NOVARTIS

Clinical Development

DRB436+TMT212/Dabrafenib+Trametinib/Tafinlar®+Mekinist®

CDRB436X2201 (GSK Study ID: BRF117019) / NCT02034110

A Phase II, Open-label, Study in Subjects with BRAF V600E-Mutated Rare Cancers with Several Histologies to Investigate the Clinical Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib

Final Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse Event
ASI	Adenocarcinoma of the small intestine
ATC	Anaplastic Thyroid Cancer
BTC	Biliary Tract Cancer
CRF	Case Report Form
CSR	Clinical Study Report
DMS	Document Management System
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eCRS	electronic Case Retrieval Sheet
[redacted]	[redacted]
GIST	Gastrointestinal stromal tumor
HCL	Hairy Cell Leukemia
HGG	High Grade Glioma
[redacted]	[redacted]
IA	Interim Analyses
LGG	Low Grade Glioma
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MRD	Minimal Residual Disease
NGGCT	Non-geminomatous germ cell tumor
NSGCT	Non-seminomatous germ cell tumor
PK	Pharmacokinetics
PRO	Patient-reported Outcomes
RAP	Reporting & Analysis Process
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) details all planned analyses to support the final clinical study report (CSR) and publication of final study results from BRF117019/CDRB436X2201. This is a phase II study to evaluate the clinical efficacy and safety of the combination therapy of dabrafenib (DRB436) and trametinib (TMT212) using a single-arm multi-histology study design in several rare cancer types.

In this SAP, references will be made to the following documents:

- Protocol amendment 11 dated 04 Jun 2020
- Annotated electronic Case Report Form (eCRF) BRF117019/CDRB436X2201 SV16.0
- Charter for the Independent Data Monitoring Committee (IDMC) version 2.0 dated 23 Jun 2016

1.1 Study design

This is a Phase II, open-label, non-randomized, multi-center study of oral dabrafenib in combination with oral trametinib in subjects with rare cancers with the BRAF V600E mutation. The following histologies will be included in this study: ATC, BTC, GIST, WHO Grade 1 or 2 glioma, WHO Grade 3 or 4 glioma, NSGCT/NGGCT, ASI, HCL and MM (Cohorts 1 to 9, respectively).

For each cohort, up to 25 evaluable subjects will be enrolled in the primary analysis cohort. If a given cohort is stopped early for efficacy, a histology specific expansion cohort may be opened to allow for additional patient enrollment.

The primary analysis cohort is comprised of those patients enrolled within a histology-specific group prior to capping at 25 patients per cohort or prior to early stopping for efficacy or futility. The primary analysis cohort will form the basis of the Bayesian modelling of ORR.

If a cohort closes early at an interim analysis because it meets the rules for early stopping for efficacy, an expansion cohort may be opened to allow additional patient enrollment for that particular histology. The patients in the expansion cohort will provide supportive efficacy data and will NOT contribute to the Bayesian modeling of ORR. The expansion cohort(s) will enroll subjects for the duration of trial enrollment.

Only subjects with histologically or cytologically confirmed advanced disease with no available treatment options as determined by locally or regionally available standards of care and by the treating physician's discretion will be eligible for enrollment. Subjects may be enrolled based on local testing of the BRAF V600E mutation and mutation status will be confirmed by a central reference laboratory.

Subjects will receive dabrafenib 150 mg BID orally plus trametinib 2 mg once daily orally on a continuous dosing schedule. An adaptive design with multiple interim evaluations will determine if one or more histologic cohorts should discontinue enrolment early due to either success or futility. Evaluations are based on a hierarchical statistical model that borrows information in a limited way from histologies that demonstrate similar response rates based on the accumulated trial data. A complete description of the study design and rationale is included in the Protocol.

1.2 Study objectives and endpoints

The study objectives and corresponding endpoints are presented in Table 1-1.

Table 1-1 Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
• To determine the ORR of dabrafenib and trametinib anti-cancer combination therapy in subjects with selected rare BRAF V600E mutated solid tumors or hematologic malignancies.	• Tumor response as defined by: RECIST, v1.1 for solid tumor histologies, Modified RANO and RANO for glioma or established response criteria for specific hematologic malignancies
Secondary	
• To determine the duration of response of dabrafenib in combination with trametinib in subjects with selected rare BRAF-mutated cancers	• Duration of response
• To determine PFS of dabrafenib in combination with trametinib in subjects with selected rare BRAF-mutated cancers	• Investigator-assessed PFS
• To determine OS of dabrafenib in combination with trametinib in subjects with selected rare BRAF-mutated cancers	• OS
• To determine the safety of dabrafenib in combination with trametinib in subjects with selected rare BRAF-mutated tumors	• Change from baseline in physical examination findings, vital signs, AEs, laboratory values and cardiac assessments
[redacted]	

Abbreviations: AE, adverse events; [redacted] ORR, overall response rate; OS, overall survival; [redacted] PFS, progression-free survival; [redacted] PK, pharmacokinetics; RANO, Response Assessment for Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumors; [redacted]

2 Statistical methods

2.1 Data analysis general information

Analysis datasets and outputs will be produced in the GPSII system using SAS version 9.4 (or later).

Data from all participating centers will be pooled prior to analysis. Subject accrual is spread thinly across centers and summaries of data by center would be unlikely to be informative and therefore will not be provided.

All data up to death or study withdrawal will be included in each analysis. Unscheduled visits will not be included in summaries, except to derive minimum/maximum post-baseline or on-treatment values. Unscheduled visits will be presented in subject listings.

Planned times relative to study drug dosing will be used in all tables and summary figures.

Unless otherwise stated, continuous variables will be summarized with n, mean, median, standard deviation, minimum and maximum, and categorical variables will be summarized with frequency counts and percentages.

2.1.1 General definitions

Study treatment

Study treatment in this study refers to either dabrafenib or trametinib.

Reference dates

There are two reference dates:

- The date of screening is the reference date for determination of age, since age is an eligibility requirement.
- The study treatment start date is the reference date for efficacy and safety.

Study day

If the date of interest occurs on or after the reference date then the study day will be calculated as (date of interest - reference date) + 1. If the date of interest occurs before the reference date then the study day will be calculated as (date of interest – reference date). There is no study day 0.

Duration and elapsed time

Durations (e.g., the duration of an adverse event, duration of exposure, etc.) are calculated as the stop date minus the start date plus one.

For elapsed time (e.g., the time since initial diagnosis):

- If the event date is on or after the reference date, then the elapsed time is the event date minus the reference date + 1
- If the event date is before the reference date then the elapsed time is the event date minus the reference date

When reporting time to event (TTE) durations such as PFS in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25.

Baseline

Baseline will be defined as the most recent, non-missing value prior to or on the first study treatment dose date. For laboratory data, baseline will be defined as the most recent, non-missing value from a central laboratory prior to or on the first study treatment dose date. If there are no central labs collected for a subject and lab test prior to or on the first dose of study treatment, the most recent, non-missing value from a local laboratory prior to or on the first dose of study treatment will be defined as the baseline value.

Change from baseline

Change from baseline will be presented for safety data. Change from baseline is calculated as:
For records occurring after baseline: (visit value) - baseline value.

Percent change from baseline is calculated as:
For records occurring after baseline: ((change from baseline) / Baseline value) *100.

If either the baseline or visit value is missing, the change from baseline and/or percent change from baseline is set to missing as well.

Time in relation to treatment

Adverse events, serious adverse events, death, laboratory data, vitals, ECG and ECHO, will be assigned to the study time periods defined below. Partial dates will be imputed into full dates, if applicable, for slotting data to the appropriate categories below (see Section 4.4). Flag variables (time in relation to study treatment) indicating the study time periods will be added to these datasets.

Pre-therapy is defined as the time prior to the subject's first dose of study treatment.

On-therapy is defined as the time from first dose of study treatment until 30 days after the last dose date of study treatment.

Post-therapy is defined as any time beyond the on-therapy period.

Some datasets include the first dose day as On-therapy and some exclude the first dose date as On-Therapy. The first dose day (Day 1) is considered pre-therapy for ECOG, ECG, vital signs, liver events, lab tests, and cardiac scan. The first dose day (Day 1) is considered to be On-therapy for adverse events and concomitant medications.

Study time period for concomitant medications and blood and blood supportive care products

Concomitant Medication and Blood and Blood Supportive Care Product start and end dates will be assigned to study time periods in relation to first dose of study treatment as defined below. The start date reference time flag variables and end date reference time flag variables will be added to the concomitant medications and blood and blood supportive products datasets, respectively.

Start relative to treatment: Assign to 'BEFORE' if start date is prior to study treatment start date or if subject has not taken any study treatment or (start date is missing and end date is before study treatment start date). Else assign to 'DURING' if the start date falls on or between the first and last dose dates of study treatment or if subject is ongoing (not all study treatment

discontinuation records completed) or start date is missing. Else assign to 'AFTER' if start date is after the on-therapy period.

End relative to treatment: Assign to 'BEFORE' if end date is prior to study treatment start date or if subject has not taken any study treatment. Else assign to 'DURING' if end date falls on or between the first and last dose dates of study treatmentor if subject is ongoing (not all study treatment discontinuation records completed) or (end date is missing and start relative to treatment not 'AFTER'). Else assign to 'AFTER' if start date is after the on-therapy period or (end date is missing and start relative to treatment='AFTER').

Only on-therapy blood and blood supportive care products that start after the start of study treatment are included in the Blood Products and Blood Supportive Care Product summaries. Therefore, for summary tables, include blood and blood supportive care product records where start relative to treatment in ('DURING') and end relative to treatment in ('DURING','AFTER'). All data will be reported in listings.

Concomitant medication start relative to treatment and end relative to treatment flags are used to select data to include in the Concomitant Medication summaries as follows:

- Summary of Concomitant Medications: This summary will contain medications including those with start date prior to study treatment start date and continue (missing end date or end date after study treatment start date) on therapy. Note that any medications with start date and end date prior to study treatment start date will be excluded. In addition, any medication that was started during post-therapy will be excluded. Include concomitant medication records where start relative to treatment in ('BEFORE','DURING') and end relative to treatment in ('DURING','AFTER').
- Summary of Concomitant Medications with On-Therapy Onset: This summary will contain medications with start date after study treatment start date. In addition, any medication that was started during post-therapy (see above for definition of post-therapy) will be excluded. Include concomitant medication records where start relative to treatment in ('DURING') and end relative to treatment in ('DURING','AFTER').

Other derivations or data handling procedures related to this analysis plan are given in section 4.

2.2 Analysis sets

As specified in the protocol, for the final analysis the Intent-to-Treat population will be used for primary analysis of efficacy endpoints. The BRAF V600E population will be used for supportive analysis of efficacy. The All Treated Subjects population will be used for Safety analysis. These analysis populations are defined below:

The Intent-to-Treat (ITT) population is defined as all enrolled subjects regardless of whether or not treatment was administered.

The BRAF V600E population is defined as all enrolled subjects regardless of whether or not treatment was administered, who obtain positive verification of the BRAF V600E mutation from a certified central reference laboratory.

The All Treated Subjects population is defined as all subjects who receive at least one dose of dabrafenib or trametinib.

A summary of the number of subjects in each of the analysis populations will be provided. A listing of subjects included in each analysis population will also be provided.

2.2.1 Subgroup of interest

Efficacy data (investigator and independent reviewer-assessed ORR, DoR, PFS and OS) will be presented for the following subgroups within the WHO Grade 3 or 4 Glioma cohort:

- By grade (3 or 4)
- By age group (18-39 or 40+)

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

A summary of subject status and reason for study withdrawal will be provided for the ITT population. This display will show the number and percentage of subjects who withdrew from the study, including primary reason for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF. A listing of the subject disposition/end of study record for all subjects who discontinued the study prematurely will be produced.

2.3.2 Demographics and baseline data

The demographic characteristics including age, sex, race, ethnicity, child-bearing potential, baseline height and weight will be summarized and listed for each histologic cohort. The count (n), mean, standard deviation, median, minimum value, and maximum value will be computed for age, height, and weight. The count and percentage will be computed for sex, race, ethnicity, child-bearing potential, and age categories (<18, 18-64, 65-74, and 75-84, and >=85 years).

Disease history and characteristics at initial diagnosis and screening will be listed. Separate summaries of disease characteristics at initial diagnosis and screening will be provided for each histologic cohort.

Medical conditions will be graded according to the CTCAE, Version 4.0 and coded to preferred term using the MedDRA dictionary. Medical conditions present at screening will be summarized and listed.

2.3.3 Study treatment / compliance

A summary of study treatment status will be provided for the ATS population. This display will show the number and percentage of subjects who are ongoing or discontinued study and the primary reason(s) for discontinuation of study treatment. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. Separate tables will be produced for dabrafenib and trametinib. Separate listings for study treatment discontinuation will also be generated for dabrafenib and trametinib.

Summary of exposure to study treatment will be provided. The summary will include subject daily dose, population level daily dose, cumulative dose, duration on treatment for dabrafenib, duration on treatment for trametinib, and duration on combination treatment. The subject average daily dose is defined as the subject's cumulative dose divided by the duration on study

treatment. For the analysis of population level daily dose, a dose on each day for each subject will be treated as an observation and the summary will be based on the dose on each individual day for all subjects. Duration on treatment for dabrafenib or trametinib is defined as months from the first dose to the last non-zero dose, regardless of dose interruption before the last non-zero dose. In addition to mean, median, min and max, duration on dabrafenib, duration on trametinib and duration on combination treatment will also be summarized in the following categories: <3 months, 3-6 months, >6-9 months, >9-12 months, >12-24 months, >24-36 months, and >36 months.

Dose reductions will be summarised by number of reductions and reasons for reductions for dabrafenib and trametinib separately.

Dose interruptions will be summarised by number of interruptions and reasons for the interruptions for dabrafenib and trametinib separately.

A summary of overall compliance based on the exposure data will be produced separately for dabrafenib and trametinib for the ATS population. Percentage overall compliance will be summarized using the mean, standard deviation, minimum, median, and maximum. In addition, percentage overall compliance will be categorized and summarized by <80%, 80%-105%, and >105%.

The calculation of overall compliance is based on the entire interval of dosing for dabrafenib and trametinib. The formula for daily dose medication is compliance (%) = [total cumulative actual dose / (duration of study treatment x prescribed dose)] x 100 where duration of study treatment is last dose-first dose +1. For dabrafenib, the prescribed dose is 300mg per day, and for trametinib, the prescribed daily dose is 2mg per day.

Listings of overall compliance will be produced separately for dabrafenib and trametinib.

2.3.4 Prior, concomitant and post therapies

Concomitant medications will be coded using WHO Drug coding dictionary, summarized, and listed. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the data listing only. In order to be considered a concomitant medication, the concomitant medication must have been taken at some point during the on-therapy window.

Prior anti-cancer therapy will be coded using WHO Drug coding dictionary, then summarized by type of therapy and listed. Separate tables will be produced displaying prior medications by ingredient (counting multiple ingredients taken as part of a combined treatment on separate rows) and displaying combination regimens as single rows e.g. cisplatin + gemcitabine. Combined regimens will be defined based on common start dates of each ingredient, which are entered separately on the eCRF. A summary of the number of prior anti-cancer therapy regimens will also be produced.

Prior anti-cancer radiotherapy and prior cancer and non-cancer surgical procedures will be listed.

The number and percentage of subjects that received chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy, radiotherapy and cancer-specific surgery as post study treatment anti-cancer therapy will be summarized.

Summary statistics for the time from study treatment discontinuation to the first post study treatment anti-cancer therapy (in weeks) will also be included in this summary table.

Follow-up anti-cancer therapy will be coded using WHO Drug coding dictionary, then summarized by ingredient. A listing of the type of follow-up anti-cancer therapy received (chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy) and details of the anti-cancer therapy for each subject will be provided.

Anti-cancer radiotherapy and both cancer- and non-cancer related surgical procedures will be listed separately.

2.3.5 Protocol Deviations

Protocol deviations identified during the study are reviewed by the study team. During this review, deviations are classified as important or not important based on their impact on data reliability and/or patient safety, wellbeing or rights.

Important protocol deviations including inclusion/exclusion criteria deviations will be summarized. A separate summary of inclusion/exclusion criteria deviations will also be provided. All important protocol deviations will be listed. Following the COVID-19 pandemic, separate tables will be created to display the protocol deviations related to COVID-19 and those not related to COVID-19. Deviations related to COVID-19 will be classified as important to ensure transparent presentation of the impact of the pandemic in the clinical study report. Where applicable, the relationship of a protocol deviation to COVID-19 will be displayed in the listing.

Deviations will not result in subject exclusion from any population. However, for protocol deviations that are deemed by clinical team as having a significant impact on the interpretation of the efficacy results (e.g. subject with incorrect histologic type enrolled), sensitivity analysis for efficacy may be conducted by excluding subjects with such deviations.

2.4 Analysis of the primary objective

The analyses of the primary endpoint will take place once all patients have either died or been transitioned off the study. The primary analysis population for efficacy analyses is ITT. The BRAF V600E population will be used for supportive analyses of efficacy. Summaries of primary endpoint results may be provided for the primary analysis cohort, the expansion cohort and primary and expansion cohorts combined.

2.4.1 Primary endpoint

The primary efficacy assessment will be the evaluation of overall response rate (ORR) calculated as a proportion of the subjects who have a confirmed response relative to the total number of subjects in the analysis population. Clinical response to dabrafenib in combination with trametinib will be assessed according to the appropriately established response criteria for each histologic cohort. Table 2-1 outlines the response criteria and subcategories for overall response for each histologic cohort. Following feedback on the WHO Grade 1 and 2 Glioma cohort from the FDA, additional summaries of best response and duration of response will be produced excluding Minor Response (MR) from the subcategories defined as Response for this cohort.

Table 2-1 Response Criteria and Definition of Response by Histology

Histology	Response Criteria	Response Subcategories defined as Overall Response
ATC, BTC, GIST, ASI	RECIST 1.1	CR, PR
NSGCT/NGGCT	RECIST 1.1; Serum tumor markers normalization or not will be considered as part of response criteria (serum tumor markers: AFP, β-HCG)	Marker-Negative CR (CR-), Marker-Positive CR (CR+), Marker-Negative Partial Remission (PR-), Marker-Positive Partial Remission (PR+)
WHO Grade 1 and 2 Glioma	Response Assessment Criteria for WHO Grade 1 or 2 Glioma: RANO Working Group	CR, PR, MR
WHO Grade 3 and 4 Glioma	Updated Response Assessment Criteria for WHO Grade 3 or 4 Glioma: RANO Working Group	CR, PR
MM	IMWG Uniform Response Criteria for MM	sCR, CR, PR, VGPR
HCL	Adapted from NCCN guidelines, Consensus Resolution Criteria and previous studies definition	CR without MRD (CR-MRD), CR with MRD (CR+MRD), PR

Abbreviations: AFP, alpha-fetoprotein; ASI, adenocarcinoma of the small intestine; ATC, anaplastic thyroid cancer; β-hCG, beta-human chorionic gonadotropin; BTC, biliary tract cancer; CR, complete response; GIST, gastrointestinal stromal tumor; HCL, hairy cell leukemia; IMWG, International Myeloma Working Group; MM, multiple myeloma; MR, minor response; MRD, minimal residual disease; NCCN, National Comprehensive Cancer Network; NGGCT, non-geminomatous germ cell tumor; NSGCT, non-seminomatous germ cell tumor; PR, partial response; RANO, Response Assessment for Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumors; sCR, stringent complete response; VGPR, very good partial response; WHO, World Health Organization

The best confirmed overall response is the best confirmed response recorded from the start of treatment until disease progression or start of new anti-cancer therapy, whichever earlier, and will be determined programmatically based on investigator assessment at each time point.

If there are two assessments separated by not evaluable (NE) assessment(s) the best response shall be assessed applying the algorithm below, collapsing data by ignoring NE assessments.

Subjects with best response of Not Evaluable (NE), unknown or missing will be considered non-responders; i.e. they will be included in the denominator when calculating the percentage.

The first assessment may occur before the first planned assessment. Confirmation of response may be based on planned and/or unscheduled assessments.

Table 2-2, Table 2-3, and Table 2-4 below outline the programming algorithm used to define confirmed response for each of the histologic cohorts.

Table 2-2 Confirmed Response Criteria for Solid Tumors following RECIST 1.1 (ATC, BTC, GIST, ASI, NSGCT/NGGCT) or RANO (WHO Grade 1&2 Glioma, WHO Grade 3&4 Glioma)

Confirmed Response Category	Criteria for Definition of Confirmed Response
CR, PR, MR, CR-, CR+, PR- and PR+. (MR only applicable for WHO Grade 1&2 glioma) (CR-, CR+, PR-, and PR+ only applicable to NSGCT/NGGCT)	• Two consecutive assessments are required. A confirmatory disease assessment should be performed no less than 4 weeks (28 days) from the time of initial CR, PR, MR, CR-, CR+, PR- or PR+. If a response of any type is assessed and the consecutive assessment is a response of lower magnitude then the confirmed response corresponds with the latter assessment which is the response of lower magnitude. For example, a CR followed by PR results in a confirmed PR response. • If there is 1 assessment within this category, the timing of this assessment is less than 6 weeks after the first dosing and all other assessments are either NE, missing or not done then the confirmed response is NE. • Confirmed responses in this category cannot be assigned for assessments after a patient has an overall response assessment of PD. • For NSGCT/NGGCT, ordering of response magnitude from high to low is CR-, CR+, PR-, PR+. For WHO Grade 1&2 glioma, ordering of response magnitude from high to low is CR, PR, MR. For all other solid tumors, the ordering of response magnitude from high to low is CR, PR.
SD	• SD does not need to be confirmed by a second assessment if the disease assessment meets the SD criteria after first dose of study drug at a minimum interval of 6 weeks (42 days). No further minimum window adjustment for assessment will be permitted. If the minimum time for SD is not met, the best response will depend on the subsequent assessments or will be NE. For example, if an assessment of SD is followed by PD and SD does not meet the minimum time requirement for SD, the best response will be PD. When the only assessment (other than NE) after initiation of treatment is SD and the minimum time of 6 weeks from first dose of study drug is not met, the best confirmed response is NE. • If an assessment in the following categories (CR, PR, MR, CR-, CR+, PR- and PR+) is followed by SD or PD, and the timing of the initial assessment is greater than or equal to 6 weeks after the first dosing, then the confirmed response is SD. • If there is 1 assessment in the following categories (CR, PR, MR, CR-, CR+, PR- and PR+) and the timing of the assessment is greater than or equal to 6 weeks after the first dosing, and consecutive assessments are either missing, not done or NE then the confirmed response is SD. • Confirmed responses in this category cannot be assigned for assessments after a patient has an overall response assessment of PD.
PD	• PD does not need to be confirmed by a second assessment of PD to confirm PD as the best response. When the only assessment (other than NE) at any point after initiation of treatment is PD the confirmed response is PD.
NE	• When a confirmation (of any above category except SD and PD) cannot be made due to lack of assessments the confirmed response is NE.

	• If there is 1 assessment in the following categories (CR, PR, MR, CR-, CR+, PR- and PR+) and the timing of the assessment is less than 6 weeks after the first dosing, and consecutive assessments are either missing, not done or NE then the confirmed response is NE. • If all assessments were NE or missing then the confirmed response is NE. • If only non-measurable disease exists at baseline and the response is given as Non-CR/Non-PD then the confirmed response is NE.

Table 2-3 Confirmed Response Criteria for MM

Confirmed Response Category	Criteria for Definition of Confirmed Response
sCR, CR, VGPR, PR, Minimal Response (MnR), SD	• Two consecutive assessments are required. At least one day of separation between two consecutive assessments is required to confirm response. • If a response of any type is assessed and the consecutive assessment is a response of lower magnitude then the confirmed response corresponds with the latter assessment which is the response of lower magnitude. For example, a PR followed by MnR results in a confirmed MnR response, or a PR followed by SD results in a confirmed SD. Two consecutive assessments of SD will constitute a confirmed SD. • If there is 1 assessment and consecutive assessments are either missing or not done then the confirmed response is NE. • The ordering of response magnitude from high to low is sCR, CR, VGPR, PR, MnR SD. • Confirmed responses in this category cannot be assigned for assessments after a patient has an overall response assessment of PD.
PD	• PD does not need to be confirmed by a second assessment of PD to confirm PD as the best response. When the only assessment (other than NE) at any point after initiation of treatment is PD the confirmed response is PD.
NE	• When a confirmation (of sCR, CR, VGPR, PR, MnR or SD) cannot be made due to lack of assessments the confirmed response is NE. For example, if there is 1 assessment in the following categories (sCR, CR, VGPR, PR, MnR, SD) and consecutive assessments are either missing, not done or NE then the confirmed response is NE. • If all assessments were NE or missing then the confirmed response is NE.

Table 2-4 Confirmed Response Criteria for HCL

Confirmed Response Category	Criteria for Definition of Confirmed Response
CR-MRD, CR+MRD, PR, MR	• Two consecutive assessments are required. A confirmatory disease assessment should be performed no less than 4 weeks (28 days) from the time of initial CR - MRD, CR + MRD, PR or MR. • If a response of any type (CR-MRD, CR+MRD, PR, MR) is assessed and the consecutive assessment is a response of lower magnitude then the confirmed response corresponds with the latter assessment which is the response of lower magnitude. For example, a PR followed by MR results in a confirmed MR response. • The ordering of response magnitude from high to low is CR- MRD, CR+ MRD, PR, MR. • Confirmed responses in this category cannot be assigned for assessments after a patient has an overall response assessment of PD.
SD	• SD does not need to be confirmed by a second assessment if the disease assessment meets the criteria after first dose of study drug at a minimum interval of 4 weeks (28 days). If the minimum time for SD is not met, the best response will depend on the subsequent assessments or will be NE. For example, if an assessment of SD is followed by PD and SD does not meet the minimum time requirement, the best response will be PD. When the only assessment (other than NE) after initiation of treatment is SD and the minimum time for SD is not met, the best confirmed response is NE. • If an assessment in the following categories (CR-MRD, CR+MRD, PR, MR) is followed by SD or PD, and the timing of the initial assessment is greater than or equal to 4 weeks after the first dosing, then the confirmed response is SD. • If there is 1 assessment in the following categories (CR-MRD, CR+MRD, PR, MR) and the timing of the assessment is greater than or equal to 4 weeks after the first dosing, and consecutive assessments are either missing, not done or NE then the confirmed response is SD. • Confirmed responses in this category cannot be assigned for assessments after a patient has an overall response assessment of PD.
PD	• PD does not need to be confirmed by a second assessment of PD to confirm PD as the best response. When the only assessment (other than NE) at any point after initiation of treatment is PD the confirmed response is PD.
NE	• When a confirmation (of CR-MRD, CR+MRD, PR or MR) cannot be made due to lack of assessments the confirmed response is NE. • If there is 1 assessment in the following categories (CR-MRD, CR+MRD, PR, MR) and the timing of the assessment is less than 4 weeks after the first dosing, and consecutive assessments are either missing, not done or NE then the confirmed response is NE.

Confirmed Response Category	Criteria for Definition of Confirmed Response
	• If all assessments were NE or missing then the confirmed response is NE.

2.4.2 Statistical hypothesis, model, and method of analysis

Confirmed ORR will be calculated as the proportion of subjects that have a confirmed response relative to the total number of subjects in the corresponding analysis population.

Confirmed ORR will be analyzed using an integrated analysis across the histologic cohorts with the hierarchical model. Model-based interim decision rules have been used through the study to identify whether one or more histologic cohorts halt enrolment early for futility/harm or benefit based on efficacy data.

Model-based decision rules for the final analysis are provided in the protocol. At the final analysis, a minimum of 2 subjects will be required in a histologic cohort in order to meet statistical success. A histologic cohort will be declared active if the posterior probability that the ORR exceeds its corresponding historical control is sufficiently high (>92%) based on the hierarchical model. That is,

$$P(\pi_j > C_j\ \% \mid \text{current data}) > 92\%, \text{ for the j-th histology.}$$

This decision rule has been determined based on extensive simulations of the study design as described in the protocol.

A summary of the Bayesian hierarchical model-based analysis will be provided. For each histology the following measures will be reported: the total number of subjects, the protocol-specified historical control response rate, the estimated response rate and 95% credible interval (based on the posterior mean and 2.5% and 97.5% percentiles), and the posterior probability that the ORR exceeds its corresponding historical control response rate.

Descriptive summaries of best confirmed response along with the corresponding 95% exact confidence intervals will be provided for each response criteria for the varying histologic cohorts in order to characterize the observed response data and support the model-based analyses for ORR. Best response and ORR will be presented for the primary cohort, expansion cohort and primary and expansion combined for each histology for which an expansion cohort was opened.

The model-based analysis of ORR and supporting summaries of best confirmed response will be re-produced based on the BRAF V600E Population.

All supporting individual response and lesion data will be listed. For histologic cohorts using RECIST 1.1 (ATC, BTC, GIST, ASI), a listing of all investigator-assessed lesion assessments will be provided. For glioma cohorts (WHO Grade 1 or 2 and WHO Grade 3 or 4), listings of measureable, non-measureable, and new lesions will be provided. For HCL, separate listings of lymph nodes including palpable lymph nodes will be provided. For MM, supportive laboratory results including serum and urine monoclonal protein, serum free light chain (FLC) and FLC ratio will be listed.

2.4.3 Handling of missing values/censoring/discontinuations

Response assessments occurring after disease progression or the start of new anti-cancer therapy will not be included in the determination of best response. Response assessments occurring after end of study treatment but before disease progression or the start of new anti-cancer therapy will be included. There will be no imputation of missing values.

2.4.4 Supportive analyses

Descriptive summaries of best response based on independent radiology review will be provided for the ATC, BTC, ASI, WHO Grade 1 or 2 Glioma and WHO Grade 3 or 4 Glioma cohorts as sensitivity analyses. Specifically, the best response based on independent reviewer assessment will be determined programmatically and summarized in the same way as the best response based on investigator assessment.

An assessment of the concordance between the investigator-assessed response and independent reviewer-assessed response will be performed for each of the cohorts listed above. Kappa coefficient will be reported along with the corresponding 95% confidence interval.

The concordance rate is calculated as percent agreement (the proportion of best response that agree between investigator assessment and independent reviewer assessment):

$$Percent\ agreement = \frac{\#\ of\ matched\ responders + \#\ of\ matched\ non-responders}{total\ \#\ of\ subjects\ assessed}$$

If ORR from either investigator assessment or independent reviewer assessment for a subject is missing, then the subject will be excluded from the calculation of the concordance rate.

An overall listing of subject response data based on independent radiology review will be provided alongside the investigator assessed responses for the ITT population in the ATC, BTC, ASI, GIST, WHO Grade 1 or 2 Glioma and WHO Grade 3 or 4 Glioma cohorts. This listing will display both independent reviewer-assessed and investigator assessed response evaluations, the best confirmed responses, and BRAF V600E central confirmation status.

2.5 Analysis of the key secondary objective

There is no key secondary objective for this study.

2.6 Analysis of secondary efficacy objective(s)

The secondary efficacy endpoints include duration of response (DoR), progression free survival (PFS) and overall survival (OS). The secondary efficacy endpoints will be analyzed for ATC, BTC, ASI, WHO Grade 1 or 2 Glioma, WHO Grade 3 or 4 Glioma, MM and HCL cohorts. The analyses of the secondary endpoints will take place once all patients have either died or been transitioned off the study. The main population for efficacy analyses is ITT. The BRAF V600E population will be used for supportive analyses of efficacy.

2.6.1 Duration of response

For the subset of subjects who show a confirmed response as defined for each cohort in **Error! Reference source not found.** 2.4.1, duration of response (DoR) is defined as the time (in weeks) from the first documented evidence of response (the first response prior to confirmation) until the time of documented disease progression or death due to any cause.

For the cohorts assessed using RECIST 1.1 and RANO criteria, the analysis of DoR will be based on radiological response from investigator assessment. The date of disease progression is defined as the date of radiological disease progression based on the appropriate disease response criteria. Clinical progression, defined as investigator assessed clinical progression in the absence of radiological confirmation, is not considered a progression event in this analysis. Specifically, in the event of clinical progression leading to discontinuation of study treatment and radiological assessment, if radiological assessments do not indicate radiological progression, then the subject will be censored at the time of last radiological assessment. If a subject has not progressed, not died, and not started new anti-cancer therapy, DoR will be censored at the date of the last adequate assessment.

For the HCL cohort, the overall investigator-assessed response will be used to determine timing of response and/or progression. Relapsed disease will be considered as progression for the analysis.

Details of censoring after extended time without adequate assessment are given in section 4.2.

For subjects who receive subsequent anti-cancer therapy, the following rule will apply:

- If anti-cancer therapy is started without documented progression or is started prior to progression, then DoR will be censored at the date of the last adequate disease assessment that is no later than the date of initiation of anti-cancer therapy (i.e. if disease assessment occurs on the same day as the start of new anti-cancer therapy then the assessment will be used, as it will be assumed that the assessment occurs prior to the administration of new anti-cancer therapy).

DoR based on the investigator response will be summarized for ATC, BTC, ASI, WHO Grade 1 or 2 Glioma, WHO Grade 3 or 4 Glioma and HCL cohorts. If data warrant, Kaplan-Meier method will be used to summarize DoR descriptively and graphically. The median DoR and the first and third quartiles will be presented, along with corresponding 95% confidence intervals. Brookmeyer-Crowley method will be used for the confidence interval calculation. DoR will also be summarized at 6 months, 12 months and 24 months.

Listing of DoR based on investigator assessment will also be provided.

In addition, swim lane plots will be generated for response data based on investigator assessment. These plots will present the best confirmed response category, duration of treatment, time of the first response, duration of response, time of the first disease progression based on radiological assessment and study treatment status at the time of data cut-off for the analysis.

As a sensitivity analysis, DoR based on independent radiology review will be summarized and listed for the ATC, BTC, WHO Grade 1 or 2 Glioma, and WHO Grade 3 or 4 Glioma cohorts, including the estimated median, first and third quartiles, 6 and 12 month Kaplan-Meier estimates. The derivation of DoR based on independent radiology review is similar to that based on the investigator assessment.

For the HCL cohort only, and for the subset of subjects who have a confirmed complete response (with or without MRD), the complete response duration will be calculated as the time from first CR until the earliest of the first subsequent non-CR adequate assessment or death due to any cause. Censoring rules will be applied the same as with Duration of Response. Kaplan-Meier estimates will be used to estimate the median and quartiles of the complete response duration as well as the complete response duration at 180 days. The number and proportion of

the ITT population with complete response duration of at least 180 days will be calculated along with the corresponding Clopper-Pearson exact confidence interval. The time to first confirmed complete response and time to first confirmed overall response will both be summarized with the minimum, maximum, 1st and 3rd quartiles and median displayed in weeks. Only confirmed responders will be included in each of the summaries.

Summaries of reasons for censoring DoR by both investigator assessment and independent radiology review will be produced with additional information about censoring due to COVID-19 related protocol deviations. The number and percentage of subjects with each censoring reason (1. PD or death after >=2 consecutive missed visits, 2. New anti-cancer treatment started prior to documented PD, 3. No baseline (or adequate post-baseline) assessments, 4. No progression or death, separated into follow-up ended and follow-up ongoing) will be displayed along with relevant COVID-19 related censoring reasons (study withdrawal due to COVID-19 and missing visits due to COVID-19) derived from protocol deviations data. Further details of these outputs are given in the programming notes to the TFL shells.

2.6.2 Progression-free survival

Progression-free survival (PFS) is defined as the interval (in weeks) between the first dose of study treatment and earlier date of disease progression or death due to any cause.

For the cohorts assessed using RECIST 1.1 and RANO criteria, the primary analysis of PFS will be based on radiological response from investigator assessment. The date of disease progression is defined as the date of radiological progression based on imaging data. Subjects who do not meet the RECIST 1.1 or RANO criteria for progression and are still alive will be censored. Clinical progression, defined as investigator assessed clinical progression in the absence of radiological confirmation, is not considered a progression event in this analysis. Specifically, in the event of clinical progression leading to discontinuation of study treatment and radiological assessment, if radiological assessments do not indicate radiological progression, then the subject will be censored at the time of last radiological assessment. If a subject has not progressed, not died, and not started new anti-cancer therapy, PFS will be censored at the date of the last adequate assessment. For the HCL cohort, the overall investigator-assessed response will be used to determine timing of progression.

Details of censoring after extended time without adequate assessment are given in section 4.2.

For subjects who receive subsequent anti-cancer therapy, the following rule will apply:

- If anti-cancer therapy is started without documented progression or is started prior to progression, then PFS will be censored at the date of the last adequate disease assessment that is no later than the date of initiation of anti-cancer therapy (i.e. if disease assessment occurs on the same day as the start of new anti-cancer therapy then the assessment will be used, as it will be assumed that the assessment occurs prior to the administration of new anti-cancer therapy).
- If a subject does not have an adequate post-baseline assessment that is no later than the date of initiation of anti-cancer therapy, PFS will be censored at the date of the first dose. If any adequate post-baseline assessment exists after the date of initiation of anti-cancer therapy, the reason for censoring will be recorded as “new anti-cancer treatment started prior to disease progression”. Otherwise if no adequate post-baseline assessments exist,

the reason for censoring will be recorded as "no baseline (or post-baseline adequate) tumor assessments".

PFS based on the investigator assessment will be summarized descriptively and graphically using Kaplan-Meier methods. The Kaplan-Meier estimate for the median progression-free survival time and the first and third quartiles will be determined along with approximate 95% confidence intervals. Brookmeyer-Crowley method will be used for the confidence interval calculation. Kaplan-Meier estimate of PFS at 6 months, 12 months and 24 months will be summarized.

Listing of progression free survival based on investigator assessment will also be provided.

As a sensitivity analysis, PFS based on independent reviewer assessment will be summarized and listed (except for the MM and HCL cohorts which have no independent review) similarly as that of PFS based on investigator assessment.

Summaries of reasons for censoring PFS by both investigator assessment and independent radiology review will be produced with additional information about censoring due to COVID-19 related protocol deviations. The number and percentage of subjects with each censoring reason (1. PD or death after >=2 consecutive missed visits, 2. New anti-cancer treatment started prior to documented PD, 3. No baseline (or adequate post-baseline) assessments, 4. No progression or death, separated into follow-up ended and follow-up ongoing) will be displayed along with relevant COVID-19 related censoring reasons (study withdrawal due to COVID-19 and missing visits due to COVID-19) derived from protocol deviations data. Further details of these outputs are given in the programming notes to the TFL shells.

2.6.3 Overall survival

Overall survival (OS) is defined as the time (in weeks) from first dose until death due to any cause. The length of this interval is estimated as the date of death minus date of first dose plus 1 day. Subjects who have not died will be censored at the date of last contact (as recorded in the eCRF). The last date of contact will be defined as the maximum date of any visit date, survival follow-up date, or date of study withdrawal. Only patient contacts recorded in the eCRF can be used for the calculation of last date of contact.

Overall survival will be summarized descriptively and graphically using Kaplan-Meier method. The Kaplan-Meier estimate for the median overall survival time and the first and third quartiles will be presented, along with approximate 95% confidence intervals. Brookmeyer-Crowley method will be used for the confidence interval calculation. Overall survival at 6 months, 12 months and 24 months will be summarized using the Kaplan-Meier method.

Listing of overall survival data will also be provided.

2.7 Safety analyses

All safety analyses will be based on the All-Treated subjects (ATS) population.

2.7.1 Adverse events (AEs)

Adverse events (AEs) will be graded according to the CTCAE, Version 4.0. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For the final analysis, version 24.1 of MedDRA will be used.

All AEs will be summarized based on frequency and proportion of total subjects experiencing the event, grouped by system organ class and preferred term (PT).

A summary of number and percentage of subjects with any adverse events by maximum grade will be produced for each histologic cohort. In this summary AEs will be sorted by PT in descending order of total incidence. The summary will use the following algorithms for counting the subject:

Preferred term row: Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.

Any event row: Each subject with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables of on-therapy adverse events which are not serious adverse events with an incidence of at least 5% and on-therapy serious adverse events and SAEs suspected to be related to study treatment will be provided by system organ class and preferred term for the all treated subjects population.

If for the same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

All SAEs and fatal SAEs will be tabulated based on the number and percentage of subjects who experienced the event. The summary tables will be displayed in descending order of total incidence by PT only.

Separate listings with subject-level details will be generated for fatal SAEs and non-fatal SAEs. These listings will include PT, verbatim text, onset date, data of resolution, outcome, event duration, time since first and last dose, maximum grades, seriousness, action taken with study treatment and relatedness to study treatment.

The following categories of AEs will be summarized in descending order of total incidence by PT only:

- AEs Leading to Permanent Discontinuation of Any Study Treatment
- AEs Leading to Dose Interruptions
- AEs Leadings to Dose Reductions.

2.7.1.1 Adverse events of special interest / grouping of AEs

A comprehensive list of MedDRA terms based on the program-level electronic case retrieval sheet (eCRS) will be used to identify each type of events. Changes to the MedDRA dictionary

may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety management team (SMT) agreements in place at the time of reporting.

Adverse events of special interest include:

- Skin related toxicities
- Ocular events
- Cardiac related events
- Hepatic disorders
- Pneumonitis/Interstitial lung disease
- Bleeding events
- Hypertension
- Hypersensitivity
- New primary or secondary malignancy
- Venous thromboembolism
- Pyrexia
- Uveitis
- Pre-renal and Intrinsic Renal Failure
- Pancreatitis
- Hyperglycemia
- Neutropenia

The summary of number and percentage of subjects with each type of adverse event of special interest by maximum grade will be produced for each histologic cohort and all cohorts combined. AEs will be sorted by PT in descending order of total incidence.

2.7.2 Deaths

All deaths will be summarized based on the number and percentage of subjects, by time of death (on-therapy and post-therapy) and the primary cause of death. On-therapy and post-therapy are defined in section 2.1.1. A supportive listing will be generated to provide subject-specific details for subject who died.

2.7.3 Laboratory data

The full list of laboratory tests is given in the study protocol section 7.4.8.

Laboratory grades will be reported using the Common Terminology Criteria for Adverse Events (CTCAE v4.0).

Summaries of worst case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE v4.0. These summaries will display the number and percentage of subjects with a maximum on-therapy grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. In addition, the summary will include grade increase from baseline by scheduled

visits. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

For lab tests that are not gradable by CTCAE v4.0, summaries of worst case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized at each scheduled visit as well as for the worst case on-therapy. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories. Detailed derivation of baseline assessment is specified in Section 2.1.1.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

An eDISH plot showing the peak on-therapy total bilirubin versus peak on-therapy ALT will be plotted by histological cohort combining primary analysis and expansion cohorts. Upon data review during the conduct of the study, an additional eDISH plot might be considered showing peak on-therapy total bilirubin versus peak on-therapy AST if there are potential cases based on AST rather than ALT. Subject plots showing the time course of ALT, AST, ALP and total bilirubin will also be produced. The number and percentage of subjects with ALT, AST and bilirubin above relevant thresholds (e.g. 3 x ULN) at any time on-therapy will be displayed. Criteria relating to the combined elevations of ALT or AST and bilirubin are based on the peak values at any time on-therapy and do not have to be concurrent.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

The results of scheduled assessments of ECG will be summarized. A summary of ECG findings will classify each result into "Normal", "Abnormal, not clinically significant" or "Abnormal, clinically significant" as entered on the eCRF. Bazett's and Fridericia's corrections of QT values will be summarized using the categories in section 4.7 for both an increase in grade from baseline and the amount of increase. The summaries will display results by visit and for the worst case (largest increase) post-baseline.

2.7.4.2 Vital signs

Systolic and diastolic blood pressure, heart rate, temperature in degrees Celsius will be summarized by histologic cohort and visit. The worst case post baseline will display the largest value after baseline in the study. Changes from baseline in systolic and diastolic blood pressure, heart rate and temperature in degrees Celsius will be summarized including the categories in section 4.10.

2.8 Pharmacokinetic endpoints

Summary statistics of concentration-time data for trametinib, dabrafenib and metabolites of dabrafenib (Hydroxy-dabrafenib and Desmethyl-dabrafenib) will be provided, both for the full PK population and separately for subjects from Japanese and non-Japanese race categories. Concentration-time data for trametinib, dabrafenib and its metabolites will be listed.

[redacted]

2.10 Biomarkers

BRAF V600E central confirmation status will be summarized and listed. BRAF V600E results from local laboratories will also be presented including the method of analysis (e.g. immunohistochemistry or next generation sequencing), the specimen type and location where the sample was taken. Another summary will show the positive percentage agreement (PPA) between local and central tests for BRAF V600E.

Baseline results for MGMT methylation and IDH1/2 mutation status will be summarized and listed for the high and low grade glioma cohorts. MGMT results are available from both local and central labs. IDH1/2 will be presented from local labs only, because central lab data comes from next generation sequencing (NGS) analysis and records are only created in the dataset when the mutation is detected.

Other biomarker analyses (e.g. to support companion diagnostic development) may be included in a separate analysis plan as required.

2.11 Other Exploratory analyses

No further exploratory analyses are required for the final CSR.

2.12 Interim analysis

Interim analyses have been carried out to monitor efficacy and safety at regular intervals through the study enrollment and for health authority submission and publication after the end of enrollment. Details of interim analyses are given in section 18.3.2 of the protocol and the interim reporting and analysis plans.

3 Change to protocol specified analyses

No changes were made to analyses specified in the protocol.

4 Appendix

4.1 Clinical review of anti-cancer therapies for censoring criteria

Due to the inconsistent recording of anti-cancer therapies (including surgeries) in the eCRF, a manual review of all relevant therapies will be carried out to ensure that the correct records are used to censor the best confirmed overall response, progression-free survival and duration of response. Specifically, spreadsheets of unique on-therapy or follow-up anti-cancer therapies, radiotherapies, and cancer-related surgeries will be sent to a clinical reviewer to identify the interventional treatments for the disease under study and distinguish them from diagnostic procedures, such as biopsies, and surgeries for adverse events not connected with the disease under study, such as squamous cell carcinoma.

4.2 Extended Loss to Follow-up or Extended Time without an Adequate Assessment

Since missing scheduled disease assessments prior to progression or death increases the uncertainty about when the event actually occurs, PFS and DoR will be censored for subjects who have progression or die after missing two or more scheduled disease assessments. Specifically, if there are two or more scheduled assessments which are missing followed by progression or death, PFS and DoR will be censored at the last adequate assessment prior to progression or death.

For the purpose of this calculation, the last adequate assessment is defined as the last assessment prior to progression or death with response other than NE or missing.

For solid tumor cohorts (ATC, BTC, GIST, NSGCT/NGGCT, ASI, WHO Grade 1 or 2 Glioma and Grade 3 or 4 Glioma) and MM cohort, when the scheduled disease assessment is every 8 weeks (for the first 48 weeks of study treatment), a window of 119 days (16 weeks + 7 day window) will be used to determine whether there was an extended time without adequate assessment. When the scheduled disease assessment is every 12 weeks (after the first 48 weeks of study treatment), a window of 175 days (24 weeks + 7 day window) will be used to determine whether there was an extended time without adequate assessment. Specifically, extended lost-to-follow-up period is defined using different time windows as described in Table 4-1.

Table 4-1 Extended lost-to-follow-up period at different study times

Last adequate assessment	Extended lost-to-follow-up period
<= end of week 44	16 + 1 weeks (119 days)

Last adequate assessment	Extended lost-to-follow-up period
(<=308 days)	
>= beginning of week 45 – <= end of week 54 (>308 days, <=378 days)	20 + 1 weeks (147 days)
>= beginning of week 55 (>378 days)	24 + 1 weeks (175 days)

For the HCL cohort, the scheduled disease assessment is every 4 weeks for the first 48 weeks of study treatment, then at least every 8 weeks for patients tolerating the study drug in the judgement of the treating investigator. Following protocol amendment 11, the interval between assessments beyond the first 48 weeks is increased to at least every 12 weeks. To provide reasonable allowance for missed assessments within the new schedule, the same rules will be used for HCL as for the solid tumor cohorts and MM to determine whether there was an extended time without adequate assessment.

4.3 Date Associated with Response

For MM and HCL, investigator assessment of disease is entered in the eCRF on the VISIT form. The date of the VISIT is captured but the date of the response assessment is not captured separately. The date associated with response will be the visit date for the VISIT on which the investigator assessed disease. A disease assessment may occur at an unscheduled visit. The date of the unscheduled visit would be assigned to any response assessed on that date.

For all solid tumor histologies, for each disease assessment after baseline, determine a date associated with the response. For complete response (CR), partial response (PR), and when applicable minor response (MR), assign to the latest date within the disease assessments. For stable disease (SD), Non-CR/Non-PD or Not Evaluable, assign to the earliest date within the disease assessments. For progressive disease (PD), assign to the earliest assessment date associated with the progression.

4.4 Imputation rules

Partial dates may be imputed for 'slotting' data to study time periods or for specific analysis purposes as outlined below.

4.4.1 Demography (ADSL)

Dataset	Date	Missing Element	Rule
ADSL	Birth date (BRTHDT)	day, month, and year	No Imputation for completely missing dates
		day and month	Imputed to June 30

4.4.2 Initial diagnosis of primary tumor type under study

Dataset	Date	Missing Element	Rule
Disease Characteristics (ADDC)	Initial Diagnosis Date	day, month, and year	No imputation for completely missing date
		day, month	Impute the missing month and day as January 1
		day	Impute the missing day as 1st of the month.

4.4.3 Adverse events (ADAE)

Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings.

Dataset	Date	Missing Element	Rule
Adverse Events (ADAE)	Start Date	day, month, and year	No Imputation for completely missing dates
		day, month	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing: o If year of start date = year of study treatment start date then • If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1. • Else set start date = study treatment start date. o Else set start date = January 1.
		day	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: o If month and year of start date = month and year of study treatment start date then • If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month. • Else set start date = study treatment start date. o Else set start date = 1st of month.
	End Date		No imputation for partial end dates will be performed

4.4.4 Surgery and radiotherapy

The following imputation will be used for surgical procedures and start dates of radiotherapy. End dates of radiotherapy will not be imputed.

Dataset	Missing Element	Rule
Surgical Procedures and Radiotherapy (ADPR)	day, month, and year	• No Imputation for completely missing dates
	day, month	• If partial date contains a year only set to January 1st.
	day	• If partial date contains a month and year set to the 1st of the month

4.4.5 Concomitant medication and blood and blood supportive care products

Impute start and end dates for use in derivation of the reference variables, concomitant medication start and end relative to treatment and blood and blood supportive care start and end relative to treatment, but do not permanently store the imputed start and end dates in the analysis datasets. The reference variables will be used to differentiate before, during and after for the concomitant medication or blood or blood supportive care start and end dates.

Dataset	Date	Missing Element	Rule
Concomitant Medication Blood and Blood Supportive Care Products	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing: o If year of start date = year of study treatment start date then ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.

Dataset	Date	Missing Element	Rule
			▪ Else set start date = study treatment start date. o Else set start date = January 1.
		day	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: o If month and year of start date = month and year of study treatment start date then ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month. ▪ Else set start date = study treatment start date. o Else set start date = 1st of month.
	End Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If partial end date contains year only, set end date = earliest of December 31 or date of last contact.
		day	• If partial end date contains month and year, set end date = earliest of last day of the month or date of last contact.

4.4.6 Time to event (Duration of response and Progression-free survival) and best confirmed overall response

On-therapy or follow-up anti-cancer therapy, including radiotherapy and cancer-related surgery start dates, may be imputed to determine date of first new anti-cancer therapy, in order to define event and censoring dates for progression-free survival and duration of response and inclusion of correct records in derivation of best confirmed overall response.

Dates will only be imputed when a month and year are available but the day is missing. In this case, only the date of first new anti-cancer therapy (not all anti-cancer therapy and radiotherapy start dates) will be stored on appropriate efficacy datasets.

The date of first new anti-cancer therapy is derived as the earliest date of new anti-cancer therapy (e.g. chemotherapy), radiotherapy, or cancer related surgical procedure and will include imputed dates. If the date is an imputed date, then the flag variable is assigned the value of 'D' to indicate that the day portion of the date is imputed (following ADaM convention).

As multiple dates are used to derive the new anti-cancer therapy date ensure that the flag is only set to 'D' if the derived date is imputed. For example, if the date of new radiotherapy is imputed but the date of new systemic anti-cancer therapy is prior to date of new radiotherapy and the new systemic anti-cancer therapy date is not a partial date then the flag should be set to missing as the date used for first new anti-cancer therapy is not an imputed date. The following rules will be used to impute the date when partial start dates are present.

Dataset	Date	Missing Element	Rule
Anti-Cancer Therapy Where applicable: Radiotherapy Surgical Procedures	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• No imputation for missing day and month (note the eCRF should only allow for missing day)
		day	• If partial date falls in the same month as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment+1, last day of month). • If partial date falls in the same month as the subject's first occurrence of PD, then assign to earlier of (date of PD+1, last day of month). • If both rules above apply, then assign to latest of the 2 dates • Otherwise, impute missing day to the first of the month.
	End Date		• No imputation for partial end dates will be performed

4.4.7 Imputation of missing exposure end dates

Exposure end dates should be completed for the final study analysis. For any subjects with missing exposure end dates at the final analysis, the missing date will be imputed to the earliest of date of withdrawal from the study or death date. If none of these dates are available then the date of last patient last visit will be used. The imputed exposure end date will be stored in the exposure analysis dataset and an exposure end date imputation flag variable will be derived indicating which exposure end date records are imputed. Imputed exposure end dates will also

be stored on the study treatment end date variable (ADSL.TRTEDT). This variable will hold the last date of exposure across both study treatments.

4.5 Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation). Unscheduled data will only be included in the display sections that report worst-case on-therapy.

If multiple assessments are reported on the same date for the same scheduled planned time, then the mean of multiple measurements reported for the same date will be analyzed, with the exception of laboratory data reported from both central and local laboratories. If laboratory data is reported from both central and local laboratories with the same date, then the central laboratory data will be analyzed to provide consistency with measurements from other subjects.

4.6 Laboratory parameters derivations

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) will be used to assign grades to the relevant laboratory parameters.

4.7 ECG parameters

To identify QTc (Bazett's and Fridericia's) values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign grades (see adverse event 'Electrocardiogram QT corrected interval prolonged').

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute QTcB or QTcF interval	≥450 to <481 (Grade 1) ≥481 to <501 (Grade 2) ≥501 (Grade 3)	Msec
Increase from baseline	Increase of ≥31 to ≤60 Increase of >60	Msec

The following criteria will be used to flag other ECG values that are values of potential clinical importance:

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
PR interval	<110 (L) and >220 (H)	Msec
QRS interval	<75 (L) and >110 (H)	Msec

4.8 Cardiac Scan Modalities (ECHO)

An ECHO modality will be used for determining cardiac scan data (e.g., left ventricular ejection fraction (LVEF)) for all subjects throughout the study. The absolute change from baseline value will not be calculated for any time point in which the post-baseline value was determined by a cardiac scan modality other than ECHO.

4.9 Left ventricular ejection fraction

The following criteria will be used to flag LVEF values that are values of potential clinical importance:

To identify LVEF values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Ejection fraction decreased'.

LVEF Parameter	Unit	Potential Clinical Importance (PCI) Range
Absolute change from baseline LVEF	%	• No change or any increase • Any decrease o >0-<10 decrease o 10-19 decrease o ≥20 decrease o ≥10 decrease and ≥ LLN o ≥10 decrease and below LLN o ≥20 decrease and ≥ LLN o ≥20 decrease and below LLN
Relative change from baseline LVEF	%	• ≥20 decrease and ≥ LLN • ≥20 decrease and below LLN

4.10 Vital signs

To identify heart rate values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Sinus bradycardia', 'Sinus tachycardia', 'Supraventricular tachycardia', and 'Ventricular tachycardia'.

The following criteria will be used to flag heart rate values that are values of potential clinical importance:

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Decrease from baseline Heart Rate	Decrease to <60	bpm
Increase from baseline Heart Rate	Increase to >100	bpm

To identify blood pressure values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypertension'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline Systolic Blood Pressure	≥120 to <140 (Grade 1) ≥140 to <160 (Grade 2) ≥160 (Grade 3)	mmHg
Increase from baseline Diastolic Blood Pressure	≥80 to <90 (Grade 1) ≥90 to <100 (Grade 2) ≥100 (Grade 3)	mmHg

To identify temperature values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypothermia' and 'Fever'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline temperature	Increase to ≥38	Degrees C
Decrease from baseline Diastolic Blood Pressure	Decrease to ≤35	Degrees C

4.11 Statistical models

For the evaluation of ORR, extensive simulation studies were conducted and described in the Protocol to evaluate the performance of the design that incorporates multiple interim analyses, and develop the Bayesian statistical model. No Type I error rate adjustments for multiplicity in primary or secondary analyses will be conducted.

5 Reference