Official Title: A Phase 1-2 Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors

NCT ID: NCT03520075

Document Date: Statistical Analysis Plan (SAP) Version 1.0: 03 April 2024

STATISTICAL ANALYSIS PLAN

VERSION: v0.1

DATE OF PLAN: 2 APR 2024

STUDY DRUG:

ASTX029

PROTOCOL NUMBER:

ASTX029-01

STUDY TITLE:

A Phase 1-2 Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects with Advanced Solid Tumors

SPONSOR:

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This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

No table of figures entries found.

VERSION HISTORY

SAP Version	Approval Date	Change	Rationale
V1.0	*2Apr2024*		*Original*

ABBREVIATIONS AND DEFINITIONS

ADaM	analysis data model
AE	adverse event
ALK	anaplastic lymphoma kinase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BDM	Biostatistics and Data Management
bpm	beats per minute
BRAF	B isoform of RAF kinase
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
C_{max}	maximum concentration
C_{min}	minimum concentration
CR	complete response
CRC	colorectal cancer
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CxDx	Cycle x Day x
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSRC	Data and Safety Review Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
ERK	extracellular signal-regulated kinase
FIH	first-in-human
HRAS	Harvey RAS
IB	Investigator Brochure
ICF	informed consent form
ID	identification
IV	intravenous
KRAS	Kirsten RAS
m	minute(s)
mm	millimeter
mmHg	millimeters of mercury
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated extracellular signal-regulated kinase
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NRAS	neuroblastoma RAS

ORR	overall response rate
OS	overall survival
PAP	Pharmacokinetic Analysis Plan
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
pRSK	phosphorylated ribosomal s6 kinase
PT	Preferred Term
QTc	QT interval corrected for heart rate
QTcF	QTc corrected for heart rate using Fridericia's formula
RAF	rapidly accelerated fibrosarcoma
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SDTM	Study Data Tabulation Model
SOC	System Organ Class
$t_{½}$	elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	maximum concentration
WHO	World Health Organization

1.0 INTRODUCTION

The purpose of this document is to provide details of the planned analyses for the Phase 1 and 2 ASTX029-01 study. The study is to assess the safety, PK, pharmacodynamics, and preliminary clinical activity of ASTX029 administered orally to subjects ≥18 years of age with advanced solid malignancies who are not candidates for approved or available therapies.

The primary objectives of the Phase 1 portion of this study are to assess safety and to identify the MTD, the RP2D, and the recommended dosing regimen of ASTX029 administered orally. The primary objective of the Phase 2 portion of this study is to assess preliminary clinical activity, as determined by objective response rate (ORR) in tumors characterized by gene aberrations in the MAPK signal pathway that may confer sensitivity to ASTX029.

The analyses specified in this document supersede the high-level analysis plan described in the protocol. Analyses and statistical reporting for ASTX029-01 subjects, with the exception of the analyses that are described in a separate Pharmacometrics Analysis Plan (PAP), will be conducted by Taiho Oncology Biostatistics department using SAS version 9.4 or higher.

This Statistical Analysis Plan (SAP) is based on the ASTX029-01 protocol amendment 5.0 (dated 14 April 2022).

Specifications for data tables, listings and figures are detailed in a separate document.

1.1 Background

Historically, medical approaches to treat advanced malignancies have typically involved surgery, radiotherapy, and/or cytotoxic chemotherapy. Advances in genomics and molecular biology have led to successful development of therapies targeting specific driver mutations in cancer cells (e.g., epidermal growth factor receptor [EGFR], B isoform of RAF kinase [BRAF], ALK, BCR-ABL, KIT) (Friedman et al 2015; Xu et al 2014). More recently, cancer immunotherapy has also been shown to significantly improve the outcomes of many cancers. However, a significant proportion of patients eventually relapse due to acquired resistance, and others present intrinsic resistance mechanisms (Farkona et al., 2016). Thus, there is an unmet need for new approaches to stop the uncontrolled growth of cancer .

1.2 Treatment Option

Targeting the MAPK pathway has been clinically validated by BRAF inhibitors (e.g., vemurafenib and dabrafenib) and MEK inhibitors (e.g., trametinib and cobimetinib) (https://www.accessdata.fda.gov/scripts/cder/daf/). These agents elicit profound antitumor responses in BRAFV600E-mutant melanoma patients, although responses are often short-lived, due to the onset of acquired drug resistance (Flaherty et al 2012; Hauschild et al 2012; Little et al 2012; Chapman et al 2011; Solit and Rosen 2011). A common feature of RAF or MEK inhibitor resistance mechanisms is the reactivation of ERK signaling, which drives proliferation and

survival of the cells, even in the presence of BRAF and MEK inhibitors (Little et al 2012; Wagle et al 2011; Nazarian et al 2010; Emery et al 2009). As ERK is the primary downstream effector of the MAPK pathway, it is hypothesized that ERK inhibitors may prove to be less susceptible to oncogenic bypass than RAF and MEK inhibitors and, therefore, have the potential to improve clinical outcomes in these patient populations (Nissan et al 2013).

Several ERK inhibitors have recently entered clinical development, although none have gained regulatory approval yet. ERK inhibitors in clinical development include GDC-0994 (Genentech; oral route), ulixertinib (BioMed Valley; oral route), LY3214996 (Eli Lilly; oral route), CC-90003 (Celgene; oral route), LTT462 (Novartis; oral route), KO-947 (Kura Oncology; intravenous [IV] route), and MK-8353 (Merck Sharp & Dohme Corp; oral route) (https://clinicaltrials.gov/). Notably, in the Phase 1 study of GDC-0994 (an ERK1/2 inhibitor), partial responses were observed in 2 subjects with BRAF mutant CRC (Varga et al abstract 2016; Varga et al presentation 2016). Responses were also observed in subjects with BRAF and NRAS mutations enrolled in a Phase 1-2 study of ulixertinib (Sullivan et al 2018; Li et al presentation 2017; Infante et al abstract 2015; Infante et al presentation 2015).

1.2.1 ASTX029

ASTX029 is a synthetic small molecule that was developed using Taiho's fragment-based drug discovery platform. Unlike most ERK inhibitors currently in the clinic, ASTX029 both prevents the phosphorylation of ERK and directly inhibits ERK kinase activity, which is expected to produce a more effective blocking of the MAPK pathway. For detail information on ASTX029, refer to the current ASTX029 Investigator Brochure (IB) Section 4.1.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

- Phase 1 (Parts A and B): To assess safety and to identify the MTD, the RP2D, and the recommended dosing regimen of ASTX029.
- Phase 2: To assess preliminary clinical activity, as determined by ORR, in tumors characterized by gene aberrations in the MAPK signal pathway that may confer sensitivity to ASTX029.

2.2 Secondary Objectives

- To determine the PK profile of ASTX029 including the food effect on PK parameters.
- To evaluate other clinical activity parameters, such as duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).
- To evaluate relevant pharmacodynamic markers and target engagement (i.e., phosphorylated ribosomal s6 kinase [pRSK] inhibition) in tumor biopsies.

2.3 Exploratory Objectives

- To identify and evaluate biomarkers of ASTX029 activity.

3.0 STUDY DESIGN

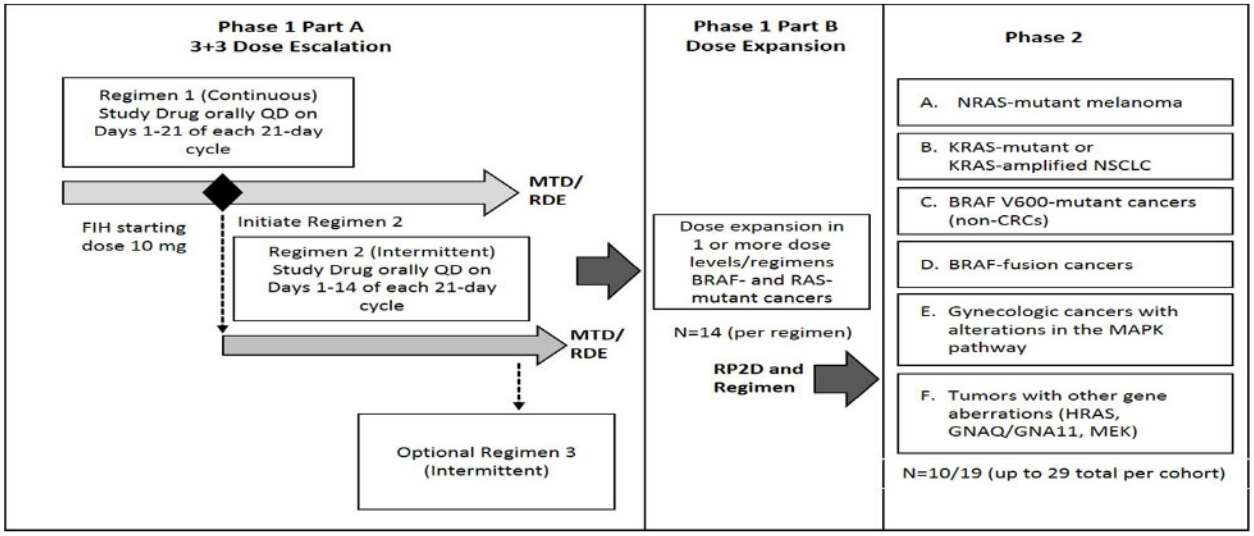
3.1 Overall Study Design

This is a first-in-human (FIH), open-label, multicenter, Phase 1-2 study to assess the safety of ASTX029, determine the MTD, RP2D, and recommended dosing regimen for ASTX029, and to obtain preliminary clinical activity, PK, and pharmacodynamic data in subjects with advanced solid tumors for whom standard life-prolonging measures or approved therapies are not available.

It is anticipated that up to 300 evaluable subjects will be enrolled in this study if the study fully enrolls both Phases 1 and 2. This includes approximately 120 subjects in Phase 1 at up to 14 study centers in the US and Europe and up to approximately 180 evaluable subjects in Phase 2 at up to 30 study centers in North America and Europe. The expected study duration is approximately 3.5 years (42 months), including approximately 36 months for recruitment and approximately 6 months for safety follow-up.

This study consists of 2 phases, as shown in the study schema below (Figure 1).

Figure 1: Study Schema



BRAF=B isoform of RAF kinase; FIH=first-in-human; MTD=maximum tolerated dose; RAS=rat sarcoma virus; QD=daily; RDE=recommended dose for expansion; RP2D=recommended Phase 2 dose.

Note: The RP2D and recommended dosing regimen will be used in Phase 2 as indicated by arrow.

The Phase 1 portion of the study consists of Parts A (Dose Escalation) and B (Dose Expansion). Part A is a dose-escalation stage to identify the MTD for up to 2 dosing regimens of ASTX029 and the recommended dose for expansion (RDE), defined as either the MTD or a dose below MTD that the Data and Safety Review Committee (DSRC) agrees shows adequate safety, PK, and/or preliminary biological or clinical activity. Subjects enrolled in Regimen 1 (continuous dosing)

receive ASTX029 orally once a day on Days 1 through 21 of each 21-day cycle. If Regimen 2 (intermittent dosing) is opened to enrollment, subjects enrolled in Regimen 2 will receive ASTX029 orally once a day on Days 1 through 14 of each 21-day cycle. Initially, subjects will be allocated to Regimen 1 (continuous dosing). The sponsor, with approval of the DSRC, will determine if Regimen 2 is to be opened for enrollment. Randomization to either Regimen 1 or Regimen 2 will begin if both regimens are open for enrollment. If the MTD is reached in 1 regimen before the other regimen, all subsequent subjects will be enrolled, without randomization, to the remaining regimen until the MTD is determined for each regimen evaluated.

The starting dose in Regimen 1 will be escalated stepwise in successive cohorts of at least 3 evaluable subjects each with additional allowed expansion to 6 subjects (3+3 study design) until the MTD is determined for the regimen. Dose levels and dosing regimens, the number of cohorts, and the number of subjects per cohort may be modified, as needed, in response to emerging data and recommendations from the DSRC.

Dose-escalation/de-escalation decisions will be based on the occurrence of dose-limiting toxicities (DLTs) during the first cycle of each dose level and the recommendations of the DSRC following review of all available safety, PK, and biomarker data from the completed first cycle of at least 3 subjects in each cohort. The DSRC RDE decision will be based on all available safety, PK, biomarkers, and preliminary activity data from all cycles (including potential for late or cumulative toxicity). The DSRC will also advise whether it is appropriate to proceed to Part B (Dose Expansion).

In Part B, one or more dose levels (and regimens) may be studied to supplement available safety, PK, and/or clinical activity data and to evaluate target engagement in fresh tumor tissue biopsies. A total of 14 evaluable subjects will be treated at each dose/regimen selected. If more than 1 dose/regimen is selected, subjects will be randomized in a 1:1 ratio. Subjects will have to meet the following molecular eligibility criteria: documented activating gene mutations in BRAF (BRAF V600 mutation or activating atypical non-V600 aberrations), Kirsten RAS (KRAS), NRAS, or Harvey RAS (HRAS). The RP2D decision by the DSRC will be based on all available PK, pharmacodynamic, safety, and preliminary activity data from all cycles (including the potential for late or cumulative toxicity). The RP2D could be the same or lower than the RDE.

The DSRC will advise when it is appropriate to proceed to Phase 2. The Phase 2 portion of the study will explore the preliminary single-agent antitumor activity of ASTX029 at the RP2D of the selected dosing regimen identified in Phase 1 Parts A and B in tumors characterized by gene aberrations in the MAPK signal pathway that may confer sensitivity to ASTX029. The Phase 2 part of the study will consist of the following 6 cohorts:

- Cohort A: NRAS-mutant melanoma.
- Cohort B: KRAS-mutant or KRAS-amplified non-small cell lung cancer (NSCLC).
- Cohort C: BRAF V600-mutant cancers (non-colorectal cancers).
- Cohort D: BRAF-fusion cancers.

- Cohort E: Gynecological cancers with alterations in the MAPK pathway.
- Cohort F: Tumors characterized by other gene aberrations that upregulate the MAPK signal pathway. In the Phase 2 part of the study, molecular eligibility will be based on the presence of documented gene aberrations in MAPK pathway.

For Phase 2, the sample size is based on a Simon's Optimal 2-stage design. Each cohort will enroll 10 subjects into the first stage of Simon's 2-stage design at the RP2D and the dosing regimen identified in Phase 1 Parts A and B. Should ≥2 first-stage subjects respond, an additional 19 subjects will be enrolled into the second stage. Therefore, up to 29 subjects will be enrolled into each cohort.

3.2 Study Endpoints

3.2.1 Primary Endpoint

- Phase 1: Incidences of DLTs and adverse events (AEs) to determine the MTD of up to 2 dosing regimens of ASTX029 and the RP2D and regimen to be taken to Phase 2.
- Phase 2: Clinical activity assessed by ORR according to RECIST v1.1 criteria.

3.2.2 Secondary Endpoints

- PK parameters of ASTX029, including area under the curve (AUC), maximum concentration (Cmax), minimum concentration (Cmin), time to reach maximum concentration (Tmax), elimination half-life ($t_{½}$), food effect on ASTX029 PK parameters, and other secondary PK parameters of ASTX029 if data permit; analysis of ASTX029 metabolites if applicable.
- Inhibition of pRSK protein in response to ASTX029 treatment in tumor biopsies.
- Progression-free Survival (PFS).
- Overall Survival (OS).
- Disease Control Rate (DCR).
- Duration of Response (DOR).

3.2.3 Exploratory Endpoints

- Suppression of mutant clones in circulating tumor DNA (ctDNA).
- Explore additional biomarkers of ASTX029 activity.

4.0 SAMPLE SIZE

The dose-escalation part of the study (Phase 1 Part A) follows a standard 3+3 study design, with a cohort size of 3 or 6 evaluable subjects. Dose escalation will continue until the MTD for each regimen evaluated is determined. Evaluable subjects for dose-escalation decisions in Part A are those who have completed the first cycle and have received at least 85% of planned doses in the first cycle of treatment (or were not able to receive at least 85% of planned doses due to safety concerns). The final sample size of part A will depend on the assessed dose levels and occurrence of dose limiting toxicities.

For Part B (of Phase 1), a sample size of 14 evaluable subjects will ensure a 90% probability of observing at least 1 adverse reaction to treatment for any adverse reaction with a ≥15% incidence. Evaluable subjects for Part B are all subjects who receive any amount of study drug.

For Phase 2, the sample size is based on a Simon's Optimal 2-stage design (Simon 1989). Each cohort will enroll 10 subjects into the first stage. Should ≥2 first-stage subjects respond, an additional 19 subjects will be enrolled into the second stage. Therefore, up to 29 subjects will be used for each treatment cohort. The sample size, (10+19), or 29, under this Simon's Optimal 2-stage design, will achieve a power of 80% to test the null hypothesis of ORR p0 ≤0.1 at a 1-sided alpha of 0.05 assuming the response rate p1 is 0.3. For Stage 2, the null hypothesis will be rejected if ≥ 6 responses are observed in a cohort of 29 subjects. For Cohort F (which will enroll patients with various tumor types and gene aberrations [Protocol Table 2]), the sponsor, with approval of the DSRC, may expand enrollment to 10 or 29 subjects for a particular molecularly defined subpopulation in which the most number of responses are observed, under the same Simon's Optimal 2-stage design as for the other cohorts for better assessment of activity in that disease subpopulation (Optional Cohort F expansion). It is expected that no more than 2 subpopulations will be expanded in this manner.

5.0 ANALYSIS SETS

5.1 All Subject Analysis Set

The 'All Subject Analysis Set' will include all screened subjects, including those who did not meet the study entry criteria and/or did not receive any study drug. This data set will only be used for disposition summaries.

5.2 Enrolled Subject Analysis Set

All subjects who sign an informed consent form (ICF) and meet all eligibility criteria as assessed by the investigator and sponsor. In addition, each subject who signs the ICF is assigned a unique identification (ID) number that reflects the study center number assigned to the investigator and the subject at that site.

5.3 Efficacy Analysis Set

The Efficacy Analysis Set will include all subjects who receive any amount of study drug. Efficacy analyses will be based on the actual treatment received on Cycle 1 Day 1, which should be the assigned cohort. The overall response rate (ORR) and DCR analysis will be based on subjects who are in the Efficacy Analysis Set and who had disease assessment at baseline and at least 1 follow-up disease assessment or subjects who died or stopped treatment before the first scheduled disease assessment due to clinical progression or toxicity.

5.4 Safety Analysis Set

The Safety Analysis Set will include data from all subjects who receive any amount of study drug. Safety analysis will be based on the actual treatment received on Cycle 1 Day 1, which should be the assigned cohort. All data will be included, and no subjects excluded because of protocol violations.

5.5 Pharmacokinetics Analysis Set

The PK Analysis Set will include all subjects who have received study drug with available plasma concentrations and PK parameters for ASTX029.

5.6 Pharmacodynamic Analysis Set

Subjects will be included in the pharmacodynamic and biomarker analyses if they have received study drug and their samples were successfully collected and analyzed.

6.0 SCHEDULE OF ANALYSES

Analysis will be conducted after all subjects have completed at least one RECIST assessment. The expected study duration is approximately 3.5 years (42 months), including approximately 36 months for recruitment and approximately 6 months for safety follow-up. The study started in Q2 2018.

7.0 STATISTICAL ANALYSIS

Unless otherwise specified, all statistical tests and confidence intervals (CIs) described in this document will be two-sided with alpha 0.05. Data summaries and listings will be generated using SAS version 9.4 or a more recent version (SAS Institute Inc., Cary, NC, USA).

The first dosing date is defined as the first date the subject received any study drug.

Analysis tables will be summarized by cohorts and all cohorts combined for phase 1 part A, phase 1 part B and phase 2 unless specified otherwise. For example,

- Phase 1A: Cohort 1, Cohort 2, …, Cohort n
- Phase 1B powder in bottle and tablets
- Phase 2: Cohort A, Cohort B, …, Cohort F
- Phase 1A, Phase 1B, and Phase 2

Tables may be combined and/or separated as allowed by number of cohorts.

The AEs will be summarized by assigned cohort at the onset of the AE (Section 7.6.2). Efficacy analyses, laboratory tests, vital signs, electrocardiogram (ECG), and Eastern Cooperative

Oncology Group (ECOG) performance status will be summarized by assigned cohort and all subjects combined (Total), unless otherwise specified.

The following will be summarized by assigned cohort and all subjects combined (Total), unless otherwise specified:

- Efficacy analyses,
- Treatment emergent adverse events (TEAEs),
- Laboratory tests,
- Vital signs,
- Electrocardiogram (ECG), and
- Eastern Cooperative Oncology Group (ECOG) performance status.

The following data listings by subject identification (ID) number (which includes the study center number) will be provided:

- All enrolled subjects
- Screen failure subjects (with reason for screen failure)
- Disposition (with reason(s) for discontinuation of treatment and withdrawal from study)
- Protocol deviations
- Demographic and baseline characteristics
- Study drug administration
- Individual efficacy data
- Subjects excluded from the efficacy analysis
- TEAEs
- Deaths (including primary cause of death)
- Serious adverse events (SAEs)
- Other significant TEAEs (including treatment discontinuation due to AEs)
- Concomitant medications

- Selected laboratory measurements

Additional data listings may be generated to support other relevant discussions in the clinical study report.

Generally, all tables/figures presented will be supported by a listing of the data summarized in table/figure.

Taiho/Biostatistics and Data Management (BDM) and Clinical Data Interchange Standards Consortium (CDISC) standards will be followed.

7.1 Subject Disposition

Subject disposition including number of subjects enrolled, treated, and discontinued from study drug by reason, as well as reasons for withdrawal from study (ie, death, complete consent withdrawal, or lost to follow-up) and subjects ongoing at data-cut will be summarized using frequencies and percentages based on information collected on the study electronic case report form (eCRF). Subjects in the All-Subject Analysis Set (Section **Error! Reference source not found.**) will be included in the disposition analysis.

7.2 Demographic and Other Baseline Characteristics

Subject demographic and baseline characteristics will be summarized by mean, standard deviation, median, minimum, and maximum for continuous variables; and by counts and percentages for categorical variables. For the Safety Analysis Set (section 5.4), all subjects who received any amount of study drug will be included in the analysis of demographic and baseline characteristics.

Summaries will be provided separately for each regimen in Phase 1 Part A, for the RDE cohort(s) in Phase 1 Part B, and for each cohort in Phase 2.

The demographic variables include age, age category ((<18, 18 <65, 65 <75, ≥75 years), sex, ethnicity, and race. Baseline characteristics may include height, weight, ECOG performance status, prior anti-cancer therapy, and best responses to prior therapy.

Baseline is defined as the last value(s) available before or on the 1st dosing date unless otherwise specified.

7.3 Pharmacokinetics Analyses

The PK Analysis Set (Section 5.5) will be used for PK analyses.

The PK parameters will be derived for each subject using a non-compartmental approach. The food effect on ASTX029 PK parameters will also be evaluated. Descriptive statistics including mean, standard deviation, median, and range for PK parameters for ASTX029 will be summarized.

Detailed and additional PK analyses are described in a separate PK analysis plan.

7.4 Pharmacodynamic Analyses

Assessment of target engagement and biomarker analyses will be performed in blood and tumor tissue biopsies. Secondary endpoint biomarker investigation may include the following:

• Demonstration of target engagement in fresh tumor tissue biopsies (when available) (eg, pRSK and pERK inhibition following ASTX029 treatment).

This analysis of parameters/biomarkers may include descriptive summaries such as mean, standard deviation, median, minimum, and maximum for continuous variables and counts and percentages for categorical variables.

This pharmacodynamic data will be captured as Study Data Tabulation Model (SDTM) data, and listings provided of any analysis that is done.

Exploratory biomarker investigations will include the following:

• Evaluation of cancer cell proliferation and induction of apoptosis in fresh tumor tissue biopsies (when available).

• Suppression of mutant clones in ctDNA.

• Identification of potential biomarkers of ASTX029 activity (DNA, RNA, or protein) in blood and tumor tissue biopsies (archival and fresh biopsies, when available).

The exploratory pharmacodynamic data will not be analysed, listed, or captured as Study Data Tabulation Model (SDTM) data.

7.5 Efficacy Variables and Analyses

Efficacy analyses will be based on the Efficacy Analysis Set (Section 5.3). Efficacy variables will be summarized using descriptive statistics. No comparison between treatment sequences will be performed.

Anti-tumor response is based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer et al 2009). The details of RECIST v1.1 evaluation of responses can be found in protocol Appendix 3. The principal investigator assessment of RECIST v1.1 response will be analyzed.

Table 1 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline. Details of complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD) assessments for Target and Nontarget Lesions are provided in Appendix 3 of the protocol.

Table 1: Summary of Overall Assessment of Response

Time Point Response: Subjects with Target (±Nontarget) Disease			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Assessment of Response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, NE=inevaluable, PD=progressive disease, PR=partial response; SD=stable disease.

7.5.1 Overall Response and Disease Control Rate

The ORR will be calculated as the number of evaluable subjects whose best response is CR or PR, divided by the total number of subjects evaluable for ORR analysis (Section 5.3). The DCR will be calculated as the number of subjects whose best response is CR, PR, or SD, divided by the total number of subjects evaluable for DCR analysis (Section 5.3). The 90% Clopper-Pearson CIs for the ORR and DCR will be provided.

Best response for a subject is defined as the best overall response from all post baseline assessments of a subject in the study. When SD is believed to be the best response, it must also meet the protocol-specified minimum time from baseline (6 weeks). If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments.

7.5.2 Duration of Response

Duration of response will be calculated for all responders from the date of the first documentation of CR or PR to the date of progress or death, whichever occurs first. Duration of SD will be calculated for subjects whose best response is CR, PR, or SD from the day study drug was first taken to the date of disease progression or death, whichever occurs earlier, or the last disease assessment for subjects without disease progression or death.

Duration of response and duration of SD will not be estimated for subjects who leave the study prior to a first assessment of response nor for subjects whose best response is progressive disease.

Duration of response and duration of SD will be analyzed using a K-M method, with the duration being censored at the time of the date of study termination for subjects without a relapse or disease progression. Duration of response and duration of SD will be summarized.

7.5.3 Survival

The OS is defined as the number of days from the day study drug was first taken to the date of death (regardless of cause). Subjects without a documented death date will be censored on the last date they were known to be alive. The OS will be presented using a Kaplan Meier estimate. The 95% CI for median OS will be provided using the Kaplan-Meier method with the log-log transformation. All subjects in the Efficacy Analysis Set (Section 5.3) will be included in the OS analysis. The OS rate at 3, 6, 9 and 12 months (and in subsequent 6-month increments if there are participants still at risk) will be estimated with corresponding two-sided 95% CIs.

Frequency (number and percentage) of participants with death events and censoring reasons will be presented with the overall event and censor rates. The event and censoring reasons are as follows:

- Death
- Ongoing and no death
- Withdrawal of consent
- Lost to follow-up.

The OS time or censoring time and the reasons for censoring will also be presented in a listing

The PFS is defined as the number of days from the start of the study drug to disease progression or death, whichever occurs first. The PFS will be analyzed using a Kaplan-Meier method, with PFS time being censored on the date of the last disease assessment. The 95% CI for median PFS will be provided using the Kaplan-Meier method with the log-log transformation. All subjects in the Efficacy Analysis Set (Section 5.3) will be included in the PFS analysis.

Progression of disease (PD) is included as an overall response in Table 1 above, and combines evaluation target, non-target, and new lesions. Target lesion response of PD is at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). Non-target lesion response of PD is unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression of disease. Additional details can be found in Appendix 3 of the protocol, which is based on RECIST v1.1 (Eisenhauer et al 2009).

7.6 Safety Variables and Analyses

Safety Analysis will be performed using the Safety Analysis Set (Section **Error! Reference source not found.**). Safety is assessed by subject-reported and investigator-observed AEs, along with physical examinations, clinical laboratory tests (hematology, coagulation, chemistries, and urinalysis), vital signs, concomitant medications, ECOG performance status, and ECGs. Exposure to study drug, TEAEs, deaths, and causes of deaths will be tabulated.

7.6.1 Study Treatment and Exposure

Study drug administration will be summarized by numbers of treatment cycles received, delayed and dose-reduced cycles, as well as duration of exposure (in months). These measures of exposure will be based on dose administrations, dose reductions, dose interruptions and dose delays identified by the investigator and collected on the study drug administration eCRFs. Duration of exposure, in months, is defined as the last treatment date minus the first date of treatment + 1 divided by 30.4375.

Summaries of delayed, dose interrupted, and dose reduced cycles will be provided at both subject and cycle levels.

Dose intensity, presented as the incidence of subjects receiving <80% of their intended dose, will be summarized by cycle. Dose intensity will be calculated as the actual total dose divided by planned total dose for each treatment cycle.

Both completed or partially completed dose cycles are counted in these summaries.

7.6.2 Adverse Events

Adverse events reported by study subjects or observed by investigators will be mapped to the appropriate System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (protocol Appendix 2).

TEAEs are defined as events that first occurred or worsened on or after the date of the first dose of study treatment until 30 days after the last dose of study treatment or until the start of a post-treatment alternative anti-cancer treatment, whichever occurs first, with the following exceptions: events that occurred after 30 days beyond the last dose of study treatment or the start of a post-treatment alternative anti-cancer treatment will also be considered treatment-emergent if the events are both serious and related to the study treatment. For the purpose of determining whether an AE is a TEAE, incomplete AE start and stop dates will be imputed conservatively following the data programming conventions as detailed in the Taiho Data Programming Standards.

All AE data collected in the study database with an AE start date on or before the data cutoff date will be included in the data listings, including those that are not treatment emergent. Only TEAEs will be included in the AE summary tables.

An overall safety summary table containing counts and percentages of subjects with any AE, any AE Grade ≥3, AE leading to treatment discontinuation, any SAE, and subcategories of SAEs (fatal SAEs) will be produced.

Related events are those that the Investigator considered to be related to study treatment as described in the study protocol. All summaries of AEs will be summarized by cohorts and all cohorts combined within regimen within parts (A&B), and within Phase (I&II). Tables may be combined when space allows.

For example,

- Phase 1A: Cohort 1, Cohort 2, …, Cohort n
- Phase 1B powder in bottle and tablets
- Phase 2: Cohort A, Cohort B, …, Cohort F
- Phase 1A, Phase 1B, and Phase 2

The number and percentage of subjects experiencing AEs will be summarized by MedDRA SOCs (sorted alphabetically) with PTs sorted alphabetically within each SOC. The number and percentage of subjects experiencing AEs will also be summarized by PT and sorted by event frequency of the Total column. Related AEs, SAEs, and related SAEs will be summarized similarly. A summary of AEs with fatal outcomes, AEs resulting in permanent treatment discontinuation, and AEs resulting in treatment delay, interruption or dose reduction will also be provided. Additional summaries will be generated by SOC, PT and CTCAE grade. For these summaries, if the occurrence of a particular AE for a given subject is reported more than once, the event is only counted once with its worst CTCAE grade.

7.6.3 Dose Limiting Toxicities

DLTs are AEs that occur during the first cycle of treatment and meet 1 or more of the criteria outlined in Section 7.4 of the protocol. The AEs meeting 1 or more of the criteria are indicated on the AE eCRF. The number and percentage of subjects who have DLTs will be summarized by cohort and treatment arm in Phase 1.

7.6.4 All-cause Mortality

The percentage of 30- and 60-day all-cause mortality will be calculated based on each subject's date of death relative to C1D1 (ie, date of death minus date of C1D1).

7.6.5 Concomitant Medications

Concomitant medications are medications taken with a start date on or after the date of the first dose of study drug or those with a start date before the start of the administration of study drug and a stop date on or after the start of the administration of study drug. Medications taken beyond 30 days from the last dose of study drug or after the start of a post-treatment alternative anti-cancer treatment are not considered concomitant medications, unless they are used for treating a related SAE. For the purpose of inclusion in the concomitant medication tables, incomplete medication start and stop dates will be imputed conservatively following the data programming conventions as detailed in the Taiho Data Programming Standards.

Concomitant medication will be coded by the latest version of the World Health Organization (WHO) Drug Dictionary before the data download and summarized by Anatomical Therapeutic Chemical (ATC) level 2 and drug name, sorted alphabetically, using counts and percentages.

7.6.6 Laboratory Tests

Shift tables will display (1) shift from baseline grade to the worst grade during the study, and (2) shift from baseline grade to the last grade at the end of study.

Laboratory values recorded as an interval such as "≥x", "<x", or "2+" will be handled, if necessary for calculation purposes, following the data programming standards as detailed in the ADaM data reviewer guide.

7.6.7 Vital Signs

Vital signs will be summarized by visit and treatment group using proportion of subjects with each vital sign being too high or too low according to conventionally accepted vital sign normal ranges as follows:

- Pulse rate 110 bpm or greater.
- Pulse rate 50 bpm or less.
- Diastolic blood pressure 110 mmHg or greater.
- Diastolic blood pressure 55 mmHg or less.
- Systolic blood pressure 180 mmHg or greater.
- Systolic blood pressure 80 mmHg or less.
- Respiration rate 20 breaths/min or greater.
- Body temperature 39°C or greater.

7.6.8 Electrocardiogram (ECG)

The 12-lead ECGs will be performed at screening and predose and 2 hours (±30 minutes) postdose on C1D1 and C2D1; they will be performed predose at all other time points on the dosing days and at the Treatment Termination visit as indicated. For each ECG parameter (heart rate, RR interval, PR interval, QRS duration, QT interval, and QT corrected for heart rate using Fridericia's formula (QTcF)), the mean of the available triplicate ECG values will be calculated.

ECG findings will be listed by subject and, if data permit, may be summarized as follows:

- The values and respective changes from baseline may be summarized by visit. .
- Summaries may also be provided of the maximum post-baseline absolute QTcF and the maximum post-baseline increase in QTcF.

7.6.9 ECOG Performance Status

Shift tables for ECOG from baseline to the worst grade, and from the baseline to the last available grade will be provided.

7.6.10 Echocardiogram / Multigated Acquisition (ECHO/MUGA)

Data will be preserved in a Study Data Tabulation Model (SDTM) dataset. No particular analysis will be conducted.

7.6.11 Physical Examination

Physical examination data will be preserved in a SDTM dataset. No particular analysis will be conducted.

7.7 Handling of Missing Data and Other Data Anomalies

No missing data imputations are planned for the study, except for selecting treatment emergent AEs as specified in Section 7.6.2, and for inclusion in concomitant medication analysis as specified in Section 7.6.5. Subjects lost to follow-up will be included in statistical analyses to the point of the data cut-off date.

7.8 Handling of Protocol Deviations

Protocol deviations will be tabulated by category (major/minor) and listed by subject.

Major deviations are those that might significantly affect completeness accuracy and or readability of study data or that may significantly affect a subject right, safety or wellbeing. Minor deviations are any changes/alterations that have not or do not have the potential to: 1) adversely affect the

rights, welfare, or safety of the subjects, 2) adversely affect the integrity of the research data, or 3) affect the subject's willingness to participate in the study.

7.9 Changes from Protocol

'Overall Response' in Table 13 of the protocol (amendment 5) has been changed to 'Overall Assessment of Response' in Table 1 of this SAP.

The protocol planned for possible Regimen 1 (continuous), Regimen 2 (intermittent), and optional Regimen 3 (intermittent). However, only Regimen 1 (continuous) was opened to enrollment. The analyses in Section **Error! Reference source not found.** will describe the analysis to be conducted using the data available at completion of Phase 1.

In section 5.2, the Enrolled Subject Analysis Set has been added.

8.0 SUPPORTING DOCUMENTATION

8.1 Appendix 1: Absolute Neutrophil Count (ANC) Derivation

When a hematology differential is completed, the absolute neutrophil count (ANC) will be derived as follows:

- If the differential is reported in absolute values, ANC is equal to the reported "Neutrophils (absolute)" value with the associated units for that value.
- If the differential is reported in percentages, and the segmented neutrophils and band neutrophils are NOT reported separately, ANC is equal to the reported "Neutrophils %" value multiplied by the WBC value and divided by 100. The corresponding units will be the same as the WBC units.

If the differential is reported in percentages, and the segmented neutrophils and band neutrophils ARE reported separately, ANC is equal to the sum of the reported "Segmented Neutrophils %" and "Band Neutrophils %", multiplied by the WBC value and divided by 100. The corresponding units will be the same as the WBC units.

8.2 Appendix 3: Summary of Changes

Rationale for Version x.x

Summary of Changes: NA

9.0 REFERENCES

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[redacted]	Biostatistics Approval	02-Apr-2024 17:47:08