Statistical Analysis Plan

Title: *A Phase 2a, Double-Blind, Placebo-Controlled, Multi-Center, Randomized Study Evaluating LSTA1 When Added to Standard of Care (SoC) Versus Standard of Care Alone in Subjects with Advanced Solid Tumors (BOLSTER)*

Protocol Number: *LSTA1-P02*

Protocol Version: *8.0 / 16 JUL 2024*

SAP Version: *Version 1.0, Date 25 SEP 2025*

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Previous SAP Versions

N/A

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SAP Amendments before Database Lock

N/A

REVIEW / APPROVAL SIGNATURES

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Plan Approver, Sponsor Clinician	**Plan Approver, Sponsor**
[redacted]	[redacted]

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[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
CCA	Cholangiocarcinoma
CR	complete response
CRT	chemoradiotherapy
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
d	day
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Treatment
FU	follow up
GCP	Good Clinical Practice
HNSCC	head and neck squamous cell carcinoma
ICH	International Conference on Harmonization
IHC	intrahepatic cholangiocarcinoma
IRT	interactive response technology
IV	Intravenous
LTFU	long term follow-up
MRI	magnetic resonance imaging
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response

[redacted]

Abbreviation	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SoC	standard of care
TEAE	treatment emergent adverse events

1 INTRODUCTION

This document details the planned clinical and safety statistical analyses for *Lisata Therapeutics, Inc.*, protocol "*LSTA1-P02*" study titled "*A Phase 2a, double-blind, placebo-controlled, multi-center, randomized study evaluating LSTA1 when added to standard of care (SoC) versus standard of care alone in subjects with advanced solid tumors (BOLSTER)*". A separate analysis plan will be provided for the Pharmacokinetic analyses.

The proposed analyses are based on the contents of the amended version of the protocol (v8.0, dated *16-JUL-2024*).

This is a Phase 2a, multicenter, randomized, placebo-controlled, double-blind trial evaluating the safety and efficacy of LSTA1 when added to SoC versus SoC alone in patients with advanced solid tumors. The study will consist of a screening period, a run-in period, a treatment period, an end-of-treatment (EoT) follow-up visit, and a long-term follow-up (LTFU) period. On-going safety, survival, and subsequent anti-cancer therapies will be assessed during the LTFU.

The study includes patients with advanced Head and Neck Squamous Cell Carcinoma (HNSCC) and Cholangiocarcinoma (CCA). However, the enrollment of the cohort for advanced HNSCC was discontinued after only 3 subjects were randomized and treated due to a slower than anticipated enrollment rate. No HNSCC data will be presented in the analyses.

During the screening period, patients who provide informed consent will be screened for eligibility within 28 days (d) prior to beginning the study run-in period.

During the randomization/run-in period, eligible patients will be randomized 1:1 within their respective tumor type basket arm to one of the two treatment groups (i.e., SoC + placebo vs. SoC + LSTA1). The run-in (72-hours) must occur no more than 28 days after the patient has signed the ICF. Patients will only receive the LSTA1 or placebo components of their randomized treatment regimen; they will not receive SoC chemotherapy. On Day 1 of the run-in, patients will either be given LSTA1 or matching placebo as a slow intravenous (IV) push over one minute (± 30 seconds). Safety will be assessed for the duration of the run-in period.

After the 72-hour run-in, the treatment phase begins on Cycle 1, Day 1 and continues up to the point at which the investigator determines the patient will be permanently discontinued from the study drug.

Tumor assessments will be performed at baseline and every 8 weeks (56 days ± 7 days) after the first dose of study drug (C1D1) until disease progression or a new anti-cancer therapy is commenced. Tumor assessments will occur at this interval for up to 12 months and then be performed every 12 weeks (± 7 days) thereafter until treatment is discontinued. Imaging for screening and tumor assessments must be performed using the same imaging modality as the

baseline scans. Those who do not progress will continue to have scans for up to 12 months after the last patient is enrolled.

Dose modifications/reductions of SoC chemotherapies are allowable to manage toxicities. Every effort should be made to provide maximal supportive therapy prior to implementing a dose reduction. The dose of LSTA1/matching LSTA1 placebo will not be adjusted.

The study was terminated early on 27 AUG 2025. Due to the premature termination of this study, the scope of reporting for this protocol has changed to support an abbreviated clinical study report (aCSR).

This document details the planned safety and clinical statistical analyses to support an aCSR. Details regarding changes from the planned statistical analyses as described in the protocol (v8.0, dated 16 JUL 2024) are described in Section 8 of this document.

2 STUDY OBJECTIVES AND ENDPOINTS

Below are the study objectives and associated endpoints as defined in the protocol.

2.1 Efficacy Objectives/Endpoints

Objective: *To determine the effect of LSTA1 in combination with SoC chemotherapy on survival relative to placebo in combination with SoC in patients with advanced solid tumors*
Endpoint: *Median time from first dose (C1D1) until death due to any cause*
Objective: *To determine the effect of LSTA1 on milestone survival endpoints*
Endpoint: *3-month, 6-month, and 12-month survival*
Objective: *To determine the effect of LSTA1 on PFS*
Endpoint: *Median progression-free survival (PFS) based on RECIST 1.1 [Time Frame: From first dose (C1D1) until objective radiological progression, or death from any cause, whichever comes earlier, assessed until the data cut-off is reached.]*
Objective: *To determine the effect of LSTA1 on response rate*
Endpoints: • *Objective response rate (ORR) [Complete response (CR) + Partial response (PR)] based on RECIST 1.1. ORR is relative to the screening tumor measurement.* • *Disease control rate (DCR) [CR+PR+SD for > 16 weeks based on RECIST 1.1].*

Objective: *To determine the effect of LSTA1 on duration of response (DOR) in responding patients with measurable disease at baseline*

Endpoint: *Duration of response (DOR) for responding patients with measurable disease at baseline, which is measured from the first timepoint where an objective response is determined until the last timepoint the patient is found to have an objective response.*

2.2 Safety Objectives/Endpoints

Objective: *To evaluate the safety of LSTA1 in combination with SoC therapies compared to SoC therapies alone*

Endpoints:

- *Incidence and severity of adverse events, with severity determined according to NCI CTCAE v. 5.0*
- *Frequency of Grade ≥ 3 treatment-related adverse events*
- *Frequency of treatment-related serious adverse events (SAEs)*
- *Electrocardiograms*
- *Clinical laboratory investigations*
- *Physical examinations*
- *Vital signs*

Objective: *To evaluate the impact on dose of SoC when administered in combination with LSTA1*

Endpoints:

- *Mean SoC drug dose delivered per cycle*
- *Mean dose of SoC over 3 cycles and over 6 cycles*
- *Mean number of dose modifications (i.e., dose reductions, interruptions, and discontinuations per cycle (up to first 6 cycles)*

Objective: *To assess the baseline safety of LSTA1 monotherapy when administered during 72-hour run-in period to patients with advanced solid tumors*

Endpoints:

- *Incidence and severity of adverse events, with severity determined according to NCI CTCAE v. 5.0*
- *Frequency of Grade ≥ 3 treatment-related adverse events*
- *Frequency of treatment-related SAEs*

2.3 Pharmacodynamic Objective/Endpoints

Objectives:

- *To evaluate the pharmacodynamic profile of LSTA1 when administered in combination with SoC therapies*

Endpoints:

- Retrospective assessment of tissue biomarkers in optional pre-treatment archival tissue (or pre-treatment core biopsy) and on-treatment optional core biopsy.
- Assessment of baseline and on treatment serum biomarkers

2.4 Pharmacokinetic Objectives/Endpoints

- **Objective:** *To characterize the Pharmacokinetic (PK) profile of LSTA1 when administered in combination with SoC therapies*
- *To characterize the population PK profile of LSTA1 when administered in combination with SoC therapies*

Endpoints:

- PK of LSTA1 via:
  - Half life
  - T_{max}
  - C_{max}
  - AUC_{0-t}
  - $AUC_{0-\infty}$
- Other PK parameters as described in the SAP (or PK analysis plan, if separate).

3 SAMPLE SIZE

At least 40 subjects are planned for each cholangiocarcinoma cohort (~N=20/arm) will be randomized. Enrollment in the HNSCC cohort was discontinued after 3 subjects were randomized and treated due to an unanticipated slow enrollment rate. Enrollment in the second line cholangiocarcinoma cohort was also discontinued after 22 subjects were enrolled. The expected total sample size is approximately ~69 subjects.

Formal sample size calculations were not performed for this Phase 2a, placebo-controlled, proof-of-concept basket trial.

4 RANDOMIZATION

During the Run-In Period, patients who meet all the inclusion criteria and none of the exclusion criteria will be randomized within their respective tumor type basket arm using a ratio of 1:1 and assigned to one of the two treatment groups (i.e., SoC + placebo vs. SoC + LSTA1) via

interactive response technology (IRT). The number of patients in each dosing regimen is considered sufficient to achieve the study objectives.

This is a double-blind study. Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigators from the IRT system when needed. Routines for this will be described in the IRT user manual that will be provided to each site.

The randomization will be stratified by the following stratum:

- ECOG performance status

The randomization schedule for the study will be produced by an independent statistician from Worldwide Clinical Trials (Worldwide), under a specification provided by the Sponsor.

A dummy schedule will be produced before the study start and will be checked by the Sponsor to confirm the specifications. After approval of the dummy schedule, the independent Worldwide statistician will modify the random generator and issue the final live randomization for the study.

5 PLANNED ANALYSES

The Statistical Analysis Plan (SAP) and Table, Figure, Listing (TFL) Shells (and any amendments) must be approved prior to database lock. If post database lock, additional statistical analyses or changes to the statistical analysis are required, then those will be documented in a Post Database Lock Statistical Analysis Plan Addendum.

5.1 Analysis Sets

5.1.1 Full Analysis Set (Efficacy Analysis Set)

The Full Analysis Set (FAS) includes all patients who had a measurable lesion at baseline, received any amount of study drug, and completed a post treatment tumor assessment and/or discontinued due to documented clinical progression or death.

5.1.2 Per-Protocol Set

The Per-Protocol Set (PPS) will be a subset of the FAS excluding patients who had deviations that may impact critical efficacy variables. The PPS will be determined through blinded review of protocol deviations.

All protocol deviations will be assessed and documented on a case-by-case basis before the database lock, and deviations considered to have a serious impact on the efficacy results will lead to the relevant patient being excluded from the PPS. Before database lock, potential patient exclusions from PPS will be reviewed by the Sponsor and documented in a patient evaluability document.

No analyses will be evaluated using the PPS for the aCSR, this analysis population will not be derived (see Section 8).

5.1.3 Safety Analysis Set

The Safety Analysis Set includes all patients who have been consented in the study and have received any amount of study drug. Safety patients will be summarized in accordance with actual treatment received.

5.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

5.2.1 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the patient receives the first dose of any study drug (Day 1 of the Run-In Period).

Change from baseline (CFB) calculations are calculated as follows:

$$CFB = (Value\ at\ PostBaseline\ Visit\ or\ Timepoint) - (Value\ at\ Baseline)$$

For analysis purposes, all time-to-event analyses will define the first dose of treatment comparisons groups as Cycle 1, Day 1 (LSTA1 + SOC vs. Placebo + SOC).

5.2.2 Early Terminations Assessments

Early Termination (ET) assessments are summarized alongside the assessments from the corresponding study cycle/study day with which the ET visit most closely aligns.

5.2.3 Duration / Study Day / Time

Study day will be calculated as the number of days from first dose of study drug (C1D1).

- date of event – date of first dose of study drug (C1D1) + 1, for events on or after first dose (C1D1)
- date of event – date of first dose of study drug (C1D1), for events before first dose (C1D1)

5.2.4 Conventions for Missing and Partial Dates

It is not expected that there will be any missing dates for events occurring during study conduct. Historical dates such as dates of medical history or prior medications may be missing or partial. Dates (historical or during study conduct) will only be imputed if a full date is needed for a calculation or to support a definition.

All dates presented in the individual patient listings will be as recorded on the Electronic Case Report Form (eCRF).

5.2.4.1 Missing Adverse Events Dates

In the rare case that an Adverse Event (AE) start date or time is missing and it is unclear whether the AE is treatment emergent or not then a conservative approach will be taken, and it will be assumed that the AE is treatment emergent and occurred after first dosing. If an adverse event stop date is missing it will be assumed that the AE is ongoing.

5.2.4.2 Missing Last Dates of Study Drug Dosing

Due to the method of dosing administration, no missing dosing data is expected.

5.2.5 Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

5.2.6 Unscheduled Visits

Only scheduled post-baseline laboratory and vital signs values will be tabulated unless otherwise stated. Post-baseline repeat / unscheduled assessments will be included in all listings in the relevant appendices to the CSR.

5.2.7 Missing Assessment

Safety and clinical assessments reported as "Not Done" or are missing will be included in the descriptive statistics where applicable.

5.2.8 Adverse Event (AE) Data

Treatment emergent adverse events (TEAE) are reported according to protocol as any AE that has an onset on or after the first dose of study drug (C1D1) or any pre-existing condition that has worsened on or after the first dose of LSTA1 through 30 days following last dose of LSTA1. The following TEAE flag will be applied to distinguish AEs from TEAEs:

- Any AE that has a start date on or after the first dose of LSTA1 and before last dose of LSTA1 + *30* days

A treatment-related AE (be it LSTA1 related, Paclitaxel, Doxetaxel, Ciplatin, Gemcitabine, Durvalumab related) is defined as an AE as being possibly, probably, or definitely related to said treatment. If an AE is missing causality it is assumed to be related to the study drug for analysis purposes.

Common Terminology Criteria for Adverse Events (CTCAE v5.0) grading criteria will be used to classify AE severity. The CTCAE grading categories are as follows:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening
- Grade 5: Death

In the event of missing severity grading the missing severity will be reported as such for analysis purposes.

5.2.9 Randomization Strata

The randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) status (0 or 1) at Screening.

5.3 Conventions

5.3.1 General Conventions

All safety and clinical data summaries and statistical analyses will be generated using SAS version 9.4 or higher[1].

Raw data listings for all safety and clinical data collected during study conduct will be provided.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation (SD), and minimum and maximum values.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of patients in the column header unless otherwise specified in the footnote. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

Means, medians and percentiles will be displayed to one more decimal place than the data, dispersion statistics (e.g., standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

5.3.2 Data Labels

All summaries will be presented by treatment group for each CCA cohort. No data will be presented for the HNSCC subjects.

Safety summaries will also be presented for CCA subjects pooled across all cohorts as 'Overall' presented last, following the treatment groups.

Treatment group labels will be displayed as follows:

<Tumor Cohort: 1L-CCA / 2L-CCA>	
Placebo + SoC	*LSTA1 + SoC*
(N=XX)	(N=XX)

CCA = Cholangiocarcinoma; SoC = Standard of Care regime

5.4 Patient Disposition

Patient disposition will be summarized as follows:

- The number of patients who failed screening and the reasons for failure will be tabulated.
- The number of patients, who were screened, were randomized, and who are in each analysis set will be summarized by treatment group for each cohort.
- Additionally, the reasons for exclusion from the Per-Protocol Set will be summarized by treatment group for each cohort.
- The number of early withdrawals and the reasons for withdrawals will be tabulated by treatment group for each cohort using the Safety Analysis Set.
- The number of patients who completed the study will be summarized by treatment group for each cohort using the Safety Analysis Set.
- Recruitment will be summarized by country and / or site for the Safety Analysis Set.

5.5 Protocol Deviations

Protocol deviations will be recorded in a separate source document and converted into a SAS file for analysis purposes. Protocol deviations may include but are not limited to the following: departure from Good Clinical Practice (GCP), inclusion/exclusion criteria, dosing, failure to perform the required assessments at the specified time points, scheduling of visits not in accordance with specifications, or patient safety.

For a complete list of protocol deviation classification criteria, parameters reported, and reviewing/reporting details please refer to the Protocol Deviation Handling Plan (PDHP.

Protocol deviations will be provided via raw data listings.

5.6 Baseline Comparability

The comparability of treatment groups with respect to patient demographics will be assessed in a descriptive manner, but no formal statistical testing will be performed. Summaries will be presented by treatment group for each cohort (as applicable).

Standard continuous or categorical variable summaries will be presented by actual treatment group for the following variables based on the Safety Analysis Set.

- Demographic Data:
  - Age (yr) at time of informed consent
  - Sex at birth (Male/Female)
  - Fertility Status (Childbearing Potential, Post-Menopausal, Surgically Sterile)
  - Ethnicity (Hispanic/Latino or Not Hispanic/Latino)
  - Race (White or Caucasian, Black or African Descent, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Not reported)
- Baseline Characteristics
  - Height at Screening (cm)
  - Weight at Screening (kg)

5.7 Efficacy Analyses

No statistical comparisons between cohorts are planned for this study. All efficacy analyses will be conducted on the FAS.

All statistical tests will be performed using a two-tailed 5% overall significance level, unless otherwise stated. All comparisons between treatments will be reported with 95% confidence intervals for the difference.

5.7.1 Efficacy Endpoints

5.7.1.1 Median Overall Survival (OS)

Median OS is defined as the median time interval from the date of first dose of (C1D1) study drug until date of death due to any cause or date of last contact. OS will be censored on the date of last contact for those patients who are alive at the end of the study (Appendix 10.1.1, Censoring Rules).

$$OS_{(\text{months})} = \frac{(\text{Date of death or last follow-up}) - (\text{Date of First Dose} + 1)}{30.4375}$$

5.7.1.2 Progression-Free Survival (PFS)

PFS is defined as the time interval from the date of the first dose of the study drug until the first date at which evidence of radiological PD is objectively documented (per modified RECIST version 1.1) or death from any cause, whichever occurs first. Patients without documented PD or death by the end of study will be censored at the date of the last clinical or radiological response assessment indicating absence of PD (Appendix 10.1, Censoring Rules).

$$PFS_{(months)} = \frac{(\text{Earliest date of PD, Death, or Censor Date}) - (\text{Date of First Dose} + 1)}{30.4375}$$

5.7.1.3 Objective Response Rate (ORR)

Confirmed ORR is defined as the proportion of the patients who were confirmed to have achieved CR or PR per modified RECIST version 1.1 relative to the screening tumor measurement for patients after initiation of study drug. Patients with no evaluable post-baseline response assessment (e.g., RECIST) will be considered non-responders.

5.7.2 Efficacy Analysis

5.7.2.1 Median Overall Survival (OS)

OS will be summarized by treatment for each cohort using KM estimates. KM estimates of quartiles with 95% CI along with KM estimates (95% CI) for 6, 12, 18 and 24 months will be displayed by treatment for each cohort.

Within each cohort, LSTA1 overall survival curve will be compared to the placebo group using log-rank tests. Hazard Ratio (HR) and 95% CI will be estimated using a Cox proportional hazards model. The Cox regression analysis will be used to model all cohorts and treatment groups simultaneously with cohort, treatment group, and cohort-by-treatment group effects. Median survival will be estimated for each cohort-by-treatment group.

For example SAS code please see Appendix 10.1.3.2 Median Survival Sample SAS code and Appendix 10.1.3.3 Kaplan-Meier Estimates/Curve Sample SAS code.

5.7.2.2 Objective Response Rate (ORR)

Descriptive summaries will be provided for each ORR as assessed by the investigator. Patients with missing or no response assessments will be classified as non-responders. The point estimates of the ORR and the corresponding 2-sided 95% Wilson CI will be presented by treatment group for each cohort.

ORR will be compared for each treatment group for each cohort separately for each cohort using a Fisher's test.

For example SAS code please see Appendix 10.1.3.1 ORR Sample SAS code.

5.7.2.3 BoR and PFS

Best overall response (BoR), confirmed, will be summarized using descriptive statistics by treatment for each cohort.

PFS will be summarized by treatment for each cohort using Kaplan-Meier (KM) estimates. KM estimates of quartiles and 95% CIs for the quartiles will be provided along with KM estimates and 95% CI for 6 and 12 months.

PFS will be analyzed using similar methods as described for OS in section 5.7.2.1. LSTA1 PFS will be compared (study drug vs placebo) within each cohort using log-rank tests. Cox regression analysis will be used to model all cohorts and treatment groups simultaneously with cohort, treatment group and cohort-by-treatment group effects. Median PFS will be estimated for each cohort-by-treatment group.

5.7.3 Multiplicity

All secondary endpoints and the supportive analyses will be considered as descriptive evidence of efficacy and will be analyzed without any procedures to account for multiple comparisons.

5.8 Pharmacodynamic Analyses

Pharmacodynamic data will not be analyzed, summarized, nor listed.

5.9 Pharmacokinetic Analyses

Pharmacokinetic data will no longer be analyzed, summarized, nor listed.

5.10 Safety Analyses

The safety analyses will be presented by the treatment received for each cohort and overall using the Safety Analysis Set unless otherwise noted.

5.10.1 Adverse Events

AEs incidence and/or number of events will be reported for the following tables as appropriate:

- Overall summary of TEAEs which includes the following:
  - Any TEAEs
  - TEAEs ≥ Grade 3
  - LSTA1 Treatment-Related TEAEs
  - LSTA1 Treatment-Related TEAEs ≥ Grade 3
  - Serious Treatment Emergent Adverse Events (Treatment-Emergent SAEs)
  - Serious LSTA1 Treatment-Related TEAEs (Treatment Emergent, Treatment-Related SAEs)
  - AEs leading to Early Withdraw of Study Drug
  - SAEs Resulting in Death
- TEAEs by SOC and PT
- TEAEs ≥ Grade 3 by SOC and PT
  - Table will be repeated for the 72 **h** Run-In Period to assess LSTA1 Safety
- Serious TEAEs by SOC and PT

Additionally, the following listings will be presented for AEs:

- Listing of TEAEs Leading to Early Withdrawal
- Listing of Serious TEAEs (presented in the Table section of the appendices).
- Listing of Deaths (presented in the Table section of the appendices).

Adverse event incidence is counted only once per SOC and once per PT. The number and percent of patients experiencing events are reported. Outputs reported at maximum severity show the highest severity reported by a patient per SOC and PT.

5.10.2 Laboratory Data

For reporting purposes, lab parameters will be reported in the units recorded. A listing of any abnormal laboratory measurements recorded throughout the study will be presented.

6 INTERIM ANALYSIS

No interim analyses are planned.

7 DATA SAFETY MONITORING BOARD ANALYSIS

No data safety monitoring board (DSMB) analyses are planned.

8 CHANGES TO PLANNED PROTOCOL ANALYSIS

The following changes have been made to the planned analyses outlined in the protocol:

- Treatment compliance calculations and corresponding summaries have been removed from the analysis plan. Treatment compliance is not typically calculated for infusion-based studies. The study drug administration summary tables can be used as a proxy for adherence with planned study drug dosing.
- The operational definition for overall survival has been updated to be consistent with the PFS definition. Overall survival (OS): defined as the interval from the date of first dose of study drug (C1D1) to death from any cause, or the date of last known follow-up alive.

Additionally, due to the early termination of this study, the scope of this SAP has been reduced as follows:

- Summaries based on the following populations are not included in this SAP:
  - PPS Analysis Set
  - PK Analysis Set
- Pharmacodynamic and pharmacokinetic data will not be analyzed, summarized, nor listed.
- Safety/Clinical reporting will be limited and will only include the following key parameters:
  - Adverse Event reporting as outlined above in Section 5.10.1.
  - Abnormal clinical laboratory assessments as outlined above in Section 5.10.2.

- Efficacy reporting will be limited to the following key endpoints:
  - PFS
  - BOR
  - ORR
  - OS

9 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA

10 APPENDICES

10.1 Censoring Rules

An indicator variable, CSNR, will be created for PFS and OS where CSNR=1 if patient is censored and CSNR=0 if patient has an event (not censor).

$$Censoring\ Time\ (months) = \frac{(Date\ of\ Censoring - Date\ of\ First\ Dose + 1)}{30.4375}$$

10.1.1 Censoring for OS

Patients who alive at the end of study will be censored on date of last contact.

10.1.2 Censoring for PFS

Rule	Scenario	Date of event or censoring	Outcome
1	No baseline tumor assessment	Date of first dose	Censored
2	No post-baseline tumor assessment	Date of first dose	Censored
3	No measurable disease at baseline	Date of first dose	Censored
4	Disease progression or death	Earliest of date of death or date of disease progression	Progressed/Death
5	Disease progression or death after last evaluable tumor assessment	Date of last evaluable tumor assessment	Censored
6	No disease progression or death	Date of last evaluable tumor assessment documenting no PD before new anticancer therapy is given or missed tumor assessments	Censored
7	New anti-cancer therapy given	Date of last evaluable tumor assessment prior to initiation of the new anti-cancer therapy	Censored

10.1.3 Sample SAS Code

10.1.3.1 ORR Sample SAS code:

```
**Best Objective Response is defined as CR or PR**
  CR - 1
  PR - 2
```

```
 SD - 3
 PD - 4
 NE - 5;
data adrs; **<Where adrs is the tumor response dataset> **
        set adrs;
        if aval in (1,2) then objrespfl = 0;
        else if aval ne . then objrespfl = 1;
run;

** Best Overall Response **;
proc freq data = adrs;
        by cohort trt01pn;
        tables objrespfl/out = rs0(drop=percent);
run;

** 95% CI for ORR based on Binomial Test (Wilson CI)**;
proc freq data = adrs;
        by cohort trt01pn;
        table objrespfl/binomial (Wilson);
        ods output binomialcls = rs1;
run;

** Difference in Response **;
proc freq data = adrs;
        by cohort;
        tables trt01pn*objrespfl/riskdiff;
        fisher or;
 *The option riskdiff computes the difference based on standard normal approximation;
ods output RiskDiffCol1 = rs2;
run;
```

10.1.3.2 Median Survival Sample SAS code:

```
** Median survival time and p-value **;
ods listing close;
ods output Quartiles=_quart (keep=trt01pn estimate lowerlimit upperlimit percent
      where=(percent eq 50))
      HomTests=pval (keep=test probchisq where=(test='Log-Rank'));
         proc lifetest data = adttee;
         time aval*cnsr(1);
         strata cohort trt01pn;
run;
ods output close;
ods listing;
```

```
 ** Hazard ratio **;
ods listing close;
ods output parameterestimates=hzdata(keep=hazardratio hrlowercl
      hruppercl);
         proc phreg data = adttee;
         class trt01pn;
         model aval*cnsr(1)=trt01pn/ties=discrete risklimit;
         hazardratio trt01pn;
run;
ods output close;
```

10.1.3.3 Kaplan-Meier Estimates/Curve Sample SAS code:

```
ods graphics on;
ods output ProductlimitEstimates = _ple
          Quartiles = _quart
          CensoredSummary = _cs
          Survivalplot = _splot
          homtests = pval (where=(test='Log-Rank'));
              **_ple: Event/Cum. Event
              _quart: estimate of the median survival time
              _cs: censored summary
              _splot: info about patient at risk
              pval: p-value based on log rank test;

proc lifetest data=adttee method=km plots=(survival(atrisk(outside(0.15))) LS);
          time aval*cnsr(1);
          strata trt01pn;
run;
ods output close;
ods graphics off;
```

11 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the eCTD. The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Table Number	Table Title	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.			
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1.1	Analysis Sets – All Screened Patients	IP	
14.1.1.2	Screen Failures – All Screened Patients	IP	
14.1.1.3	Patient Disposition – Safety Analysis Set	IP	
14.1.2	**Demographics**		
14.1.2.1	Demographics - Safety Analysis Set	IP	
14.1.3	**Baseline Characteristics**		
14.2	**Efficacy Data**		
14.2.1	**Primary Efficacy Endpoint**		
14.2.1.1	Overall Survival (OS) Data, Kaplan Meier – Full Analysis Set	STAT IP	
14.2.1.2	Progression Free Survival (PFS) Data, Kaplan Meier – Full Analysis Set	STAT IP	
14.2.1.3	Confirmed BOR and ORR Data, Descriptive Statistics – Full Analysis Set	STAT IP	
14.2.2	**Secondary Efficacy Endpoints**		
14.2.3	**Exploratory Endpoints**		
14.3	**Safety Data**		
14.3.1	**Displays of Adverse Events**		
14.3.1.1	Adverse Events, Overall Summary of TEAEs – Safety Analysis Set	IP	
14.3.1.2	Adverse Events, TEAEs by System Organ Class and Preferred Term – Safety Analysis Set	IP	

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Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.1.3	Adverse Events, TEAEs ≥ Grade 3 by System Organ Class and Preferred Term – Safety Analysis Set	IP	14.3.1.2
14.3.1.4	Adverse Events, TEAEs ≥ Grade 3 by System Organ Class and Preferred Term, Run-In Period Only – Safety Analysis Set	IP	14.3.1.2
14.3.1.5	Adverse Events, Serious TEAEs System Organ Class and Preferred Term – Safety Analysis Set	IP	14.3.1.2
14.3.1.6	Adverse Events, TEAEs Leading to Early Withdrawal of Study Drug by System Organ Class and Preferred Term – Safety Analysis Set	IP	14.3.1.2
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		
14.3.2.1	All Deaths, Listing – Safety Analysis Set	IP	
14.3.2.2	SAEs, Listing – Safety Analysis Set	IP	
14.3.2.3	TEAEs Leading to Early Withdrawal of Study Drug, Listing – Safety Analysis Set	IP	
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**		
14.3.4	**Abnormal Laboratory Values**		
14.3.4.1	Abnormal Clinical Laboratory Values, Listing – Safety Analysis Set	IP	
14.3.5	**Extent of Exposure, Dosage Information, And Compliance**		
14.3.6	**Vital Signs and Physical Examination**		
14.3.7	**Other Safety**		
14.3.8	**Concomitant Medication**		
14.4	**PK Tables**		
14.5	**PD Tables**		
14.6	**Other Data**		

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