NOVARTIS

Clinical Development

GSK1120212+GSK2118436/Mekinist®+Tafinlar®

MEK116833 (CDRB436C2201) / NCT01750918

An Open-Label, Four-Part, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the MEK Inhibitor GSK1120212, BRAF Inhibitor GSK2118436 and the anti-EGFR Antibody Panitumumab in Combination in Subjects with BRAF-mutation V600E Positive Colorectal Cancer and in Subjects with CRC With Secondary Resistance to Prior Anti-EGFR Therapy

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse Event
CI	Confidence Interval
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Easter Cooperative Oncology Group
eCRF	Electronic Case Report Form
GSK	GlaxoSmithKline
HR	Hazard Ratio
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institutes
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
ULN	Upper Limit of Normal

1 Introduction

This Statistical Analysis Plan (SAP) describes the planned statistical analyses associated with the final analysis of the CDRB436C2201/MEK116833 study. [redacted]

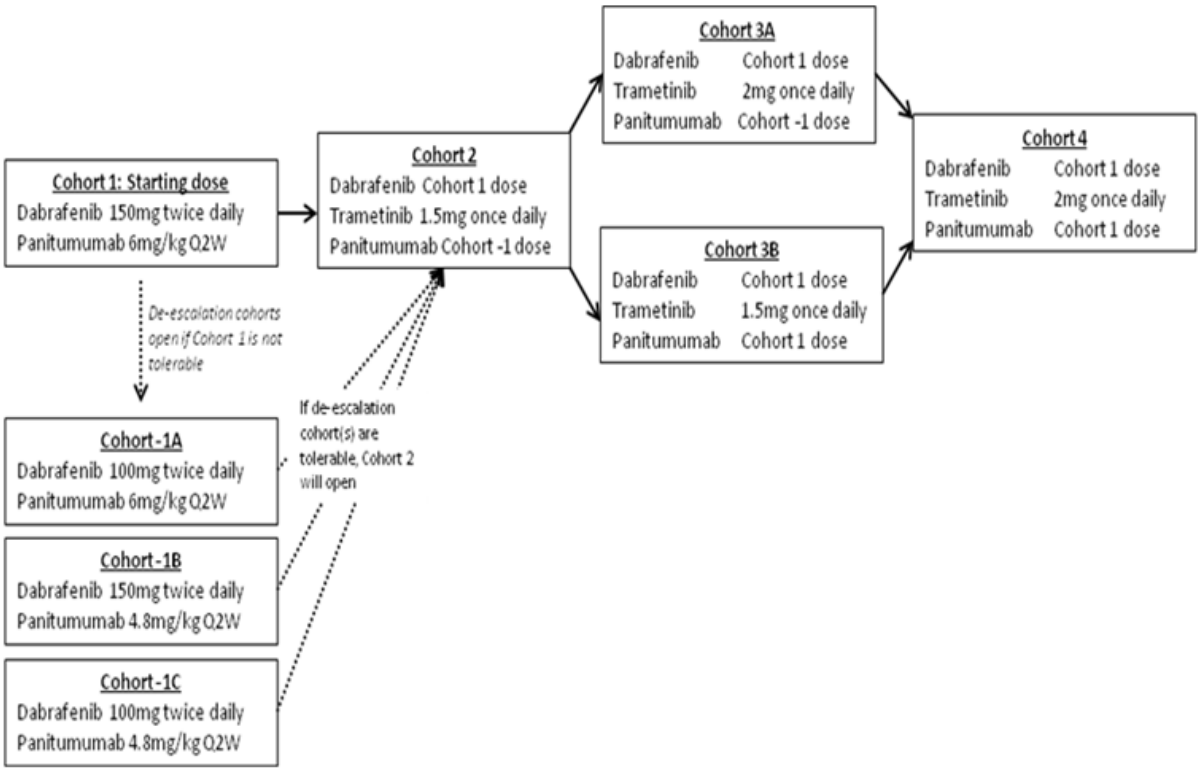
1.1 Study design

This four-part Phase 1/2 multi-center study allows for the phased evaluation of safety, tolerability, and activity of dabrafenib and/or trametinib in combination with panitumumab in subjects with BRAF-V600E mutation-positive CRC and in subjects with CRC with secondary resistance to prior anti-EGFR therapy.

The study design was intended to allow investigation of two doublet combinations (Dabrafenib (D)/ Panitumumab (P) and Trametinib (T)/Panitumumab (P)), in addition to a triple regimen (D/T/P).

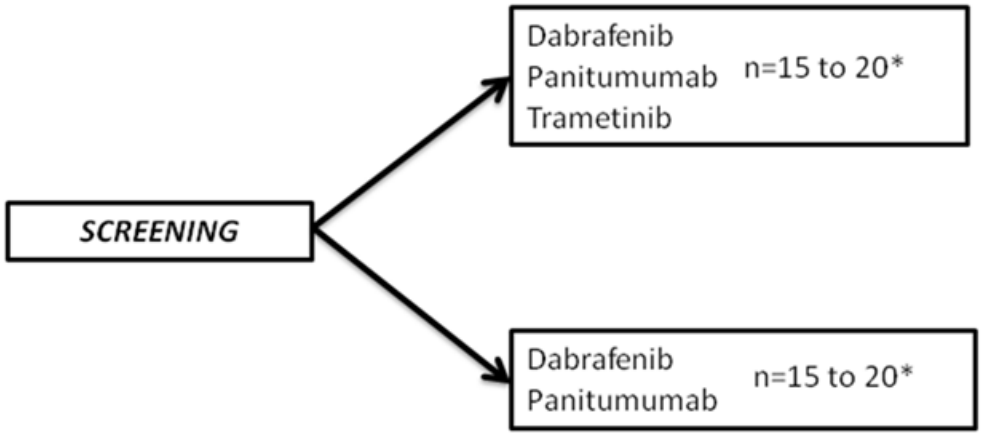
There were multiple parts to this study as described in sections 1.1.1 to 1.1.6.

1.1.1 Part 1 Dose Escalation Study Design/Schematic



In Part 1, it was the intention to define a combination dose for both the dabrafenib/panitumumab combination and the dabrafenib/trametinib/panitumumab combination. The combination dose was either be the recommended full monotheapy dose for all components of the combination or an MTD for the combination. Dosing for dabrafenib and trametinib was continuous daily dosing while panitumumab was dosed once every two weeks, and assessments will occur in 28-day intervals. Subjects were evaluated for dose-limiting toxicities during the first 28 days of treatment.

1.1.2 Part 2A: Cohort Expansions Study Design/Schematic



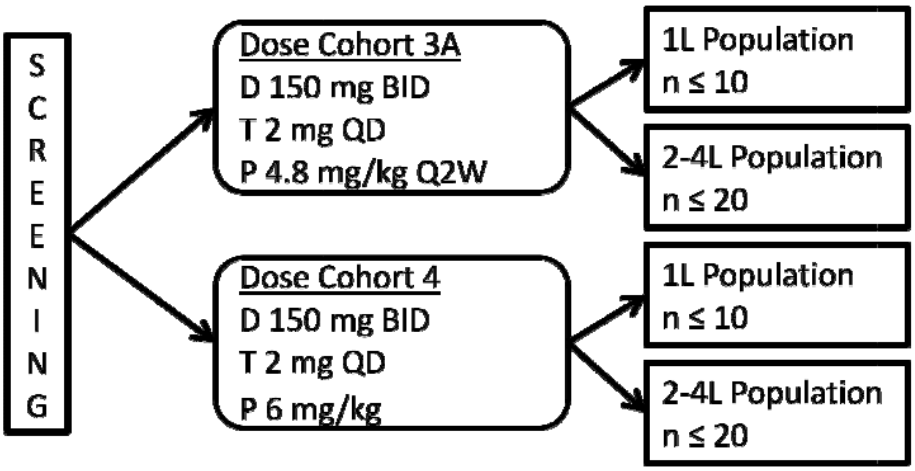
**to include subjects enrolled in Part 1 at that dose level/combination*

In Part 2, the primary objective was to further assess the safety and preliminary clinical activity of given doses and regimen(s) in subjects with BRAF-V600E mutation positive CRC.

In Part 2A, subjects were enrolled in the expansion cohorts at a selected dose of dabrafenib in combination with panitumumab and a selected dose of trametinib plus dabrafenib in combination with panitumumab.

Subjects who participated in Part 1 of the study at the doses evaluated in Part 2A were included in Part 2A analysis, and contributed to the total count of the 20 subjects enrolled in Part 2A.

1.1.3 Part 2B: Cohort Expansions Study Design/Schematic



BID, twice daily dosing; D, dabrafenib; L, line of therapy; P, panitumumab; T, trametinib; Q2W, dosing every 2 weeks; QD, once daily dosing.

After completion of Part 2A, additional subjects were enrolled into the triplet combination of dabrafenib and trametinib in combination with panitumumab. Based on the efficacy and long term tolerability observed in Part 2A, two doses were evaluated in Part 2B.

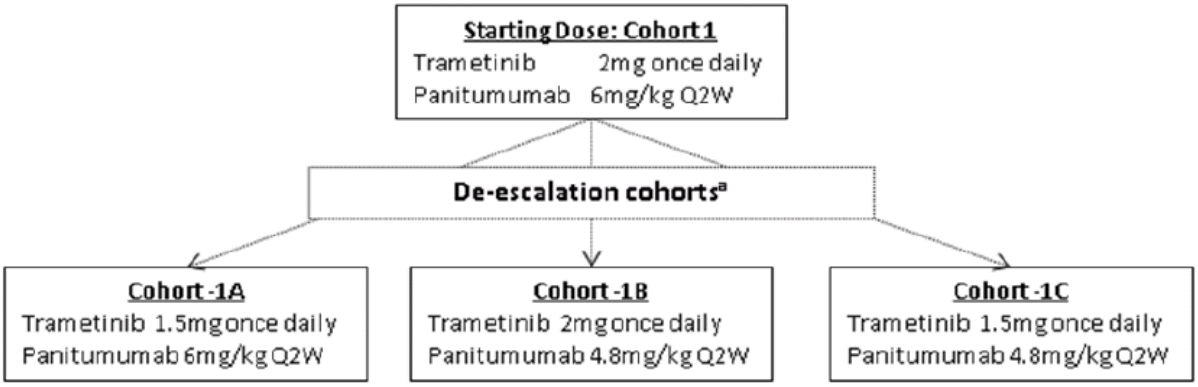
10 subjects with no prior treatment and 22 subjects with at least one prior treatment were enrolled at the Cohort 3A dose (dabrafenib 150mg BID + trametinib 2mg QD + panitumumab 4.8mg/kg IV Q2wks). 5 subjects with no prior treatment and 19 subjects with at least one prior treatment will be enrolled at the Cohort 4 dose (dabrafenib 150mg BID + trametinib 2mg QD + panitumumab 6mg/kg IV Q2wks).

1.1.4 Part 3 Randomized Phase 2 Study

The original intention of the study was to include a randomized phase 2 portion of the study (Part 3) but this will not be performed because the study failed to meet the “go criteria” with respect to response rate and progression free survival.

1.1.5 Part 4A Dose Escalation

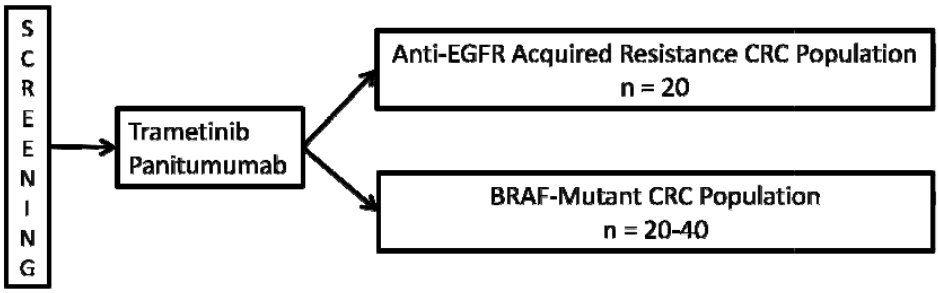
In Part 4A dose escalation, the intention was to determine the MTD for the trametinib/ panitumumab doublet.



a. If the initial combination dose of trametinib and panitumumab in Cohort 1 (starting dose) is not tolerable, the lower dose combination defined in de-escalation cohorts (Cohort -1A, -1B and/or -1C) may be evaluated.

A combination dose was defined for combination of trametinib and panitumumab as shown in the above figure.

1.1.6 Part 4B Cohort Expansion



In Part 4B cohort expansion, the primary objective was to further assess the safety and preliminary clinical activity of trametinib and panitumumab at the MTD determined in Part 4A. Clinical activity was determined in two patient populations of subjects with advanced/metastatic CRC:

1. BRAF mutant population, subjects with BRAF-V600E mutation-positive CRC (described above)

2. Anti-EGFR resistant population, subjects with CRC that developed secondary resistance to anti-EGFR therapy after initially deriving benefit.

1.2 Study objectives and endpoints

The different parts of the study each had separate objectives with specific endpoints associated with each. These objectives and endpoints are described in the protocol and are repeated for primary and secondary obejectives in sections 1.2.1 to 1.2.4 for information. [redacted]

[redacted]

The main purpose of the final analysis is to assess the overall safety and efficacy of the different combinations by dose and to publish the clinical study report.

1.2.1 Part 1: Phase 1 Dose Escalation

	Objectives	Endpoints
Primary	To determine the safety, tolerability and range of tolerated combination doses in subjects with BRAF-V600E mutation-positive CRC in two dosing groups: • dabrafenib dosed orally in combination with panitumumab • trametinib dosed orally in combination with dabrafenib and panitumumab	Adverse events and changes in laboratory values, vital signs and dose interruptions, modifications and discontinuations
Secondary	To describe the pharmacokinetics of dabrafenib, trametinib and panitumumab after combination therapy To determine preliminary clinical activity of dabrafenib dosed orally in combination with panitumumab To determine clinical activity of trametinib dosed orally in combination with dabrafenib and panitumumab To evaluate the pharmacodynamic response in colorectal tumors following combination treatment	Maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), and area under the concentration-time curve from zero (pre-dose) 8 hours (AUC(0-8)), pre-dose (trough) concentration at the end of the dosing interval ($C\tau$) of trametinib and dabrafenib. Predose ($C\tau$) and Cmax concentrations of panitumumab. Response rate (complete response [CR] + partial response [PR]) Progression free survival Duration of response Change in levels of proteins/RNA implicated in MAPK/PI3K/EGFR pathways in pre- and post-dose tumor tissue.

1.2.2 Part 2: Cohort Expansions

	Objectives	Endpoints
Primary	To confirm the safety and tolerability of combination doses in subjects with BRAF-V600E mutation-positive CRC in two dosing groups: • dabrafenib dosed orally in combination with panitumumab • trametinib dosed orally in combination with dabrafenib and panitumumab	Adverse events and changes in laboratory values, vital signs and dose interruptions, modifications and discontinuations
	To determine clinical activity in subjects with BRAF-V600E mutation-positive CRC in two dosing groups: • dabrafenib dosed orally in combination with panitumumab • trametinib dosed orally in combination with dabrafenib and panitumumab	Response rate (CR +PR)
Secondary	To characterize the population PK parameters of dabrafenib and trametinib dosed orally in combination with anti-EGFR antibody (panitumumab)	Population PK parameters, oral clearance (CL/F), oral volume of distribution (V/F), and absorption rate constant (Ka)
	To characterize the durability of response with dabrafenib dosed orally in combination with panitumumab	Duration of response Progression-free survival Overall survival
	To characterize the durability of response with trametinib dosed orally in combination with dabrafenib and panitumumab	Duration of response Progression-free survival Overall Survival

	To evaluate the pharmacodynamic response in colorectal tumors following combination treatment	Change in levels of proteins/RNA implicated in MAPK/PI3K/EGFR pathways in pre- and post-dose tumor tissue

1.2.3 Part 4A: Dose Escalation

	Objectives	**Endpoints**
Primary	To determine the safety, tolerability and range of tolerated doses in the combination of panitumumab and trametinib in subjects with advanced/metastatic CRC	Adverse events and changes in laboratory values, vital signs and dose interruptions, modifications and discontinuations
Secondary	To describe the pharmacokinetics of trametinib and panitumumab after combination therapy To determine preliminary clinical activity of panitumumab/ trametinib combination therapy in two patient populations: • subjects with BRAF-V600E mutation-positive CRC • subjects with CRC that developed secondary resistance to anti-EGFR therapy after initially deriving benefit To evaluate the pharmacodynamic response in colorectal tumors following combination therapy	Maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), and area under the concentration-time curve from zero (pre-dose) the time of the last quantifiable concentration (AUC(0-t)), pre-dose (trough) concentration at the end of the dosing interval ($C\tau$) of trametinib. Predose ($C\tau$) and Cmax concentrations of panitumumab. Response rate (complete response [CR] + partial response [PR]) Progression free survival Duration of response Change in levels of proteins/RNA implicated in MAPK/PI3K/EGFR pathways in pre- and post-dose tumor tissue.

1.2.4 Part 4B: Cohort Expansion

	Objectives	**Endpoints**

Primary	To confirm the safety and tolerability of RP2R of the panitumumab/ trametinib combination in an expansion cohorts of • subjects with BRAF-V600E mutation-positive CRC • subjects with CRC that developed secondary resistance to anti-EGFR therapy after initially deriving benefit To determine clinical activity of combination therapy in this patient population	Adverse events and changes in laboratory values, vital signs and dose interruptions, modifications and discontinuations Response rate (CR +PR)
Secondary	To characterize the population PK parameters of trametinib dosed orally in combination with anti-EGFR antibody (panitumumab) To characterize the durability of response with trametinib dosed in combination with panitumumab To evaluate the pharmacodynamic response in colorectal tumors following combination treatment	Population PK parameters, oral clearance (CL/F), oral volume of distribution (V/F), and absorption rate constant (Ka) Duration of response, Progression-free survival, Overall survival Change in levels of proteins/RNA implicated in MAPK/PI3K/EGFR pathways in pre- and post-dose tumor tissue

2 Statistical methods

2.1 Treatment group labels and ordering

The final analysis will focus on evaluating the safety and the efficacy of each separate treatment combination, from an overall perspective with all dose regimens combined, as well as assessing the individual dose regimens. To report the results, the following treatment labels and abbreviations will be used for all efficacy tables, listings and figures:

Dabrafenib (DAB), Trametinib (TRA), Panitumumab (PAN)

- Triple Combination (T+D+P)
  - DAB 150MG BID, TRA 1.5MG QD, PAN 4.8MG/KG Q2W

  - DAB 150MG BID, TRA 2MG QD, PAN 4.8MG/KG Q2W
  - DAB 150MG BID, TRA 1.5MG QD, PAN 6MG/KG Q2W
  - DAB 150MG BID, TRA 2MG QD, PAN 6MG/KG Q2W
- Double Combination (T+P)
  - TRA 2MG QD, PAN 6MG/KG Q2W
  - TRA 1.5MG QD, PAN 6MG/KG Q2W
  - TRA 2MG QD, PAN 4.8MG/KG Q2W
- Double Combination (D+P)
  - DAB 150MG BID, PAN 6MG/KG Q2W

2.2 Data analysis general information

The following sections provide a general description of the derived and transformed variables used to describe and analyze the data. Separate analysis dataset specifications provide full details on all data derivations and transformations including standard Oncology algorithms. The analysis dataset specifications will clearly communicate the content and source of the datasets supporting the statistical analyses. Each treatment combination will be analyzed separately for safety as well as efficacy analyses.

2.2.1 Multicenter Studies

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

2.2.2 Baseline Definition

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.

For subjects who did not receive study treatment during the study, baseline will be defined as the latest, non-missing collected value.

2.2.3 Change from baseline

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.

2.2.4 Withdrawal

Reason for subject withdrawal will be listed.

2.2.5 Missing Data

Missing data will not be imputed. Where appropriate, available data will be summarized over specified intervals (e.g., from start of treatment until withdrawal from study) using suitable summary statistics.

2.2.6 Protocol Deviation

A summary and listing of important protocol deviations will be provided.

2.2.7 Derived and Transformed Data

The PK parameters, AUC, Cmax, and terminal half-life will be log-transformed prior to analysis when needed.

2.2.8 Assessment Windows

Safety assessments that occur prior to the administration of study drug will be considered screening assessments. Safety assessments that occur after dosing has begun will be considered as having occurred while on treatment.

Disease assessments will be distinguished as belonging to either screening, continued therapy or post-study phases of the study.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs). See the definition of study periods in relation to treatment in section 2.7. Study Day for Safety

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

2.2.9 Study Day for Efficacy

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

2.2.10 Reference Date

The reference date for age is the date of screening as age is an eligibility requirement. For other analyses the reference date is the treatment start date, and will be used to calculate study day for safety and efficacy measures.

2.2.11 Durations and Elapsed Time

Durations (e.g. duration of adverse event, duration of response, etc) will be calculated as stop date minus start date plus one. For elapsed time (e.g. time since initial diagnosis):

- if the reference date is on or after event date then elapsed time is the reference date minus the event date +1.
- if the reference date is before the event date then 'elapse time' is the reference date minus the event date.

When reporting time to event durations (e.g., PFS, DOR) 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. These algorithms for time to event return decimal numbers, and ignore the actual numbers of days in the months or years between start date and stop date. The "year" used in these algorithms is 365.25 days long, and the "month" is one twelfth of that year.

For converting all other durations (e.g. duration of adverse events, duration of exposure, age, etc.) to weeks, months or years the following algorithms are used:

- To report the duration in weeks divide the number of days by 7.
- To report the duration in months use: (YEAR (stopdate+1) – YEAR (startdate)) * 12 + (MONTH (stopdate+1) – month (startdate) -1) + (DAY (stopdate+1) >= DAY (startdate))
- To report the duration in years use: intck('year', startdate, stopdate+1) - (month(stopdate+1)<month(startdate) or (month(stopdate+1)=month(startdate) and day(stopdate+1)<day(startdate)))

The algorithms above for age and duration return whole numbers for months and years, accurately accounting for the actual numbers of days in the months or years between the start date and the stop date.

2.2.12 Imputation of Partial Dates

Missing data will not be imputed. Imputed partial dates will not be used to derive study day, duration (e.g., duration of adverse events), or elapsed time variables.

2.2.13 Data to be Included in the Analysis

The study will be considered completed for purposes of a final analysis when the last subject has been followed up for 8 weeks after the last treatment.

For this planned analysis for the Final CSR, a unique cut-off date will be established approximately 8 weeks after the Last Patient Last Treatment. All statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these cases, the end date will not be imputed and therefore will not appear in the listings.

2.2.14 Last Contact Date

Last contact date will be used for the censoring of patients in the analysis of overall survival.

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the following:

- Last follow up visit date collected on the 'Survival information' eCRF.
- All assessment dates (e.g. tumor assessment, laboratory/PK collection dates, vital signs assessment, performance status, ECG assessment). Note, only a true on study assessment date or patient follow up visit date will be used.
- No dates post cut-off will be used.
- Medication dates including study medications, concomitant medications, and anti- cancer therapies administered after study treatment discontinuation.
- Adverse event dates.

Note: The cut-off date will not be used for last contact date, unless the patient was known to be alive on that date.

2.2.15 Other Issues

Demographic and baseline characteristics will be summarized.

2.3 Analysis sets

2.3.1 All Treated Population

All Treated will be defined as the population of all subjects that have been treated with at least one dose of the study drug at the time of the final analysis. This will be the population for summaries of safety and efficacy data.

We will also report efficacy for Anti-EGFR acquired resistance CRC population and BRAF-mutant CRC population separately for the T+P drug combination.

2.3.2 Pharmacokinetic Population

The **PK Population** is defined as those subjects in the All Treated Population and for whom a PK sample is obtained and analyzed prior to the data cut-off date. This population will be used for the secondary PK endpoints.

2.3.3 Biomarker Population

The **biomarker population** is defined as subjects in the All Treated Population for whom a tumor biopsy/tissue was obtained and analysed.

2.3.4 Crossover Population

The **Crossover Population** will comprise the subset of subjects in double combination who had intra-subject doublet to triplet crossover. It will be the primary population when summarizing data in Part 1, Part 2 and Part 4 crossover phase.

The efficacy data collected after crossover for those subjects who crossed over from dabrafenib/panitumumab combination or trametinib/panitumumab to dabrafenib/trametinib/panitumumab combination will not be included in the main efficacy analysis for dabrafenib/trametinib/panitumumab combinations. The crossover efficacy data for these subjects will be only presenting in listings. All safety analysis including treatment emergent AE's regardless of crossover will be reported.

2.4 Subgroup of interest

There are no sub group analysis planned for the final CSR analysis. Efficacy and disease characteristics analysis for T+P cohort will be done separately for BRAF mutant patients and anti-EGFR patients.

2.5 Patient disposition, demographics and other baseline characteristics

2.5.1 Patient Disposition

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.

A summary of subject status and reason for study withdrawal will be provided. 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 summary of study treatment status will be provided. 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 table will be produced for each treatment combinations.

2.5.2 Demographic and Disease Characteristics Assessments

The following demographic parameters will be captured: date of birth, gender, race, ECOG and ethnicity.

Primary tumor type including date (month and year) of first diagnosis will be taken as part of the disease characteristics assessments. Disease characteristics at screening will be reporting percentages of measurable disease, non-target lesions at baseline, primary tumor type, histology, BRAF V600E mutation, MSI status, Stages of disease, prior lines of therapy and prior anti-EGFR therapy.

Disease characteristics assessments will be separated for the BRAF V600E mutant population and the anti_EGFR acquired resistance population.

2.6 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.6.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by each drug combination separately. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number(%) of subjects in each interval. The number (%) of subjects who have dose reductions or interruptions, and the reasons, will be summarized by treatment group.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

The subject's average daily dose, defined as the cumulative dose divided by the duration of exposure for each subject, will be summarized. It will be calculated for each subject first and the summary statistics are calculated based on the subject average daily dose. In addition, summary of the population level daily dose will also be provided. In this analysis, 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 of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the investigational drug or control, and any combination partner, if applicable:

Duration of exposure to study treatment (*days*) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

The last date of exposure to study treatment is the latest of the last dates of exposure to any drug combination.

Summary of duration of exposure of study treatment in appropriate time units will include categorical summaries and continuous summaries (i.e. mean, standard deviation etc.) using appropriate units of time.

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the Dose Administration eCRF.

For patients who did not take any drug the cumulative dose is by definition equal to zero.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

For intermittent dosing, the actual cumulative dose should be defined based on the days when the subject is assumed to have taken a non-zerodose during dosing periods.

Dose intensity and relative dose intensity

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (*dosing unit / unit of time*) = Actual Cumulative dose (*dosing unit*) / Duration of exposure to study treatment (*unit of time*).

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

PDI (*dosing unit / unit of time* = Planned Cumulative dose (*dosing unit*) / Duration of exposure (*unit of time*).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (*dosing unit / unit of time*) / PDI (*dosing unit / unit of time*).

DI and RDI will be summarized *using the duration of exposure of each of the components.*

Dose reductions, interruptions or permanent discontinuations

The number of subjects who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized separately for each of the study treatment components.

'Dose interrupted', and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered/total daily dose is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change.

2.6.2 Prohibited Medications

The use of certain medications, and illicit drugs within 5 half-lives or 28 days, whichever is shorter prior to the first dose of study drug and for the duration of the trial will not be allowed.

A list of protocol deviations regarding prohibited medications will be reported. There will be no separate analysis on prohibited and permitted medications in this reporting activity.

2.6.3 Study time periods of Concomitant Medications

Concomitant Medication 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 references time flag variables and end date reference time flag variables will be added to the concomitant medications.

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 Prior 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. 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').

2.7 Study Time Periods 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 9.2.5). 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 to 30 days after the last dose date of study treatment.

Post-therapy is defined as any time beyond the on-therapy period (i.e. starting at day 30+1 after the last dose date of study treatment).

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.

2.8 Analysis of the primary objective

Please refer to Section 1.2 for objectives which relate to the individual study parts.

2.8.1 Primary endpoint

The primary endpoint to assess efficacy for the Final Analysis will be the response rate. The results will be summarized by combination.
For T+P drug combination, the efficacy will be reported for Anti-EGFR acquired resistance CRC population and BRAF-mutant CRC population separately.

2.8.2 Statistical hypothesis, model, and method of analysis

The primary endpoint, overall response rate (ORR) is defined as the percentage of subjects with evidence of a confirmed complete response (CR) or partial response (PR) as per RECIST v1.1 [Eisenhauer, 2009]. The estimated ORR along with corresponding 2-sided 95% exact CIs as derived by the Clopper-Pearson method will be presented by each treatment combination.

2.9 Analysis of the key secondary objective

There are no key secondary objective. All secondary objectives are included in Section 2.10.

2.10 Analysis of secondary efficacy objective(s)

Please refer to Section 1.2 for objectives relating to the individual study parts .

2.10.1 Secondary endpoints

The secondary endpoints relevant for this Final Analysis will be DOR, PFS and OS. The results will be summarized by cohort and by dose.

Duration of response (DOR) is defined as the time from the first documented occurrence of response (PR or CR) until the date of the first documented progression based on RECIST v1.1 or death.

2.10.2 Statistical hypothesis, model, and method of analysis

In each treatment combination, a KM curve will be constructed. The 25th, 50th (median), and 75th percentiles of the DOR and the 2-sided 95% CIs will be reported for both treatments. For PFS, the HR for treatment effect will be estimated and its 2-sided 95% CIs will be reported.

For OS, the HR will be estimated and its 2-sided 95% CIs will be reported.

All analyses will be based on the All Treated Population. For T+P drug combination, the efficacy will be reported for Anti-EGFR acquired resistance CRC population and BRAF-mutant CRC population separately.

All efficacy analyses will be summaries on drug combination and by dose groups and not by part. No formal comparison will be conducted between cohorts. All efficacy data will be listed and summarized for the treatment period before the crossover.

There are no separate analyses for the cross over population. Listings will include cross-over visits.

The methods of analysis for PK endpoints are discussed in Section 2.13.

Specifically, efficacy analyses in the each cohorts are illustrated in Table 2-1.

The primary efficacy analysis ORR will be summarized using descriptive statistics (N,%) along with 2-sided exact 95% confidence interval (CI) [Clopper and Pearson 1934].

The secondary efficacy analysis for PFS, OS and DOR will be presented using a Kaplan-Meier curve. Median survival together with their 95% confidence intervals will be reported.

Table 2-1 Efficacy analysis by Drug Combination

Endpoint	Population	Analysis
ORR DOR PFS	• Triple combination D+T+P • Double combination T+P [BRAF mutant] • Double combination T+P [Anti-EGFR] • Double combination (D+P)	• Primary analysis: based on investigator assessment • Sensitivity analysis: based on independent

		reviewer assessment (except T+P)
OS	• Triple combination D+T+P • Double combination T+P [BRAF mutant] • Double combination T+P [Anti-EGFR] • Double combination (D+P)	• OS analysis

2.10.3 Handling of missing values/censoring/discontinuations

The DOR will be analyzed based on data from responders only. Patients who did not experience progressive disease and are still alive will be censored at the last adequate response assessment. PFS is defined as the time from the date of randomization to the date of the first documented PD or relapse or death due to any cause.

Subjects who progressed or died after an extended period without adequate assessment or who started a new anti-cancer therapy prior to a PFS event will be censored at their date of last adequate assessment prior to progression or death. An adequate assessment is defined as an assessment where the determined response is CR, PR or SD. As the assessment schedule changes through the course of the study, the following rules will be used for identifying extended loss to follow-up or extended time without an adequate assessment:

- If death or PD is on or prior to Day 175 (Week 24 + 7 day window) then a patient will be identified as an extended loss to follow-up if the patient did not have an adequate assessment during the time period of 91 days (2*6 weeks + 7 day window) prior to death or PD;
- If death or PD is after Day 175 then a patient will be identified as an extended loss to follow-up if the patient did not have an adequate assessment during the time period of 119 days (2*8 weeks + 7 day window) prior to death or PD.

OS is defined as the time from date of randomization to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last contact.

2.10.4 Supportive analyses

A sensitivity analysis of ORR, DOR and PFS based on independent reviewer assessed response (RECIST 1.1) will also be provided.

2.11 Safety analyses

To report the results, the following treatment labels and abbreviations will be used for all safty tables, listings and figures: Dabrafenib (DAB), Trametinib (TRA), Panitumumab (PAN)

- Triple Combination (T+D+P)
  - DAB 150MG BID, TRA 1.5MG QD, PAN 4.8MG/KG Q2W
  - DAB 150MG BID, TRA 2MG QD, PAN 4.8MG/KG Q2W

- DAB 150MG BID, TRA 1.5MG QD, PAN 6MG/KG Q2W
- DAB 150MG BID, TRA 2MG QD, PAN 6MG/KG Q2W

- Double Combination (T+P)
  - TRA 2MG QD, PAN 6MG/KG Q2W
  - TRA 1.5MG QD, PAN 6MG/KG Q2W
  - TRA 2MG QD, PAN 4.8MG/KG Q2W
- Double Combination (D+P)
  - DAB 150MG BID, PAN 6MG/KG Q2W

2.11.1 Dose-Limiting Toxicity

There were no DLTs reported in the escalation phase of the study and as a result there are no analyses performed relating to dose-limiting toxicities.

2.11.2 Adverse events (AEs)

Adverse events (AEs) were graded according to the CTCAE, Version 4.03. and coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

A summary of number and percentage of subjects with any adverse events by maximum grade will be produced. AEs will be sorted by Preferred term (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.

2.11.2.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest (AESI) is a grouping of adverse events that are of scientific and medical concern specific to dabrafenib and trametinib. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need.

AESI for the dabrafenib therapy are:

- Hyperglycemia
- Hypersensitivity
- New Primary or Secondary Malignancy
- Pancreatitis

- Pre-renal and intrinsic renal failure
- Pyrexia
- Uveitis

AESI for the trametinib therapy are:

- Bleeding events
- Cardiac related events
- Hepatic disorders
- Hypersensitivity
- Hypertension
- Ocular events
- Pneumonitis and Interstitial Lung Disease
- Skin toxicity
- Venous Thromboembolism

AESI for the dabrafenib + trametinib combination therapy are:

- Bleeding events
- Cardiac related events
- Hepatic disorders
- Hyperglycemia
- Hypersensitivity
- Hypertension
- Neutropenia
- New Primary or Secondary Malignancy
- Ocular events
- Pancreatitis
- Pneumonitis and Interstitial Lung Disease
- Pre-renal and intrinsic renal failure
- Pyrexia
- Skin toxicity
- Uveitis
- Venous Thromboembolism

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

The events of special interest will be analysed using the most updated asset specific AESI (Adverse Event of Special Interest) at the time of analysis.

2.11.3 Deaths and Serious Adverse Events

All deaths will be summarised based on the number and percentage of subjects. This summary will classify subjects by time of death (on-therapy and post-therapy) and the primary cause of death. A supportive listing will be generated to provide subject-specific details for subject who died.

All 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.

2.11.4 Adverse Events Leading to Discontinuation of Study Treatment and/or Withdrawal from the Study and Other

For each cohort, the following categories of AEs will be summarized separately in descending order of total incidence by PT only:

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

2.11.5 Laboratory data

The assessment of laboratory toxicities will examine the following laboratory tests:

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total bilirubin
- Complete blood count and platelets
- Serum creatinine
- Glucose
- Serum calcium
- Lactate dehydrogenase (LDH)

Laboratory grades will be reported using the Common Terminology Criteria for Adverse Events (CTCAE v4.03).

Summaries of worst case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE v4.03. 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 v4.03, 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 9.

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.

2.11.5.1 Laboratory Parameters Ranges

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 v4.03) will be used to assign grades to the relevant laboratory parameters.

For laboratory data which are not listed in the NCI CTCAE v4.03, a summary of values outside the normal range will be provided.

2.11.6 ECG and cardiac imaging data

To identify QTc (Bazett's) values of potential clinical importance, NCI-CTCAE v4.03 will be used to assign grades (see adverse event 'Electrocardiogram QT corrected interval prolonged'). The following tables will define interval values that will be use in ECG summary displays.

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute QTcB interval	≥450 to <481 (Grade 1) ≥481 to <501 (Grade 2) ≥501 (Grade 3)	Msec
Increase from baseline QTcB	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

2.11.7 ECHO

ECHO data including left ventricular ejection fraction (LVEF) values, the institution's lower limit of normal (LLN), absolute change from baseline LVEF, percentage change from baseline in LVEF, and ECHO scan results will be listed for each subject. Vital Signs

Vital sign data (blood pressure, heart rate, respiration rate and temperature) and change from baseline will be listed for each subject. For the analysis of vital signs the clinically notable vital sign criteria are provided below.

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body temperature	>= 39.1	-

The number and percentage of patients with notable vital sign values (high/low) will be presented by treatment group.

2.11.8 ECOG

ECOG performance status at baseline will be summarized. ECOG shift from baseline will be produced for the worst case post-baseline. A summary of change from baseline will be performed for the worst-case post-baseline and the best case post-baseline changes during the study (improved, no change, and deteriorated).

A listing of ECOG performance status values for all subjects will be produced. Baseline value for each subject will be specified in the listing.

2.12 Biomarkers

Measurements for levels of proteins/RNA implicated in MAPK/PI3K/EGFR pathways (pERK and pS6 H-score) will be summarized separately for pre- and post-dose and as changes from pre-dose for patients with both pre- and post-dose values.

BRAF mutation central testing results will be listed and summarized. [redacted]

2.13 Pharmacokinetic endpoints

The PK results will be reported based on the drug combination and doseage. The tratment labels will follow the labels listed in safety section (2.11).

PK parameters for dabrafenib, trametinib and panitumumab for subjects in whom the full blood sampling scheme was used will be calculated with standard non-compartmental methods according to current working practices and using WinNonlin Professional version 5.2 or higher. All calculations of non-compartmental parameters will be based on actual blood sampling times.

The following parameters will be calculated for dabrafenib (and its metabolites) and trametinib as data permit:

- The first occurrence of the maximum observed plasma concentration determined directly from the raw concentration-time data (Cmax)
- The time at which Cmax is observed will be determined directly from the raw concentration-time data (tmax)
- The area under the plasma concentration-time curve to the last quantifiable concentration (AUC(0-t)) determined using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations.
- The area under the plasma concentration-time curve to 8 hours (AUC(0-8)) determined using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations.
- The trough (pre-dose) plasma concentration determined directly from the raw concentration-time data ($C\tau$)

The following parameters will be calculated for panitumumab as data permit:

- Cmax
- Cτ

[redacted]

2.13.1 Statistical Analysis of PK Concentration Data

No formal comparison will be conducted between the cohorts within the treatment combinations.

Concentrations of trametinib, dabrafenib and metabolites and panitumumab will be listed and summarized by nominal time/visit and each treatment cohort. Average pre-dose concentration for each subject will be calculated using pre-dose concentration at Day 1, Day 15, Week 8, 12, and 16 (where applicable), and will be included in the listing and summary table. Standard summary statistics will be calculated, including n, geometric mean and geo-mean CV%, mean, median, SD, minimum and maximum.

PK parameters of trametinib, dabrafenib and metabolites and panitumumab will be listed and summarized by nominal visit and each treatment cohort. Descriptive statistics (e.g., n, geometric mean, geometric CV%, mean, median, SD, minimum, maximum) will be presented for all PK parameters, except for tmax, where only n, median, minimum and maximum will be presented.

Coefficient of variation (CV) (%) is calculated as follows:

100*(SD/arithmetic mean).

Geometric CV (%) is calculated as follows:

sqrt (exp (variance for log transformed data)-1)*100.

Subjects may be excluded from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. Specific time points might be excluded from the analysis set if technical issues with the sample are reported (e.g. sampling issues, missing information) or if LLOQ sample is observed in between measurable concentrations. These patients and concentration data points will be identified at the time of analysis.

3 Sample size calculation

3.1 Part 1 and Part 4 Dose Escalation

The total number of subjects in Part 1 and Part 4 dose escalation will depend on the number of dose escalations needed. However, the maximum anticipated number of subjects will be approximately 24 in Part 1 and approximately 22 in Part 4 dose escalation.

Table 3-1 Statistical Basis for Phase 1 Dose Escalation

True incidence of dose-limiting toxicity	10%	20%	30%	40%	50%	60%
Probability of escalating the dose	0.91	0.71	0.49	0.31	0.17	0.08

3.2 Part 2 and Part 4 Cohort Expansions

Part 2 will enroll up to 90 subjects in total. Part 4 cohort expansion will enroll 40-60 subjects in total (20 subjects in the anti-EGFR acquired resistance CRC population and 20-40 subjects in the BRAF mutant CRC population). Subjects will be evaluated separately by dose cohort and population at the end of Part 2 and Part 4.

To determine the sample size for dabrafenib in combination with panitumumab expansion cohort, and trametinib in combination with panitumumab expansion cohort, a traditional, 2-stage Green-Dahlberg design [Green, 1992] was evaluated and the sample size for the first stage will be used for the futility analysis. To test the hypotheses (RR=30% vs. RR=15%), using a Green-Dahlberg design, 20 subjects per drug combination would be needed for Stage 1 (assuming a type 1 error of 10% and power of 80%). The chance to effectively terminate the trial after 20 subjects due to futility (true RR=15%) is 33%; the risk to incorrectly stop the trial after 20 subjects if the treatment is effective (true RR=40%) is less than 2%. To determine the maximum sample size for any cohort or patient population in trametinib plus dabrafenib in combination with panitumumab, Bayesian predictive adaptive design will be used for testing hypotheses:

$$H_0: RR \leq 15\%$$

$$H_A: RR \geq 30\%$$

When maximum sample size is 54, the design will have a Type I error (α) of 0.089 and 88% power with the probability of termination is 0.911 when the treatment is futile and probability of early termination 0.116 when the treatment is effective (true RR=0.3).

Table 3-2 Futility Analysis Design Performance

True RR	Probability of Termination, after 20 pts	Probability of Termination, after 34 pts	Probability of Termination, after 40 pts	Probability of Termination, after 54 pts
15%	0.329	0.548	0.603	0.911
20%	0.180	0.288	0.324	0.641
30%	0.044	0.054	0.057	0.116
40%	0.007	0.011	0.011	0.013

A Bayesian posterior probability will also be calculated to further inform decision making. Since neither dabrafenib in combination with panitumumab, trametinib in combination with panitumumab, nor trametinib in combination with dabrafenib and panitumumab has been tested previously in the clinic in CRC subjects, a Beta (0.003, 0.007) prior is assumed. This prior is equivalent to the information from 0.01 subject. The posterior probabilities of ORR exceeding

20%, 30% and 40% based on 20 subjects and the posterior probabilities of ORR exceeding 20%, 30% and 40% based on 54 subjects are shown in Table 3-3.

Table 3-3 Bayesian Posterior Probabilities of Response Rate for Given Number of Observed Responses

# of Responses Observed out of 20 Subjects	Posterior Probability RR ≥20%	Posterior Probability RR ≥30%	Posterior Probability RR ≥40%
4	0.45	0.14	0.024
5	0.69	0.29	0.075
6	0.83	0.48	0.17
7	0.93	0.66	0.31
8	0.97	0.81	0.49
# of Responses Observed out of 34 Subjects	**Posterior Probability RR ≥20%**	**Posterior Probability RR ≥30%**	**Posterior Probability RR ≥40%**
5	0.18	0.01	0.000
6	0.33	0.04	0.002
7	0.50	0.09	0.007
8	0.67	0.18	0.019
9	0.80	0.30	0.044
10	0.89	0.45	0.092
11	0.95	0.60	0.169
12	0.98	0.73	0.276
# of Responses Observed out of 40 Subjects	**Posterior Probability RR ≥20%**	**Posterior Probability RR ≥30%**	**Posterior Probability RR ≥40%**
6	0.18	0.01	0.000
7	0.31	0.03	0.001
8	0.47	0.07	0.003
9	0.62	0.13	0.008
10	0.76	0.22	0.020
11	0.86	0.35	0.045
12	0.93	0.48	0.088
13	0.96	0.62	0.155
# of Responses Observed out of 54 Subjects	**Posterior Probability RR ≥20%**	**Posterior Probability RR ≥30%**	**Posterior Probability RR ≥40%**
11	0.50	0.05	0.001
12	0.63	0.09	0.002
13	0.75	0.15	0.006
14	0.84	0.24	0.014

15	0.91	0.34	0.028
16	0.95	0.46	0.053
17	0.97	0.58	0.092

Using these sample sizes, a Bayesian design that allows the trial to be monitored more frequently at multiple stages was evaluated. A Bayesian analysis expresses uncertainty about a parameter in terms of probability. A prior is defined to characterize the level of knowledge about a parameter before the data are collected. Once the data are collected, a posterior distribution is formed using the prior and the likelihood (i.e., the data). Since none of the treatment has been tested previously in the clinic in the target population, a weak prior Beta (0.003, 0.007) is assumed. Thus, the posterior distribution for the response rate will be primarily driven by the data and can be derived as follows: Let p denote the response rate for the treatment, the number of responses in the current n patients, x, follows a binomial distribution, Binomial (n, p). Taking the Bayesian method and combining the weak prior and the likelihood of the observed data x, the posterior distribution of the response rate follows a beta distribution, i.e., $p \sim \text{Beta}(0.003 + x, 0.007 + n-x)$ with the posterior mean $(0.003 + x)/(0.01 + n)$.

Based on this posterior distribution of the response rate, the predictive probability that the response rate >15% or ≥30% after 19 or 53 subjects will be calculated for decision- making. The decision rule and a minimal required sample size of 10 patients for the first interim look are determined to generate the design that leads to a reasonable chance of early termination due to futility.

The design property, by utilizing the decision rule specified in [Section 5.1.2 of protocol], and sample size of 20 subjects or 54 subjects are shown (Table 3-4). The probability of early termination of the trial is calculated by simulations. The probability of early termination after the first 19 evaluable subjects is 33% under the null hypothesized response rate, and the risk to incorrectly stop the trial early if the drug is effective is approximately 5%. Thus, the study will employ the Bayesian design that allows the trial to be monitored more frequently at multiple stages with the constraint of satisfactory stop for futility rate. Bayesian model is designed for the futility analysis, and no Bayesian analysis will be performed in the final CSR.

Table 3-4 Bayesian Design Performance by Response Rate

If True Response Rate to the Treatment is: (%)	Probability (early stop for futility) after 19 subjects	Probability (early stop for futility) after 53 subjects
0.15	0.326	0.853
0.2	0.180	0.483
0.3	0.043	0.086

4 Appendix

This section will be used for drafting CSR Appendix 16.1.9.

4.1 Imputation rules

4.1.1 Imputation of Partial Dates

This section describes the rules to be used for imputation of partial dates.

Imputed partial dates will not be used to derive study day, duration (e.g., duration of adverse events), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.

With the exception of new anti-cancer start date on the Oncology time to event analysis dataset and exposure end date on the Exposure analysis dataset imputed dates will also not be stored on datasets.

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In addition partial dates may be imputed for 'slotting' data to study time periods or for specific analysis purposes as outlined below.

The partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'. blank: indicates that no imputation was done

D='Day': indicates that the day portion of the date is imputed

M='Month': indicates that the month and day portions of the date are imputed

Y='Year': indicates that the entire date (year, month, and day) is imputed

Example of Date Variables:

XYZD_ - character date variable

XYZDT - numeric date variable

XYZDTFL - flag variable

Details on imputing partial dates for specific datasets are outlined below.

4.1.1.1 Adverse Events (AE):

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 (AE)	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.

Dataset	Date	Missing Element	Rule
			• 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

4.1.1.2 Anti-Cancer Therapy and Radiotherapy

Start and end dates are generally not imputed. If start or end dates need to be imputed for an analysis (e.g., to calculate duration or elapsed time as covariates for efficacy analyses), the rules for imputation will be defined within the algorithm of the derived covariate.
Additionally, post treatment anti-cancer therapy and radiotherapy start dates may be imputed to determine date of new anti-cancer therapy. In this case only, the date of new anti-cancer therapy (not all anti-cancer therapy and radiotherapy start dates) will be stored on appropriate efficacy datasets. Imputed partial dates will not be used to derive time since most recent prior therapy. In addition, the cancer therapy treatment status variable, and not any variables that use imputed partial dates, will be used to differentiate prior and follow-up anti-cancer therapy and radiotherapy.

Dataset	Date	Missing Element	Rule
Anti-Cancer Therapy	Start	day, month,	• No Imputation for completely missing dates

Dataset	Date	Missing Element	Rule
Radiotherapy	Date	and year	
		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.
	End Date		• No imputation for partial end dates will be performed

4.1.1.3 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. The derived time in relation to treatment variables are not needed for reporting of these data.

Dataset	Date	Missing Element	Rule
Concomitant Medication	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	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 (MSTONE.LCONTDT).

4.1.2 Imputation of Missing Exposure End Dates

For subjects with missing exposure end dates at the time of data cutoff, the exposure end date will be imputed to the earliest of: the date of the data cutoff, the date of withdrawal from the study, or the death date. The imputed exposure end date will be used to calculate cumulative dose and exposure duration. 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.

4.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Note: The latest available MedDRA version at the time of the analyses should be used. The MedDRA version used will be specified in the footnote of relevant tables.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1). The CTCAE grade of 5 (death) is used for death due to an AE; 'fatal' is collected as AE outcome and all death information is also collected on a separate (e) CRF page (DTH).

4.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

4.4 Statistical models

4.4.1 Primary analysis

Overall response rate

Responses will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated [Clopper and Pearson 1934].

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – *two-sided alpha level*)) two-sided Pearson-Clopper CI.

4.4.2 Secondary analysis

Kaplan-Meier estimates

An estimate of the survival function in each drug combination will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment drug combination will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

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