STATISTICAL ANALYSIS PLAN

A Phase 2, Subprotocol of DAY101 Monotherapy for Patients with Recurrent, Progressive, or Refractory Solid Tumors with MAPK Pathway Aberrations

Protocol Number:	DAY101-002
Sponsor:	Day One Biopharmaceuticals, Inc. (Day One) 2000 Sierra Point Parkway Suite 501 Brisbane, CA 94005
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LIST OF ABBREVIATIONS

Abbreviation	Full Term
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Class
BRAF	V-Raf Murine Sarcoma Viral Oncogene Homolog B
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CPK	Creatinine Phosphokinase
CR	Complete Response
CRAF	V-Raf Murine Sarcoma Viral Oncogene Homolog C
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria For Adverse Events
ctDNA	Circulating Tumor DNA
DOR	Duration Of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End Of Treatment
INR	International Normalized Ratio
LTFU	Long-Term Follow-Up
LVEF	Left Ventricular Ejection Fraction
MAPK	Mitogen-Activated Protein Kinase
MEdDRA	Medical Dictionary For Regulatory Activities
MRI	Magnetic Resonance Imaging
MUGA	Multigated Acquisition Scan
MUGA	Multiple-Gated Acquisition
NCI	National Cancer Institute

Abbreviation	Full Term
ORR	Overall Response Rate
OS	Overall Survival
PD	Pharmacodynamic(S)
PFS	Progression-Free Survival
PK	Pharmacokinetic(S)
PR	Partial Response
PR	Pulse Rate
PT	Preferred Term
PTT	Activated Prothrombin Time
RAF	Rapidly Accelerated Fibrosarcoma
RANO	Response Assessment In Neuro-Oncology
RECIST	Response Evaluation Criteria In Solid Tumors
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
T3	Triiodothyronine
T4	Tetraiodothyronine
TEAE	Treatment-Emergent Adverse Event
TRAE	Treatment-Related Treatment-Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
TTR	Time To Response
WHO	World Health Organization

1. INTRODUCTION

DAY101-102a is a Phase 2, multi-center, open-label sub-study of tovorafenib (DAY101) as a monotherapy in patients ≥12 years of age with recurrent or progressive melanoma or solid tumors with activating BRAF fusion or CRAF/RAF1 fusions or amplification.

The statistical analysis plan (SAP) contains a detailed description of the data presentations and statistical analyses that will be included in the clinical study report for Protocol DAY101-102a. The statistical methods and analyses described here are based on those presented in the Study DAY101-102 Master Protocol Amendment 2 (dated 13 October 2022) and Study DAY101-102a Monotherapy Subprotocol Amendment 2 (dated 19 October 2022).

2. STUDY SUMMARY

2.1. Study Objectives

The primary objective is:

- To evaluate the efficacy of tovorafenib by RECIST version 1.1 or an alternative appropriate tumor response criteria.

The secondary objectives are:

- To assess the safety and tolerability of tovorafenib.
- To assess additional efficacy parameters of tovorafenib.
- To characterize the tumor responses observed with tovorafenib.
- To characterize the pharmacodynamic (PD) effects of tovorafenib.

The exploratory objectives are:

- To evaluate the genomic profile of archival tumor or fresh tumor biopsies from patients who will be treated with tovorafenib.
- To characterize pathway modulation and/or genomic alterations from tumor biopsies and/or ctDNA.
- [redacted]

2.2. Study Design

This is an open-label, multicenter, Phase 2 sub-study to evaluate tovorafenib as a monotherapy in patients ≥12 years of age with recurrent or progressive melanoma or solid tumors with activating BRAF fusion or CRAF/RAF1 fusions or amplification. Molecular assays performed at certified laboratories will be used to identify patients with these alterations. Patients will be enrolled in two separate cohorts: melanoma cohort or tissue agnostic cohort.

Adult patients (≥ 18 years) will receive tovorafenib at 600 mg orally once weekly. For patients ages 12 to <18 years, tovorafenib will be administered at a dose of 420 mg/m^2 (not to exceed 600 mg) orally once weekly. Cycles will repeat every 28 days until radiographic evidence of disease progression, unacceptable toxicity, patient withdrawal of consent, or death.

Patients will undergo radiographic evaluation of their disease at baseline, and then at the end of [redacted] for 1 year, and then [redacted] thereafter.

A response assessment will be performed according to RECIST version 1.1 for solid tumors or an alternative criteria may be used in specific disease settings, such as glioma, where response assessment will be evaluated by Response Assessment in Neuro-Oncology (RANO) criteria.

Patients who have radiographic evidence of disease progression may be allowed to continue on tovorafenib if, in the opinion of the Investigator, the patient is deriving clinical benefit from continuing study treatment, and continuation of treatment is approved by the Sponsor.

2.2.1. End of Study and Length of Study

The end of study is expected to occur 25 months after the last patient is enrolled. In addition, the Sponsor may decide to terminate this study at any time.

The total length of this study, from screening of the first patient to the end of study, is expected to be approximately 4 years.

On 03NOV2023, the sponsor announced the early termination of this study due to a change in clinical development priorities. As a result, all patients who have not ended the study will end study after being followed for at least 6 months after the first dose of the study drug. The originally planned interim analysis and primary analysis will not be performed. Instead, the final analysis will be conducted after all patients have ended the study and the data have been cleaned and finalized.

2.2.2. Sample Size and Power

The number of patients is determined by using Simon's 2-stage design (Simon 1989).

Patients are considered efficacy-evaluable if they received at least 1 dose of study drug and have measurable disease by investigator assessment at baseline. Efficacy-evaluable patients who don't have post-baseline disease assessment will be considered as non-responders.

Sample size determination for each cohort is specified in Table 1.

Table 1: Sample Size Determination

	Null/Alternative Hypotheses	Study Power	Study alpha (1-sided)	Stage 1 n (minimum number of responses to move to Stage 2)	Total Study N (minimum number of responses for trial success)
Melanoma cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tissue agnostic cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Enrollment per cohort may be terminated early independently of each other. No adjustment for multiple hypothesis testing will be made if both cohorts complete enrollment.

2.3. Planned Analyses

2.3.1. Interim Analysis

An informal interim analysis of melanoma and tissue agnostic cohort may occur when all stage 1 patients in each cohort have been followed for a minimum of approximately 6 months, respectively.

Once outstanding data queries have been resolved, the database will be locked, and the informal interim analysis of the study will be performed.

As indicated in Section 2.2.1, this interim analysis will not occur due to early study termination.

2.3.2. Primary Analysis

The primary analysis for melanoma and tissue agnostic cohorts will occur when all stage 1 and 2 patients (as applicable) enrolled in each cohort have been followed for a minimum of approximately 6 months, respectively. Once outstanding data queries have been resolved, the database will be locked, and the primary analysis of the study will be performed.

As indicated in Section 2.2.1, this primary analysis will not occur due to early study termination.

2.3.3. Final Analysis

Because of the early study termination, all patients will end study after being followed for at least 6 months after the first dose of study drug. At the end of the study, when the last visit occurs for the last patient enrolled, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the final analysis of the data will be performed. Once outstanding data queries have been resolved, the database will be locked, and the final analysis of the study will be performed.

2.3.4. Independent Data Monitoring

An Independent Data Monitoring Committee (IDMC) has been assembled under a dedicated charter specifically developed for safety oversight of DAY101-102 studies. The detailed roles and responsibilities of the IDMC and the scope of analysis to be provided to the IDMC are

provided in a mutually agreed upon charter, which defines the IDMC membership, meeting logistics, and meeting frequency.

IDMC safety data review meetings will occur approximately every 3 months as per protocol. After the first year of review, the IDMC may recommend a more appropriate meeting frequency based on the enrollment. The specific frequency of these reviews will depend upon the rate at which the trial is enrolled, the nature of any emerging safety signals, and monitoring recommendations from the IDMC. At each review, all available safety data will be summarized and evaluated. The IDMC provides advice to the Sponsor as outlined in the IDMC charter.

2.3.5. Randomization and Blinding Procedures

There is no randomization in this study. Patients will be enrolled into either a melanoma cohort or a "tissue-agnostic" cohort.

2.3.6. Efficacy Assessments

Tumors will be assessed by radiographic tumor measurements using CT and/or MRI. Tumor response disease assessments will be conducted in accordance with Table 2: Schedule of Events. The primary method for tumor response disease assessments will be by RECIST version 1.1. The alternative criteria of assessment that may be used will be RANO (Wen et al. 2017). Regardless of study treatment discontinuations, tumor assessment will progress accordingly as if on study treatment and these patients will be requested to return to site for continued monitoring and assessment.

The overall tumor burden will be estimated at baseline and subsequent measurements. Measurability of a tumor lesion will be evaluated by contrast-enhancing CT and/or MRI, and the presence of at least one measurable lesion will be characterized as measurable disease.

Additionally, date of death or last follow-up will be recorded for each patient.

2.3.7. Safety Assessments

Safety assessments include clinical laboratory tests, vital signs, physical examinations, ophthalmologic exam, visual acuity, clinical adverse events, 12-lead resting ECG (performed in triplicate), and ECHO/MUGA. These assessments will be conducted according to Table 2: Schedule of Events.

Clinical laboratory tests include:

- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils [count and percentage], lymphocytes, monocytes, eosinophils, basophils), and platelet count
- Chemistry: alkaline phosphatase, albumin, ALT, AST, CPK, BUN, creatinine, creatinine clearance, glucose, lactate dehydrogenase, total and direct bilirubin, total protein, sodium, serum calcium, phosphate, magnesium, and potassium.
- Coagulation: Prothrombin Time (PT)/International Normalized Ratio (INR), and activated prothrombin time (PTT).

- Thyroid Function Tests: thyroid stimulating hormone (TSH), and free tetraiodothyronine (free T4), and reflexive triiodothyronine (T3) may be obtained.
- Urine or Serum pregnancy test.

Vital sign measurements include:

- Body temperature
- Heart rate
- Respiratory rate
- Systolic and diastolic blood pressure
- Oxygen saturation

Physical examinations include a review of systems such as extremities, genitourinary, head/ears/eyes/nose/throat, lymph nodes, musculoskeletal, pulmonary, and skin. Any symptoms related to skin discomfort, visual disturbance and cardiopulmonary will also be assessed.

The investigator will evaluate any laboratory abnormalities or other safety assessments for clinical significance, and clinically significant abnormalities will be recorded as adverse events (AEs). Abnormal laboratory findings that result in new or worsening clinical sequelae, require therapy, or adjustment in current therapy will be considered AEs and analyzed according to NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

2.3.8. Other Assessments

- Demographics,
- Medical history,
- Eastern Cooperative Oncology Group Status/Lansky Performance Status,
- Height and weight, Bone age (patients aged 18 years or less),
- Assessment of Change in Pubertal Development (Tanner Stage) (patients < 18 years of age),
- Visual symptom assessment,
- Dermatologic Examination,
- Neurologic Examination,

In addition, archival and fresh tumor samples, ctDNA, plasma concentrations of tovorafenib for pharmacokinetic assessments, assay tumor biopsies for pharmacodynamic assessments, and concomitant medication use will be collected in accordance with Table 2: Schedule of Events.

Table 2: Schedule of Events

Assessment	[redacted]
Informed consent/ assent[b]	
Demographics	
Medical History	
ECOG or Lansky (for patients <16 years of age)	
Physical examination[c]	
Neurologic Examination[d]	
Dermatologic Examination[d]	
Bone Age[e]	
Tanner Staging[f]	
Vital signs[g]	
12-lead ECG in triplicate[g]	
Hematology[h]	
Chemistry[h]	
Creatine phosphokinase[h]	
Coagulation Panel (APTT/INR)[i]	
Thyroid function test[i]	
HBcAb, HBsAg, HCV RNA[j]	
HIV-1 Ab, HIV-2 Ab, HIV viral load and CD4+ T cell count[j]	
Echocardiogram/MUGA[k]	
Ophthalmologic exam[l]	
Visual symptom assessment[m]	
Pregnancy test[n]	
Adverse events[o]	

Assessment	[redacted]
Concomitant medication[p]	
Tumor assessment CT/MRI[q]	
Archival tumor tissue samples[r]	
Freshly acquired tumor tissue sample (PD analysis) [s,t]	
PK Sample[u, v]	
ctDNA[v]	
Additional anticancer treatment and survival status[w]	
Tovorafenib dosing[x]	
Tovorafenib Drug Dosing Diary[y]	
Tovorafenib drug Dispensation/Return[z]	

[a] Results of screening assessments must be reviewed by Investigator before patient enrollment to confirm that the patient meets the eligibility criteria.
[b] Informed consent may be obtained greater than [redacted] but must be provided before any study-specific procedures are performed; however, evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by site IRB/IEC policies.
Assessments will be performed at the end of [redacted]. Assessments are to be performed on or up to 7 days before the next cycle. For CT/MRI, assessments are to be performed per the protocol-defined schedule regardless of whether study treatment is discontinued. To ensure image consistency, the same imagine modalities and acquisition protocols used at Screening are to be used for subsequent tumor assessments.
[c] A complete physical examination, including weight, height, and vital signs will be performed [redacted] for all subjects. At subsequent physical exams only patients ages 12 to <18 should have height and weight collected. The physical exams will take place prior to the start of dosing of each [redacted]; otherwise, a symptom-directed physical examination will be done.
[d] All patients: A baseline complete neurologic examination should be performed by the Investigator and/or a neurologist. Symptom directed neurologic examinations will be completed at subsequent visits as indicated. A baseline complete dermatologic examination should be performed by the Investigator and/or a dermatologist. Symptom directed dermatologic examinations will be completed at subsequent visits as indicated. Tissue Agnostic Cohort: Patients with CNS tumors will have complete neurologic examinations performed at baseline and at subsequent visits as indicated.
[e] All patients aged 18 years or less should have an assessment of bone age at baseline via bone age radiograph of the left wrist. For patients aged 12-18 years of age without epiphyseal closure at baseline, bone age via radiograph should be assessed [redacted] thereafter.
[f] For patients 12 to < 18 years of age, pubertal stage will be measured [redacted] thereafter. For female patients, age at menarche will be recorded. Assessments will occur while on active treatment through sexual maturity. Refer to Study Protocol DAY101-102 (Master Protocol Section 6.9) for Tanner Staging details.
[g] Vitals performed on days where pharmacokinetic (PK) collection occurs should be performed prior to collection. ECGs should be collected immediately before PK sample collections on days/timepoints when PK sampling occurs (within 15 minutes prior to the PK collection). Patients will rest at least 5 minutes prior to obtaining ECGs.
[h] Assessment will be performed at [redacted]
[i] Assessment will be performed at [redacted] and as clinically indicated.

3. STATISTICAL METHODS

3.1. General Methods

3.1.1. Computing Environment

All statistical analyses will be performed using SAS® Version 9.4 or higher in a secure and validated environment.

3.1.2. Reporting of Numerical Values

Relevant descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated for continuous variables. Confidence intervals (CIs) will be provided where appropriate.

Frequencies and percentages will be presented for categorical and ordinal variables, with the frequencies reported as integers and percentages reported with one decimal place. Unless otherwise specified, the percentages will be calculated based on the total number of patients included for the analysis group. Frequencies and percentages for patients with missing data may be presented.

Means, medians, and confidence intervals will be reported to one decimal place more than the data reported on the case report form (CRF) or by the laboratory/vendor. Standard deviations will be reported to two decimal places more than the data.

A month is operationally defined to be 30.4375 days. Six months is operationally defined to be 182.625 days. One year is defined to be 365.25 days.

3.1.3. Baseline Value and Change from Baseline

Baseline value will be defined as the most recent non-missing value obtained prior to administration of first dose of study treatment. Change from baseline will be calculated by subtracting the baseline value from the relevant post-baseline assessment for each patient (i.e., post-baseline – baseline).

3.1.4. Handling of Missing/Incomplete Values

Unless otherwise explicitly specified, missing data will not be imputed; observed values will be used in the analyses.

3.1.5. Handling of Repeated Assessments

If multiple results are available for a post-dose assessment at the same scheduled time point, then the worst observation (eg, highest CTCAE grade or further away from the normal range for laboratory results, the highest value for vital signs) will be used in all descriptive summaries. All results will be displayed in patient data listings, and abnormal values will be flagged, where applicable.

3.1.6. Handling of Missing/Incomplete Date/Time

All analyses of AEs will be based on the principle of treatment emergence. Treatment emergent adverse events (TEAEs) are defined as new or worsening adverse events occurring on or after the first administration of study treatment until 30 days after the last dose of study treatment or before the start of subsequent therapy, whichever comes first. For missing or incomplete AE start dates, the following criteria will be used to determine whether an AE is treatment emergent:

Missing AE start day:

- If the partial date contains a different month or year from the date of first study dose, then impute it as the first day of the month.
- If it contains the same month and year as the date of first dose, then impute it as date of first dose.

Missing AE start day and month:

- If the partial date contains a different year from the date of first dose, then impute the missing day and month as Jan 01.
- If it contains the same year as the date of first dose, then impute the missing day and month as day and month of first dose.

Completely missing AE date:

- Missing date will not be imputed and AE is considered treatment emergent.

A medication will be considered concomitant if it is taken on or after the date of first dose of study treatment. In order to determine whether a medication with an incomplete or missing start or end date is concomitant, the following criteria will be used:

- If the start date of a medication is on or after the first dose date and the stop date of the medication is missing, that medication is considered concomitant.
- If the start date of a medication is missing and the stop date of that medication falls on or after the first dose date, that medication will be considered concomitant.
- If the start date of a medication is prior to the first dose date and the stop date of the medication is missing, that medication is considered not concomitant.
- If the start date of a medication is missing and the stop date of the medication is prior to the first dose date, that medication is considered not concomitant.
- If both the start and stop dates of a particular medication are missing, that medication will be considered not concomitant.

3.1.7. Visit Windows

3.1.7.1. Definition of Study Day

Study day is the day relative to the first dose of study drug administration. It will be calculated from the date of first dose of study drug administration and derived as follows:

- For days on or after the first dose date, assessment date – first dose date + 1

- For days prior to the first dose date, assessment date – first dose date

Therefore, study day 1 is the day of the first dose of study drug administration.

3.1.7.2. Analysis Visit Windows

No analysis visit windows will be identified for the safety summaries. Visit-based data summaries will be based on the protocol scheduled visits.

If more than one assessment is available for a given post-baseline visit, the worst observation will be selected for visit-based summaries.

Any data relating to unscheduled visits will not be assigned to a particular visit or time point. However, the following exceptions will be made:

- Unscheduled visit prior to first dose of study drug may be included in the calculation of baseline value if applicable.
- Unscheduled visits after the first dose of study drug will be considered in summaries for the extreme post-baseline value.

3.2. Analysis Sets and Subgroups

3.2.1. Efficacy Analysis Set

All patients who receive at least one dose of tovorafenib and have measurable disease as determined by the Investigator at baseline will be considered evaluable for efficacy and included in the Efficacy Analysis Set. Efficacy-evaluable patients who don't have any post-baseline disease assessment will be considered as non-responders.

Patients in the Efficacy Analysis Set who have a best overall confirmed response of CR or PR will be evaluable for duration of response (DOR) and time to response (TTR).

3.2.2. Safety Analysis Set

All patients enrolled in the study who receive at least one dose of tovorafenib will be included in the Safety Analysis Set.

3.2.3. Pharmacokinetic Analysis Set

The pharmacokinetic (PK) analysis set includes all patients enrolled on this study who have at least one documented tovorafenib administration and at least one reportable PK concentration data.

3.2.4. Subgroup Analyses

Due to the small sample size, subgroup analyses of key efficacy endpoints will only be performed for the following baseline variables:

- Sex (Female, Male)
- CNS tumor (Yes, No; tissue agnostic cohort)

3.3. Analysis Variables

3.3.1. Primary Efficacy Variable

3.3.1.1. Overall Response Rate

The primary efficacy variable is overall response rate (ORR) defined as the proportion of patients with the best overall confirmed response of complete response (CR) or partial response (PR) according to the appropriate response assessment criteria for the disease setting as assessed by the Investigator.

Complete or partial responses will be recognized if the criteria for each are met at a subsequent scan, a minimum of 4 weeks later.

Guidance on the determination of best overall confirmed response by RECIST 1.1 and RANO response criteria are provided in Section 6.1 and 6.2 of the Appendix.

3.3.2. Secondary Efficacy Variables

3.3.2.1. Duration of Response

Duration of response (DOR) is defined as the interval from the date of the first documentation of tumor response (CR or PR) that was subsequently confirmed by investigator assessment to the date of first occurrence of radiographic disease progression based on RECIST 1.1 or RANO criteria or death due to any cause, whichever occurs earlier. If a patient does not experience progression or death by the data cutoff date, then the patient will be censored at the date of the last evaluable tumor assessment.

3.3.2.2. Time to Response

Time to Response (TTR) is defined in patients with best overall response of CR or PR as determined by Investigator. It is the interval from the date of the first dose to date of first documentation of tumor response (CR or PR) that was subsequently confirmed by investigator assessment.

3.3.2.3. Progression Free Survival

PFS is defined as the interval from the date of the first dose to the first occurrence of radiographic disease progression based on RECIST 1.1 or RANO criteria or death due to any cause, whichever occurs earlier. If a patient does not experience progression or death by the data cutoff date, then the patient will be censored at the date of the last evaluable tumor assessment. Patients who complete treatment or withdraw from treatment but do not withdraw consent from the study will continue to be followed for progression during the long-term follow-up (LTFU). Patients with no relevant tumor response assessment will be censored at the start of treatment. See Appendix 6.3 for complete censoring rules for PFS.

3.3.2.4. Overall Survival

OS is defined as the interval from the date of the first dose until the recorded date of death due to any cause. Patients who are still alive and patients lost to follow-up will be censored on the date when they were last known to be alive.

3.3.3. Safety Variables

The evaluation of safety and tolerability is a secondary objective. Safety variables include clinical laboratory results, vital signs, physical examinations, visual acuity, AEs, ECOG/Lansky performance scores, 12-lead ECG, and echocardiogram/MUGA. Clinically significant abnormalities of laboratory test results or other safety assessments (eg, ECG, radiological scans, vital signs) will be reported as AEs on the CRF.

3.3.3.1. Adverse Events

All AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 24.0 or later and will be classified by MedDRA System Organ Class (SOC) and Preferred Term (PT). Analyses of AEs will be based on the principle of treatment emergence. An AE is considered to be treatment-emergent if it has a start date/time on or after the date/time of first dose of study drug up to 30 days after the last dose of study treatment and before the start of subsequent therapy, whichever comes earlier.

3.3.3.2. Clinical Laboratory Evaluations

Laboratory values will be assigned toxicity grades when available using the NCI CTCAE version 5.0 or later. For analytes without a toxicity grading scale, results will be categorized as low, normal, or high based on the laboratory normal ranges.

3.3.3.3. Vital Signs

Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, and body temperature.

3.3.3.4. Height and bone age

Height and bone age will be collected for patients 12 – 18 years (inclusive). Patients without epiphyseal closure at the time of screening will have a bone age left wrist radiograph performed [redacted].

3.3.3.5. Ophthalmology Examination and Visual Acuity

A baseline ophthalmology exam will be performed for all patients at [redacted] If the patient has noted any visual changes, ophthalmology exam will be conducted prior to the start of each new cycle starting with [redacted] If any visual changes are noted at [redacted] visit an ophthalmology exam will be conducted. Acuity of right and left eyes will be measured in logMAR.

3.3.3.6. Assessment of Change in Pubertal Development (Tanner Stage)

For patients 12 to < 18 years of age, pubertal stage will be measured according to the Tanner Stages [redacted] while on active treatment through sexual maturity (Marshall and Tanner 1969, Marshall and Tanner 1970). For female patients, age at menarche will be recorded.

3.3.3.7. Electrocardiograms (ECGs)

ECG parameters include heart rate (bpm), PR (msec), RR (msec), QRS (msec), QT (msec), and QTcF (msec). ECGs will be collected in triplicate at select timepoints (Screening, [redacted] and [redacted]) after ensuring patient has been resting for at least 5 minutes. For all continuous ECG measurements, triplicate data at each timepoint will be averaged prior to analysis.

Each ECG reading will also be categorized as normal or abnormal based on the interpretation of the assessment by the investigator and, if deemed abnormal, will also be categorized as clinically significant or not clinically significant.

3.3.3.8. Echocardiogram/MUGA

Echocardiogram/MUGA assessments will be performed at select time points ([redacted]) to measure left ventricular ejection fraction (LVEF) percent. Each ECHO/MUGA reading will also be categorized as normal or abnormal based on the interpretation of the assessment by the investigator and, if deemed abnormal, will also be categorized as clinically significant or not clinically significant.

3.3.4. Pharmacodynamic Variables

The pharmacodynamic effects of tovorafenib will be measured by assessing both [redacted] on tumor biopsies obtained at baseline [redacted] and [redacted]

3.3.5. Pharmacokinetic Samples

Blood for tovorafenib concentration measurements in plasma samples will be collected on all patients in the study. Blood sample collections will occur on [redacted] and [redacted]

3.4. Patients Disposition and Evaluability

3.4.1. Patient Disposition

Patient disposition will be presented for all enrolled patients by cohort and overall. The number and percentage of patients enrolled, included in each analysis set, and those who complete treatment and who complete the study will be presented. The number and percentage of enrolled patients who discontinue study treatment and discontinue from the study, and the primary reasons for treatment and study discontinuations will also be presented.

All patient disposition data will be presented in listings.

3.4.2. Protocol Deviations

All protocol deviations will be shown in a patient listing. Number of subjects with major protocol deviations will be tabulated by deviation type.

3.5. Demographics and Baseline Characteristics

3.5.1. Demographics

The following demographics and baseline characteristics will be summarized by cohort and overall for the Efficacy Analysis Set and Safety Analysis Set.

- Age (years)
- Age group: 12 years to <18 years, >=18 years
- Race
- Ethnicity
- Sex
- Height and weight
- Body Surface Area (BSA)
- Number of prior therapy lines
- BRAF fusion (Yes, No)
- CRAF/RAF1 fusion (Yes, No)
- CRAF/RAF1 amplification (Yes, No)
- ECOG Performance Status
- Tumor types (tissue agnostic cohort)

Demographics and baseline characteristics will be presented in a patient listing.

3.5.2. Medical History and Malignancy History

Frequencies and percentages will be presented for primary tumor diagnosis and stage at initial diagnosis by cohort and overall for the Safety Analysis Set.

Medical history will be coded by MedDRA 24.0 or higher version.

By-patient listings for medical history and malignancy history will be provided.

3.5.3. Concomitant Medications/Therapies

Concomitant medications are those taken on or after the date of first dose of study treatment or those started before the first dose of study drug and are continuing at the time of the first dose of study drug. All medications taken from 28 days prior to enrollment through 30 days following the last dose of study drug will be recorded in the eCRF. Similarly, surgeries or palliative radiotherapy that are undergone 28 days prior to enrollment through 30 days following the last dose of study drug will be recorded in the eCRF.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced (WHO-DDE, Version B3 September 2021) and classified by Anatomical Therapeutic Class (ATC) Level 3 and PT. Frequencies and percentages of patients using each concomitant medication will be presented for each cohort and overall for the Safety Analysis Set.

The summary will be sorted alphabetically by ATC level 3 term, and within ATC level 3 term, by decreasing PT frequency for all patients.

All concomitant medications and therapies will be presented in patient listings.

3.5.4. Prior Anti-cancer Therapy

The number and percentage of patients received any prior systemic anti-cancer therapy and received any prior radiotherapy will be summarized, the best response to selected types of prior therapies will be included in the table.

By-patient listings for prior systemic anti-cancer therapy, and prior and concomitant radiotherapy will be provided.

3.6. Treatment Compliance and Exposure

3.6.1. Compliance to Study Treatment

Treatment compliance will be calculated for each dosed patient as: Treatment Compliance (%) = total actual dose (mg)/ total expected dose(mg) ×100.

Treatment compliance will be summarized with descriptive statistics. Number and percentage of patients who had drug interruptions, drug reductions, or drug discontinuations will be also provided.

3.6.2. Exposure to Study Treatment

Descriptive statistics will be displayed for treatment duration (weeks), total number of cycles treated. Treatment duration (weeks) will be calculated as follows: [(date of last dose of study drug – date of first dose of study drug + 1)/7]. Patients will be counted as treated for a cycle if they received any study drug during that cycle.

All treatment exposure data will be presented in patient listings.

3.7. Efficacy Analysis

Each analysis of clinical efficacy endpoints will be performed with the efficacy analysis set, unless specified otherwise. All efficacy analyses will be presented by cohort, unless specified otherwise.

Efficacy analysis variables are defined in Section 3.3.

3.7.1. Tumor Response

ORR is defined as the percentage of evaluable patients meeting criteria of radiological CR or PR, confirmed at a subsequent time point (≥ 4 weeks), as assessed by the Investigator.

The ORR and number and percentage of patients meeting the best overall response criteria of CR and PR based on RECIST 1.1 or RANO criteria will be displayed, as well as the number and percentage of patients with the best overall response of CR, PR, SD, PD, not evaluable or with missing response. Exact 95% confidence intervals (CI) will be presented for the ORR, CR, and PR percentages.

For responders, analyses of DOR and time to response will be presented. DOR is defined as the number of days from first tumor response to radiographic disease progression based on RECIST 1.1 or RANO criteria or death by any cause, whichever occurs earlier. Censoring rules similar to those for PFS will be implemented. Summary statistics (25th percentile, median, 75th percentile, and the corresponding 95% CIs) will be presented for DOR using the Kaplan-Meier method.

Descriptive statistics will be presented for time to response, calculated as the number of days from the date of the first dose to date of first response.

All RECIST 1.1 and RANO target/measurable lesions, non-target/non-measurable lesions, new lesions and tumor response will be presented in patient listings.

3.7.2. Progression-Free Survival

PFS is defined as the interval from the date of the first dose to radiographic disease progression based on RECIST 1.1 or RANO criteria or death by any cause, whichever occurs first. Details regarding censoring are included in Appendix 6.3.

Disease progressions reported during the long-term follow up period will be included in the derivation of PFS. The number and percentage of patients who experienced event and censoring will be presented with the corresponding reason as listed in Appendix 6.3. Summary statistics (25th percentile, median, 75th percentile, and the corresponding 95% CIs) will be presented for PFS time using the Kaplan-Meier method.

3.7.3. Overall Survival

OS time is defined as the interval from the date of the first dose until the date of death due to any cause. The number and percentage of patients who died, survived, and were lost to follow-up at the end of the study will be presented. For assessment of OS, data from surviving subjects will be censored on the date when they were last known to be alive. Summary statistics (25th percentile, median, 75th percentile, and the corresponding 95% CIs) will be presented for OS time using the Kaplan-Meier method.

3.8. Safety Analysis

Safety will be evaluated by monitoring all adverse events, serious adverse events, adverse events of special interest, and abnormalities identified through physical examinations, vital signs, and laboratory assessments. Such events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0). All verbatim adverse event terms occurring on or after first study treatment will be mapped to Medical Dictionary for Regulatory Activities (MedDRA), and adverse event severity will be graded according to NCI CTCAE v5.0. All safety analyses will be performed with the Safety Analysis Set and presented by cohort and overall.

3.8.1. Adverse Events

Analyses of AEs will be based on treatment emergent AEs (refer to Section 3.3.3.1 for definition). Please reference Section 3.1.6 for the handling of partial date/time in determining treatment emergence.

For the presentation of AE incidences, the SOCs will be sorted by decreasing frequency in overall group, and within SOC, the PTs will be presented by decreasing frequency in overall group and then alphabetically. If a patient has more than one occurrence of the same PT, then the PT will be counted only once for that patient. Similarly, if a patient has more than one PT within the same SOC, the patient will be counted only once in that SOC.

All AEs (including TEAEs and non-TEAEs), treatment-related TEAEs (TRAEs), TEAEs leading to study treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to dose interruption, serious adverse events (SAEs), TEAE with outcome of death, and all deaths will be displayed in patient listings. Day of AE onset and day of AE resolution relative to the start of study drug dosing will be presented in all AE listings.

3.8.2. Summary of TEAEs

The numbers and percentages of patients who experienced any TEAE, TRAEs, TEAEs with CTCAE grade 3 or higher, SAEs, treatment-related SAEs, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to dose interruption, TEAEs leading to death, and all deaths will be presented by SOC and/or PT and highest CTCAE grade. An overall summary of the number and percentage of patients in each category will also be presented.

TEAEs with missing relationship will be presented in a by-patient listing.

3.8.3. Adverse Events of Special Interest

Adverse events of special interest (AESI) of tovorafenib will be summarized as below based on TEAEs:

- Rhabdomyolysis, based on the SMQ “Rhabdomyolysis”, narrow scope terms
- Ventricular Arrhythmias, based on SMQ “Ventricular tachyarrhythmias”
- Intra-tumoral hemorrhage, based on SMQ “Haemorrhagic central nervous system vascular conditions” and PT Tumour Haemorrhage
- Secondary primary malignancies, based on SMQ “Non-haematological malignant tumours”
- Ocular toxicity, based on MedDRA SOC “Eye disorders”, excluding HLGTs “Congenital eye disorders (excl glaucoma)”, “Ocular neuromuscular disorders”, and “Ocular neoplasms”
- Decreased growth velocity, based on PT “Growth disorder”, “Growth failure”, “Growth retardation”, “Body height decreased”, “Body height abnormal”, “Short Stature”.

The AESIs will be summarized by group term, PT and highest CTCAE grade.

3.8.4. Clinical Laboratory Evaluation

The clinical laboratory parameters will be analyzed using the Safety Analysis Set by cohort and overall.

Laboratory values will be assigned toxicity grades when available using the NCI CTCAE version 5.0. Directional shifts in laboratory toxicity grades from baseline to post-baseline highest grade will be tabulated. For analytes without a toxicity grading scale, shift tables will present directional shifts from baseline to above or below the laboratory standard normal range.

All clinical laboratory values will be presented in patient listings. Out of normal range values will be flagged.

3.8.5. Visual Acuity

Visual acuity assessments will be summarized at [redacted] timepoints by cohort and overall for all patients in the Safety Analysis Set. Descriptive statistics for right and left eye acuity values will be presented.

All visual acuity results will be included in a patient listing.

3.8.6. Pharmacokinetic Analyses

Tovorafenib plasma concentrations at specified time points will be analysed using a validated bioanalytical method. All plasma concentrations of tovorafenib will be listed and summarized by nominal sample time using standard summary statistics for PK concentrations (geometric mean, geometric coefficient of variation, geometric standard deviation, arithmetic mean, standard deviation, minimum, maximum and n).

4. DEVIATIONS FROM PROTOCOL

Definition of efficacy analysis sets, Section 3.2.1.

5. REFERENCE

Wen PY, Chang SM, Van den Bent MJ, et al, "Response Assessment in Neuro-Oncology Clinical Trials", *J Clin Oncol*. 2017 Jul 20; 35(21):2439-2449.

6. APPENDIX

6.1. Best Overall Assessment by RECIST 1.1

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Confirmed Overall Response
CR	CR	CR
CR	PR	PR[a], SD, PD
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Abbreviations: Abbreviations: CR, complete response; NE, not all evaluated; PD, progressive disease; PR, partial response; SD, stable disease.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration of 8 weeks for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

6.2. RANO Response Criteria Incorporating MRI and Clinical Factor

RESPONSE CATEGORY	CRITERIA
Complete Response	• Disappearance of all measurable and non-measurable enhancing disease • Stable or improved nonenhancing FLAIR/T2 lesions • No new lesions • Clinically stable or improved with no reliance on corticosteroids (except for physiological replacement)
Partial Response	• ≥ 50% decrease from baseline of all measurable enhancing lesions • No progression of non-measurable disease • Stable or improved nonenhancing FLAIR/T2 lesions • No new lesions • Clinically stable or improved, with stable or reduced corticosteroids compared to baseline
Progressive Disease	• ≥ 25% increase from baseline in enhancing lesions despite stable or increasing steroid dose • Significant increase in nonenhancing FLAIR/T2 lesions not attributable to other non-tumor causes • Any new lesions • Clinical deterioration no attributable to other non-tumor causes and not due to steroid decrease
Stable Disease	• Does not meet other criteria for response or progression • Stable nonenhancing FLAIR/T2 lesions • Clinically stable with stable or reduced corticosteroids compared to baseline
Abbreviations: FLAIR/T2, T2-weighted fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; RANO, Response Assessment in Neuro-Oncology.	

6.3. Censoring Rules for PFS

The following censoring rules aim to follow the Food and Drug Administration guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics and will be used for PFS analysis.

Situation	**Date of Progression or Censoring**	**Outcome**
No post-baseline tumor assessments, in the absence of documented progression or death	Date of first dose	Censored
Documented Progression	Earliest date of progression	Event
No progression, regardless of study discontinuation	Date of last evaluable assessment	Censored
Lost to follow-up without documented progression	Date of last evaluable assessment	Censored
New anticancer treatment started before documented progression	Date of last evaluable assessment prior to new anticancer treatment started	Censored
Death without documented progression and is not after two or more missed tumor assessment visits	Date of death	Event
Death or progression after two or more missed tumor assessment visits	Date of last evaluable assessment	Censored

[source: https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf]

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