach for duration of exposure.

A listing of overall treatment exposure data, including the first and last dates of treatment will be presented for the Safety Population. Further, study treatment administration / infusion data will be listed for the Safety Population.

6.7.2. Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary [Version 25.1 or a later version if updated during the study] and classified as either pre-treatment AEs or treatment–emergent AEs (TEAEs) as follows:

- Pre-treatment AEs are events that start prior to the start of the Treatment Period.
- TEAEs are events with start date after the start of the Treatment Period and up to 30/90 days (30 days if non-SAE, 90 days if SAE) after the end of the Treatment Period. If patient initiates new anticancer therapy, then 30 days will be used for SAEs.
- Treatment-Emergent Serious AEs (TESAEs) will be defined as TEAEs regarded by the investigator as Serious = "Yes".
- The relationship between a TEAE and treatment is assessed as related, possibly related, unlikely related, or not related. A treatment-related TEAE will be defined as a TEAE considered by the investigator as related to treatment or with missing relationship to treatment.
- Assessment of AE severity will be based on the National Cancer Institute-Common Terminology Criteria for AEs (NCI-CTCAE[4], Version 5.0) or the protocol grading scale for AEs that cannot be graded with NCI-CTCAE.
- TEAEs leading to discontinuation of treatment are defined as TEAEs where action taken with study drug is indicated as "Drug withdrawn".

AEs will be summarized by default descriptive summary statistics for categorical variables for the Safety Population as follows:

- An overview of TEAEs including the number and percentage of patients with at least one of each mentioned TEAE type:
  - Any TEAE
    - Leading to discontinuation of LTX-315
    - Leading to discontinuation of pembrolizumab
    - Leading to death
    - Grade 1 - Mild
    - Grade 2 - Moderate
    - Grade 3 - Severe
    - Grade 4 - Life-threatening
    - Grade 5 - Death
  - Any study treatment related TEAE

        - Leading to discontinuation of LTX-315
        - Leading to discontinuation of pembrolizumab
        - Leading to death
    - Any serious TEAE
        - Leading to discontinuation of LTX-315
        - Leading to discontinuation of pembrolizumab
        - Leading to death
    - Any serious study treatment related TEAE
        - Leading to discontinuation of LTX-315
        - Leading to discontinuation of pembrolizumab
        - Leading to death
    - Any hypersensitivity TEAEs
    - Any injection site reaction TEAEs
- The number and percentage of patients reporting each TEAE and the count of number of events will be summarized by SOC and PT for the following types of TEAEs:
    - TEAEs
    - TEAEs Leading to Discontinuation of LTX-315
    - TEAEs Leading to Discontinuation of Pembrolizumab
    - TEAEs Leading to Death
    - TEAEs by Maximum Severity
    - TEAEs by Maximum Severity (≥ Grade 3)
    - TEAEs by Relationship to LTX-315
    - TEAEs by Relationship to Pembrolizumab
    - Hypersensitivity TEAEs
    - Serious TEAEs
    - Serious TEAEs Leading to Discontinuation of LTX-315
    - Serious TEAEs Leading to Discontinuation of Pembrolizumab
    - Serious TEAEs Leading to Death
- The number and percentage of patients who died will be summarized by the primary reason of death

In the above summaries, patients with more than one TEAE within a particular SOC are counted only once for that SOC. Similarly, patients with more than one TEAE within a particular PT are counted only once for that PT.

For summaries by maximum severity, patients with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC or PT. TEAEs with missing severity will be included as missing.

Summaries by SOCs and PTs will be sorted by descending order of total incidence for SOCs, and PTs within SOC. Where SOCs or PTs tie they will be sorted alphabetically.

No statistical comparisons of AEs between treatment groups will be performed.

All AE data will be listed and pre-treatment AEs and TEAEs will be presented together. Treatment-emergence status will be flagged in the listing. The listing will present the relative start and stop day of the AE calculated relative to the first dose of treatment and will be

presented for those patients who received at least one dose of treatment. If the AE is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

In addition, the following listings will be presented:

- Listing of Deaths
- Listing of Serious TEAEs
- Listing of TEAEs Leading to Interruption of any Study Treatment
- Listing of TEAEs Leading to Discontinuation of any Study Treatment
- Listing of Hypersensitivity TEAEs
- Listing of Injection Site Reaction TEAEs

6.7.3. Laboratory Evaluations

Data for the following hematology, chemistry, serology, pregnancy, coagulation, and hypersensitivity received from local and central laboratories / recorded in the eCRF are to be measured at the scheduled visits indicated in the study flowchart.

Table 4 Laboratory Tests

Hematology (SI unit)	Chemistry (SI unit) [Fasted]	

• Red Blood Cell Count (10^{12}/L)
• Hemoglobin (g/L)
• Hematocrit (%)
• White Blood Cell Count (10^9/L)
• Differential WBC (10^9/L and %)
  ○ Neutrophils
  ○ Lymphocytes
  ○ Eosinophils
  ○ Basophils
  ○ Monocytes
• Platelet count (10^9/L)
• Mean corpuscular hemoglobin (pg)
• Mean corpuscular hemoglobin concentration (g/L)
• Mean corpuscular volume (fL)
	• Alanine aminotransferase (ALT) (U/L)
	• Aspartate aminotransferase (AST) (U/L)
	• Total Bilirubin (mmol/L)
	• Cholesterol (mmol/L)
	• Gamma-Glutamyltransferase (GGT) (U/L)
	• Alkaline phosphatase (U/L)
	• Albumin (g/L)
	• Total protein (g/L)
	• Glucose (mmol/L)
	• Creatinine (mmol/L)
	• Blood Urea Nitrogen (mmol/L)
	• Calcium (mmol/L)
	• Potassium (mmol/L)
	• Sodium (mmol/L)
	• Chloride (mmol/L)
	• Uric acid (mmol/L)
	Lactate dehydrogenase (ukat/L)	

Coagulation	**Serology**	**Hypersensitivity**
• Activated partial thromboplastin time • International normalized ratio • Prothrombin time	• Hepatitis B: HBsAg • Hepatitis B: HBsAb • Hepatitis B: HBcABb • Hepatitis C Antibody • HIV-1 Antibodies • HIB-2 Antibodies • HIV p24 Antigen	• Serum tryptase • Basophil activation test (if possible)
For Women Only:		
• Urine pregnancy test • Follicle-stimulating hormone		

In accordance with the baseline value definition in Section 5.1.2, the absolute change from baseline will be derived as follows:

Absolute change (unit) = (post-baseline value – baseline value)

All laboratory data will be reported in SI units. All quantitative laboratory test values at each assessed timepoints will be compared with the relevant reference range in SI units and categorized as:

- Low: Below the lower limit of the reference range.
- Normal: Within the reference range (upper and lower limits included).
- High: Above the upper limit of the reference range.

For summaries which present worst value with respect to the reference range at the patient level, low and high are each chosen in preference to normal values.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory values will be assigned toxicity grades, when available, using criteria based on the NCI CTCAE version 5.0[4] . For summaries which present worst CTCAE value at the patient level higher grades are used in preference to lower grades.

Laboratory data will be summarized by default descriptive summary statistics for continuous and categorical variables for the Safety Population as follows:

- Observed values and change from baseline at each assessed visit for each standard continuous laboratory parameter;
- Number and percentage of patients with categorized shift (Normal, Abnormal not clinically significant, Abnormal clinically significant) values relative to the reference range at baseline compared to each post-baseline visit for hematology, clinical chemistry, and coagulation.
- Number and percentage of patients with categorized shift NCI-CTCAE toxicity values at baseline compared to each post-baseline visit for hematology and clinical chemistry;

Listings of all clinical laboratory data including derived change from baseline will be provided for the Safety Population. Within each listing, laboratory values outside the normal ranges will be flagged as either high or low and NCI-CTCAE grading will be provided for applicable laboratory assessments.

6.7.4. Vital Signs

The analyses described below will be conducted for the following vital signs assessments respectively:

- pulse rate (bpm);
- weight (kg);
- respiration rate (breaths / min);
- body temperature (°C).

Note that systolic blood pressure and diastolic blood pressure will be reported under blood pressure monitoring.

In accordance with the baseline value definition in Section 5.1.2, the absolute change from baseline will be derived as follows:

Absolute change (unit) = (post-baseline value – baseline value)

The following will be summarized for the Safety Population:

- Observed values and change from baseline at each assessed visit for each standard vital sign parameter using default summary statistics for continuous variables.

A listing of all vital signs data including derived change from baseline will be provided for the Safety Population.

6.7.5. Electrocardiograms

The following ECG assessments will be taken during the study:

- An overall investigator assessment classified as normal, abnormal, not clinically significant / abnormal, clinically significant
- Heart rate (bpm);
- RR interval (msec);
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- Fridericia corrected QT (QTcF) interval (msec);

In accordance with the baseline value definition in Section 5.1.2, the absolute change from baseline will be derived as follows:

Absolute change (unit) = (post-baseline value – baseline value)

The maximum post-baseline QTcF values will be classified in accordance with the ICH E14[5], Boundaries as presented in Table 5.

Table 5 QTcF Interval ICH E14 Boundaries

QTcF Interval	Criteria (msec)
Observed QTcF interval	≤450 msec >450 msec >480 msec >500 msec
Change from baseline in QTcF interval	≤30 >30 to ≤ 60 msec >60 msec

The ECG findings will be summarized for the Safety Population as follows:

- Observed values and change from baseline at each assessed visit for each ECG parameter using default summary statistics for continuous variables;
- The ECG overall assessment as reported by the investigator will be summarized at each assessed visit by providing number and percentage of patients within each assessment category;
- Shifts from baseline of overall ECG assessment (normal vs. abnormal, not clinically significant vs. abnormal, clinically significant) to each post-baseline visit;
- The number and percentage of patients meeting boundaries described in Table 5 will be displayed.

A listing of all ECG data including derived change from baseline will be provided for the Safety Population.

6.7.6. Physical Examination

Abnormalities identified from physical examination are recorded in the eCRF as Medical History or AEs as appropriate and will be listed and summarized as such [See Sections 6.4.3 (Medical and surgical history) and 6.7.2 (Adverse Events)].

6.7.7. Other Safety Variables

6.7.7.1. Blood pressure monitoring

Blood pressure monitoring will be summarized for SBP and DBP for the Safety Population as follows:

- Maximum increase/decrease change from baseline and observed values of that maximum increase/decrease at each injection day (Phase A only) for each parameter using default summary statistics for continuous variables;
- The number and percentage of patients meeting boundaries described in Table 6 will be displayed for each parameter (Phase A only), utilizing their most extreme criteria, and including both positive and negative directionality.

Baseline is derived based on the last assessment prior to the first injection on each injection day. If the date and times are equal, then it is assumed to be a baseline assessment.

Blood pressure monitoring will be listed for each patient in the Safety Population at each assessed visit and timepoint.

Table 6 SBP and DBP boundaries

SBP and DBP	Criteria (mmHg)
Percentage change from baseline	< -20 ≥ -20 to < -10 ≥ -10 to < 0 No change > 0 to ≤ 10 > 10 to ≤ 20 > 20

6.7.7.2. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status score will be listed for each patient in the Safety Population at each assessed visit.

6.7.7.3. LTX-315 Injection Site Assessment

Injection site assessments will be listed for each patient in the Safety Population at each assessed visit.

6.7.7.4. Antidrug Antibody Assessment

Not applicable. Antidrug antibody assessments will be reported separately.

6.7.8. Interim Analysis and Data Monitoring

No interim analysis or data monitoring will occur. There may be cuts of data for scientific conferences.

6.7.9. Stopping rules

After 20 patients have been enrolled and have had the opportunity to show a response (I.e., reached the second post-baseline scan). If less than or equal to two responding patients (CR or PR) are observed with all other patients showing (PD in the efficacy population the study will be stopped for futility. The study may be continued at the sponsor's discretion if a substantial number of patients show sustained SD. Patients enrolled in the study will be eligible to continue on study treatment if there are signs of clinical benefit or response.

6.8. Pharmacokinetic Assessments

Not applicable. PK to be reported separately

7. Changes in the Conduct of the Study or Planned Analysis

Additional PK parameters are included as secondary PK endpoints although not detailed in the protocol.

Version 2.0 SAP was revised to be consistent with protocol amendment version 6 dated 4th December 2023. A summary of these changes are as follows:

- Study title updated to remove refractory to pembrolizumab and include refractory to PD-1/PD-L1 inhibitor therapy.
- Overall study design in Section 2.1 e.g., removal of stage m1c, new study schematic figure added etc.
- ECOG performance status removed as a secondary endpoint.
- itRECIST removed as an exploratory endpoint.
- PK required only for first 20 patients.
- ITT population was added and defined equivalent to Safety Population.
- Study stopping rules were added.

Additional changes for version 2.0 SAP:

- Adjusted company name from Labcorp Drug Development to Fortrea.
- LVEF analyses removed.
- Added description into Section 5.2.2 for missing ECGs.
- Update baseline characteristics analyses in Section 6.4.2.
- Adjusted the sort order of medical history table in Section 6.4.3.
- Efficacy section updated to exclude RECIST tumor evaluations collected via ultrasound in Section 6.6.
- Survival analysis censoring rules updated in Section 6.6.
- Criteria for achieving SD for BOR was amended to occurring 5 weeks following first treatment in Section 6.6.1.
- Removed injected lesion analyses in Section 6.6.3.3.
- Description added to Section 6.6.3.3 for Lymph nodes
- Excluded new lesions in the calculation of change from baseline in Section 6.6.3.3.
- Removal of TEAE worsening criteria in Section 6.7.2
- Included protocol grading scale for CTCAE in Section 6.7.2.
- Removed change from baseline tables for urinalysis in Section 6.7.3.
- Amended blood pressure monitoring description in Section 6.7.7.1 to include a different baseline and maximum increase/decrease analyses.

8. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary / Reason for Changes
Version 2.0, Final, 19SEP2024	Changes to the SAP to be consistent with the latest version of the protocol.
Version 1.0, Final, 21FEB2023	Not applicable; the first version

9. References

[1]ICH. *Structure and Content of Clinical Study Reports*, Guideline E3, 1995. Available at https://database.ich.org/sites/default/files/E3_Guideline.pdf

[2] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.

[3] Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143–52.

[4]*Common Terminology Criteria for Adverse Events (CTCAE) v6.0. Available at* https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_60

[5]ICH. *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.* 12 May 2005. Available at https://database.ich.org/sites/default/files/E14_Guideline.pdf

Type of Approval (select one) : ☒ **SAP** ☐ **Initiation of Programming SAP** ☐ **SAP Addendum**

Sponsor Name:	**Lytix**		
Sponsor Protocol/ CIP ID:	**C20-315-05**	[redacted]	
SAP text filename:	**LTX-315 - SAP Final_v2.0_19SEP2024 (Clean version)**		
TFL shells filename:	**LTX-315 - TFL Mocks_Final_v2.0_19SEP2024 (Clean version)**		
Version:	**2.0**	**Date:**	**19SEP2024**

Fortrea Approval(s):

Lead Statistician

Approval Signature **Print Name** **Date**	[redacted]

Sponsor Approval(s):

By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the Analysis Dataset Model (ADaM) datasets and TFLs based on these documents can proceed. Any modifications to the SAP text and TFL shells made after signing may result in a work-scope change.

Director Clinical Development

Approval Signature **Print Name** **Date**	[redacted]

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