NOVARTIS

Clinical Development

PDR001, dabrafenib, trametinib

CPDR001F2301 / NCT02967692

A randomized, double-blind, placebo-controlled phase III study comparing the combination of PDR001, dabrafenib and trametinib versus placebo, dabrafenib and trametinib in previously untreated patients with unresectable or metastatic *BRAF* V600 mutant melanoma

Statistical Analysis Plan (SAP) for Part 1 and Part 2 Amendment 3

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
18-Dec-2018	Prior to DB lock (Am1)	Incorporate changes as per protocol Amendment #5 and to implement changes to Biomarker analyses	The study design section now incorporates details of the updated design for Part 3 incorporated into Protocol Amendment #5 Biomarker section updated to meet needs of Biomarker team for CSR analysis. Also DOR definition and censoring rules were clarified. Immunogenicity section updated to incorporate new standard text. The 5% and 10% thresholds were analyzed in earlier interim analyses and it was decided they were not required for the purposes of the CSR Clarification of DOR and DCR definitions and PFS censoring rules. Previous definitions of DOR and DCR caused some confusion and so were updated. For	Sections 1 (Intro) 2.1 (Data analysis general info) 2.7.1 Secondary endpoints 2.7.3 DOR 2.10.1 Immunogenicity 2.12 Biomarker Data [redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			the analysis of PFS, Table 2-7 contained an error which was corrected	
5-May-2020	Prior to PFS Final analysis DBL (Am2)	Minor updates to dosing and PK sections for consistency with Part 3 SAP and addition of COVID-19 related PDs	Change to derivation of RDI/DI for PDR001/Placebo to align with other project trials. This is a more accurate representation of drug intensity. Update on handling of pk data below LLOQ (e.g. to include metabolytes) Alignment of Immunogenicity text with standard IG SAP and TFLs. Incorporation of COVID-19 related PDs into deviation summary table and additional listing. Update to Hy's Law criteria based on updated Novartis guidance document	2.4.1 Study Treatment Compliance 2.9 Pharmacokinetic endpoints 2.10.1 Immunogenicity 2.13.1 Impact of COVID-19 [redacted] 2.8.3 Laboratory data

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
30-July-2020	Prior to PFS Final analysis DBL (Am3)	To incorporate health authority feedback and fix some minor inconsistencies in document (Am3)	Change to DOR definition to count deaths due to any cause as an event. Change to BRAF mutation groups for baseline summary. In pk section change "plasma" to "serum" for PDR001.	2.3 Patient disposition, demographics and other baseline characteristics 2.7.1 Secondary endpoints 2.7.3 Handling of missing values/censoring/discontinuations 2.9 Pharmacokinetic endpoints

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List of abbreviations

AE	Adverse event
AESI	Adverse Events of Special Interest
ADA	Anti-Drug Antibodies
AJCC	American Joint Committee on Cancer
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
bid	bis in diem/twice a day
BIRC	Blinded Independent Review Committee
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
BOR	Best Overall Response
CD8	Cluster of Differentiation 8
CR	Complete Response
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Measured concentration at end of dosing interval
$Ctrough_{ss}$	Measured concentration at end of dosing interval at steady state
DAR	Dose Administration Record
DCR	Disease Control Rate
DDS	Dose-Determining Set
DI	Dose Intensity
DL	Dose Level
DLRT	Dose Level Review Team
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DOR	Duration of Response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
HGLT	High Level Group Term
HLT	High Level Term
IHC	Immunohistochemistry
irCR	Immune Related Complete Response
irDCR	Immune Related Disease Control Rate
irDOR	Immune Related Duration of Response
IG	Immunogenicity

irORR	Immune Related Overall Response Rate
irPD	Immune Related Progressive Disease
irPFS	Immune Related Progression-Free survival
irPR	Immune Related Partial Response
irRECIST	Immune Related Response Evaluation Criteria in Solid Tumors
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MAP	Meta-analytic-predictive approach
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MEL	Melanoma scoring system for PD-L1 expression
MUGA	Multigated Acquisition
NCI	National Cancer Institute
NMQ	Novartis MedDRA Query
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamics
PD-1	Programmed Death 1
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial Response
PRO	Patient-reported Outcomes
PT	Preferred Term
qd	Qua'que di'e / once a day
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QoL	Quality of Life
RAP	Report and Analysis Process
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP3R	Recommend Part 3 Regimen
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TBL	Total Bilirubin
TFLs	Tables, Figures, Listings
ULN	Upper Limit of Normal
UNK	Unknown
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for **part 1 (safety run-in) and part 2 (biomarker cohort)** of the clinical study report (CSR) of study CPDR001F2301, a randomized, double-blind, placebo-controlled, phase III study comparing the combination of PDR001, dabrafenib and trametinib versus placebo, dabrafenib and trametinib in previously untreated patients with unresectable or metastatic *BRAF* V600 mutant melanoma. All planned analyses for **part 3 (randomized, double-blind, placebo-controlled part)** will be described in a separate analysis plan.

The content of this SAP is based on protocol CPDR001F2301 version 00. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

This study has been designed as a phase III, multi-center study consisting of 3 parts:

- Part 1: Safety run-in part
- Part 2: Biomarker cohort
- Part 3: Double-blind, randomized, placebo-controlled part

Part 1 of this study is an open-label, multi-center safety run-in part investigating the safety and tolerability, pharmacokinetics (PK) / pharmacodynamics (PD), and preliminary efficacy of PDR001 in combination with dabrafenib and trametinib in previously untreated patients with BRAF V600 mutant unresectable or metastatic melanoma (AJCC edition 7 stage IIIC/IV). The primary objective of the safety run-in is to determine the recommended regimen of PDR001 in combination with dabrafenib and trametinib to be used in part 3 of the study.

The safety run-in part will consist of cohorts of approximately 6 newly enrolled patients who will be treated at the specified dose regimen of PDR001 with fixed doses of dabrafenib and trametinib. At least 6 patients, and up to approximately 18, will be enrolled in this part of the study. The start dose (DL1) for PDR001 in part 1 is 400 mg Q4W in combination with the labelled doses for dabrafenib (150 mg BID) and trametinib (2 mg BID). DLTs from the first 8 weeks (56 days) of treatment will be assessed.

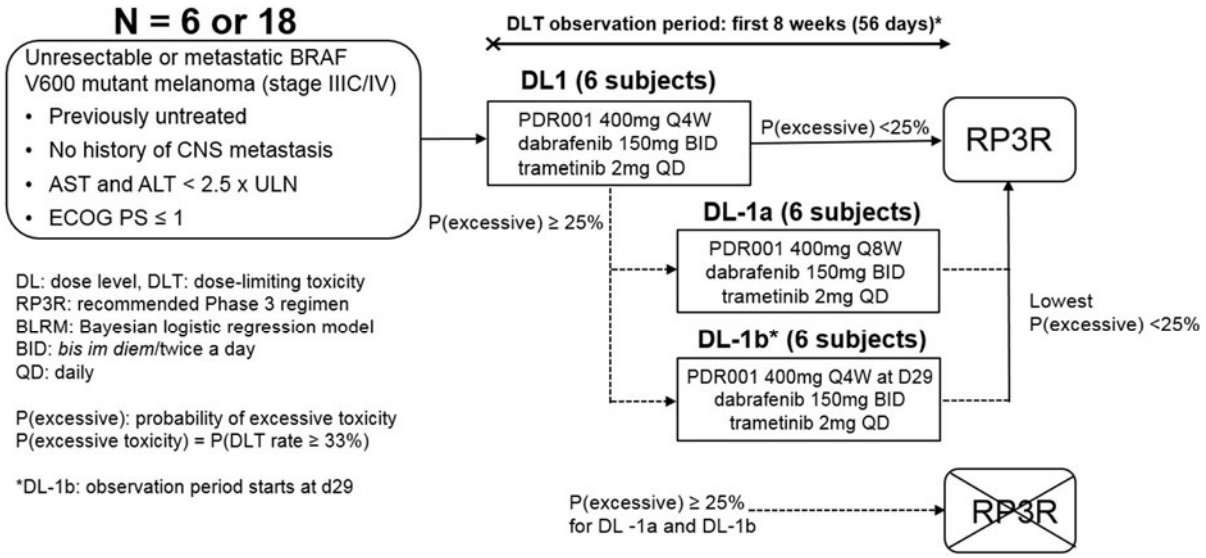
Data from each cohort, including safety and PK data, will be reviewed by a Dose Level Review Team (DLRT) consisting of the Novartis team including at least one clinician, safety representative, clinical pharmacology representative, and biostatistician and at least one investigator participating in the study who has enrolled patients in the safety run-in part of the study before the study can proceed to another dose level or next part. The decision of the PDR001 regimen will be based on the Bayesian Logistic Regression Model (BLRM) using escalation with overdose control (EWOC) principle as well as clinical judgment of the DLRT.

- If dose DL1 is tolerated, then this dosing regimen will be the recommended phase 3 regimen (RP3R)
- If DL1 is not tolerated, then fixed dose combinations will be explored in two parallel cohorts (DL-1a and DL-1b), enrolling six additional patients each, provided that both dose levels are recommended based on results from the BLRM with EWOC principle. For the

DL-1b cohort, patients who do not tolerate and discontinue dabrafenib and/or trametinib during the first 4 weeks will be replaced.

There is no formal interim analysis planned for this part of the study. Refer to Figure 1-1 for a study design diagram for part 1.

Figure 1-1 Part 1: Safety run-in overview of study design



If the first 2 subjects in a cohort experience a DLT, further enrollment to that cohort will stop, the BLRM will be updated with this new information and re-evaluation of the available safety, pharmacokinetic, and pharmacodynamic data will occur.

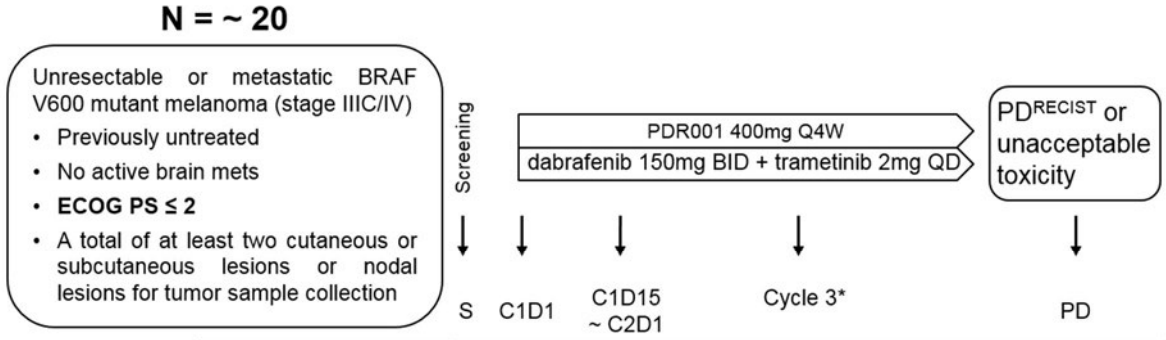
NOTE: PDR001 RP3R identified in Part 1 was 400mg Q4W.

Part 2 of this study is an open-label, multi-center biomarker cohort investigating the safety and tolerability, PK/PD, biomarker data, and preliminary efficacy of PDR001 in combination with dabrafenib and trametinib in previously untreated patients with BRAF V600 mutant unresectable or metastatic melanoma (AJCC edition 7 stage IIIC/IV). The primary objective of the biomarker cohort is to evaluate changes in PD-L1 levels and CD8+ cells upon treatment with PDR001 in combination with dabrafenib and trametinib.

The biomarker cohort will enroll approximately 20 patients, and enrollment will open when the fourth patient in dose level 1 (DL1) of part 1 completes approximately 4 weeks of study treatment and less than 3 DLTs have been observed. It is possible for additional dosing regimens to be used based on emerging data from part 1, and recruitment may be suspended at any time. Mandatory tumor tissues will be collected to characterize the kinetics of immune biomarkers and potential immune resistance mechanisms.

There is no formal interim analysis planned for this part of the study. Refer to Figure 1-2 for a study design diagram for part 2.

Figure 1-2 Part 2: Biomarker cohort overview of study design



Tumor biopsy (FFPE) Central BRAFV600 mutation confirmation, assessment of IO biomarkers	X				
Blood/Plasma for biomarker analyses	X	X	X	X	X
Tumor biopsy (FFPE) for biomarker analyses			X	X	X
Optional Tumor biopsy on treatment	Anytime – depending on investigator assessment				

*Cycle 4 if DL-1b is selected as RP3R

Part 3 of this study is a randomized, double-blind, placebo-controlled part comparing safety and efficacy of PDR001 in combination with dabrafenib and trametinib to placebo in combination with dabrafenib and trametinib in previously untreated patients with BRAF V600 mutant unresectable or metastatic melanoma (AJCC edition 7 stage IIIC/IV). After the recommended dosing regimen for the combination of PDR001 with dabrafenib and trametinib has been identified in part 1 of the study, approximately 500 patients will be randomized to one of the following treatment arms in 1:1 ratio:

- PDR001 in combination with dabrafenib and trametinib
- Placebo in combination with dabrafenib and trametinib

Randomization will be stratified by the following factors:

- LDH level (< 1 x ULN vs ≥ 1 to < 2 x ULN vs ≥ 2 x ULN)
- ECOG performance status (0 vs 1 vs 2)

Progression-free survival (PFS) as assessed by local investigators review of tumor assessments and using RECIST 1.1 criteria is the primary endpoint for this part of the study. Overall survival (OS) is the key secondary endpoint.

A maximum of two analyses (one interim and one final) is planned for PFS. An interim analysis is planned after approximately 260 PFS events have been observed and a final is planned after approximately 352 events or at approximately 24 months after the last patient has been randomized whichever occurs first.

A maximum of three analyses (two interim and one final) is planned for OS;

- at the time of the interim analysis for PFS (provided PFS is significant)..
- at the time of the final analysis for PFS (provided interim or final PFS is significant)
- and a final analysis for OS when approximately 245 deaths are observed. The final OS analysis is expected approximately 36 months from date the first patient was randomized according to a Novartis prediction analysis using actual study data This prediction is uncertain and maybe subject to change. The final OS analysis may be performed prior to 245 deaths being observed at the specific request of health authorities following a significant primary PFS outcome.

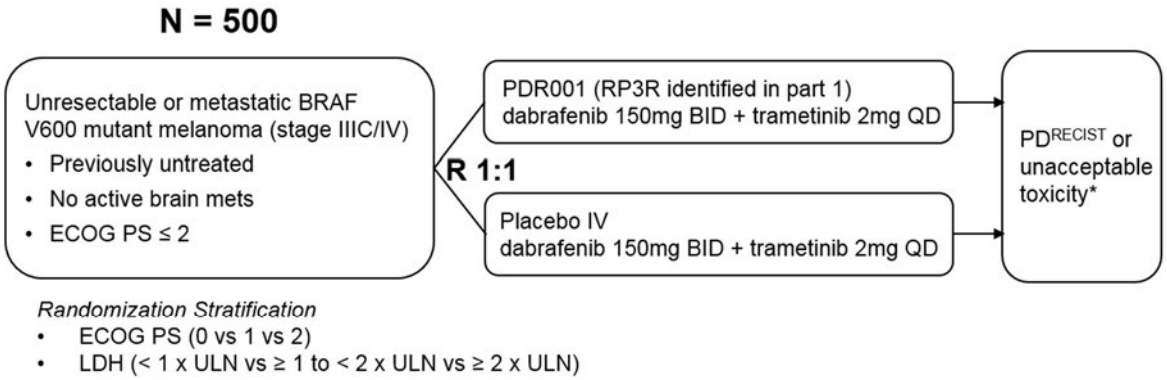
Addition details are described in Section 4 and Section 10 of the protocol.

An independent Data Monitoring Committee (DMC) will monitor unblinded safety data approximately every 6 months during the conduct of part 3.

In addition the DMC will review the primary PFS results along with other key efficacy (e.g. OS, ORR, DOR, DCR) and safety data at the time of the interim PFS analysis. Full details of the analyses required for DMC review will be described in a separate analysis plan.

Refer to Figure 1-3 for a study design diagram for part 3.

Figure 1-3 Part 3: Double-blind, randomized, placebo-controlled part overview of study design



*Treatment beyond PD^Recist is permitted if all of the following criteria are met: (1) subject has irSD, irPR or unconfirmed irPD according irRECIST, (2) the treatment will not delay an imminent intervention to prevent serious complications, (3) tolerance of study treatment, and (4) stable performance status

1.2 Study objectives and endpoints

Objectives and related endpoints for part 1 and part 2 are described in Table 1-1 below.

Table 1-1 Part 1 and Part 2 objectives and related endpoints

Objective	Endpoint
Primary	
Part 1 (safety run-in part)	**Part 1 (safety run-in part)**
• To determine the recommended regimen of PDR001 in combination with dabrafenib and trametinib for the randomized part (part 3)	• Incidence of DLTs during the first 8 weeks of treatment for each dose level associated with administration of PDR001 in combination with dabrafenib and trametinib
Part 2 (biomarker cohort)	**Part 2 (biomarker cohort)**
• To evaluate changes in PD-L1 levels and CD8+ cells upon treatment with PDR001 in combination with dabrafenib and trametinib	• Descriptive statistics of PD-L1 levels and CD8+ cells and changes from baseline by visit
Secondary	
Part 1 and Part 2	**Part 1 and Part 2**
• To determine the safety and tolerability of PDR001 in combination with dabrafenib and trametinib	• Safety: incidence and severity of AEs and SAEs, including changes in laboratory values, ECOG PS, vital signs, liver and cardiac parameters • Tolerability: dose interruptions, reductions, and dose intensity
• To evaluate preliminary anti-tumor activity of PDR001 in combination with dabrafenib and trametinib	• PFS, OS, ORR, DOR, and DCR by investigator's assessment according to RECIST 1.1
• To characterize PK of PDR001, dabrafenib and trametinib when administered in combination	• PK parameters such as, but not limited to, Ctrough and Ctroughss, for PDR001, dabrafenib and trametinib
• To evaluate the prevalence and incidence of immunogenicity	• ADA prevalence at baseline and ADA incidence on treatment
[redacted]	

Objective	Endpoint
[redacted]	

2 Statistical methods

2.1 Data analysis general information

All analyses will be performed by Novartis and/or a designated CRO. SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures, and listings.

Data included in the analysis

The analysis cut-off date for the primary analysis of study data for **part 1 (safety run-in)** will be established after all enrolled patients have completed two cycles of treatment with PDR001 in combination with dabrafenib and trametinib (between 8 and 16 weeks of treatment, dependent on selected dosing regimens) or have discontinued the study.

The analysis cut-off date for the final analysis of study data for **part 1** will be established at the time of the final analysis for part 3 (randomized part), when approximately 352 PFS events are expected to have occurred or at approximately 24 months after last patient has been randomized whichever occurs first. At this time, data for all patients from part 1 who have been followed up to the end of the on-treatment period will be included.

The analysis cut-off date for the primary analysis of study data for **part 2 (biomarker cohort)** will be established after all enrolled patients have had one baseline and two post-baseline biomarker biopsies assessed.

The analysis cut-off date for the final analysis of study data for **part 2** will be established at the time of the final analysis for part 3 (randomized part), when approximately 352 PFS events are expected to have occurred or at approximately 24 months after last patient has been randomized whichever occurs first. At this time, data for all patients from part 2 who have been followed up to the end of the on-treatment period will be included.

At the interim PFS analysis if PFS is significant and the Part 3 unblinded results are reported, both Part 1 and 2 data will be additionally analyzed and reported.

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 events, the end date will not be imputed and therefore will not appear in the listings.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to unexpected small number of patients enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, rate, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator. Data for part 1 will also be summarized by dose cohort.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum). Data for part 1 will also be summarized by dose cohort.

2.1.1 General definitions

Investigational drug and study treatment

For part 1 and part 2, ***Investigational drug***, will refer to PDR001 only. Whereas, ***study treatment*** will refer to PDR001 +/- dabrafenib and trametinib.

The term investigational treatment may also be referred to as ***study treatment*** which is used throughout this document.

Dose cohort and dose level

In part 1 (safety run-in), "Dose cohort" (treatment group) refers to the group of approximately 6 patients enrolled and intended to receive the same starting doses of PDR001 in combination with dabrafenib and trametinib with the same treatment schedule.

Three dose levels are defined in **part 1**:

- DL1: 400 mg PDR001 Q4W in combination with approved doses of 150 mg BID dabrafenib and 2 mg QD trametinib

If DL1 is tolerated, then this dosing regimen will be the recommended phase 3 regimen (RP3R). If DL1 is not tolerated, then fixed dose combinations will be explored in two parallel cohorts (DL-1a and DL-1b), provided that both dose levels are recommended based on results from BLRM with EWOC principle.

- DL-1a: 400 mg PDR001 Q8W in combination with 150 mg BID dabrafenib and 2 mg QD trametinib
- DL-1b: 4 week run-in of 150 mg BID dabrafenib and 2 mg QD trametinib, followed by 400 mg PDR001 Q4W in combination with 150 mg BID dabrafenib and 2 mg QD trametinib

In part 2 (biomarker cohort), 20 newly enrolled patients are intended to receive the same dose level (DL1). Enrollment will open when the fourth patient in DL1 of part 1 has completed approximately 4 weeks of study treatment and less than 3 DLTs have been observed. It is possible for additional dosing regimens to be used based on emerging data from part 1, and recruitment may be suspended at any time.

Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when a non-zero dose of investigational drug is administered and recorded on the Dosage Administration Record (DAR) (e)CRF. The date of first administration of study drug will also be referred as start of investigational drug.

Date of last administration of investigational drug

The date of last administration of investigational drug is defined as the last date when a non-zero dose of investigational drug is administered and recorded on DAR eCRF. The date of last administration of investigational drug will also be referred as end of investigational drug.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of any component of study treatment was administered as per the Dosage Administration (e)CRF. (Example: if 1st dose of PDR001 is administered on 05-Jan-2016, and 1st dose of dabrafenib and trametinib is administered on 03-Jan-2016, then the date of first administration of study treatment is on 03-Jan-2016). The date of first administration of study treatment will also be referred as ***start of study treatment***.

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of study treatment was administered as per Dose Administration (e)CRF. (Example: if the last PDR001 dose is administered on 15-Apr-2016, and the last dose of dabrafenib and trametinib is administered on 17-Apr-2016, then the date of last administration of study treatment is on 17-Apr-2016).

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date. The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) – reference start date + 1 if event is on or after the reference date;
- The date of the event (visit date, onset date of an event, assessment date etc.) – reference start date if event precedes the reference date.

The reference date for all assessments (safety, efficacy, PK, QoL/PRO, etc) is the start of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is defined as “baseline” assessment.

If patients have no value as defined above, the baseline result will be missing.

For cases where time of assessment and time of treatment start is captured (e.g. pre-dose ECG, laboratory assessments), the last available assessment before the treatment start date/time is used for baseline.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or collected for ECGs or vital signs, then the last value should be considered as baseline.

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of patient's informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 31 after last administration of study treatment.

For cases where time of assessment and time of treatment start/stop is captured (e.g. ECG's, laboratory assessments), the last available assessment before the treatment period start/stop date/time will be used.

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period. Refer to Section 5.1.2 for imputation rules concerning AE start and stop dates.

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). However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Additional summaries will be displayed to report deaths, all AEs, AEs related to study treatment, all SAEs and SAEs related to study treatment collected up to 150 days after last administration of PDR001.

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Windows for multiple assessments

In order to summarize performance status (ECOG), physical exam, vital sign, ECG, ECHO, laboratory, and biomarker data collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used. If multiple assessments on the same date then the worst case will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Assessments included in the EOT assessment will also be available for inclusion in the other time assessment windows.

Time windows for ECOG PS assessments (applies to Part 1 and Part 2)

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1
Cycle 2 Day 1	29	Day 15 to day 42

Cycle 3 Day 1	57	Day 43 to day 70
Cycle 4 Day 1	85	Day 71 to day 98
Cycle k Day 1 (k≥4)	d=(k-1)*28+1	Day d-14 to day d+13
End of Treatment		Assessment taken at the end of treatment visit
30-day safety follow-up	Post treatment study day 30	Assessment taken at the 30-day safety follow-up visit

Time windows for Laboratory assessments (applies to Part 1)

Assessment	Target day of assessment	Time Interval
DL1		
Baseline	1	≤ Day 1
Cycle 1 Day 8	8	Day 2 to day 11
Cycle 1 Day 15	15	Day 12 to day 21
Cycle 2 Day 1	29	Day 22 to day 35
Cycle 2 Day 15	43	Day 36 to day 49
Cycle 3 Day 1	57	Day 50 to day 63
Cycle 3 Day 15	71	Day 64 to day 77
Cycle 4 Day 1	85	Day 78 to day 98
Cycle k Day 1 (k≥5)	d=(k-1)*28+1	Day d-14 to day d+13
End of Treatment		Assessment taken at the end of treatment visit
30-day safety follow-up	Post treatment study day 30	Assessment taken at the 30-day safety follow-up visit
DL-1a		
Baseline		≤ Day 1
Cycle 1 Day 8	8	Day 2 to day 11
Cycle 1 Day 15	15	Day 12 to day 21
Cycle 2 Day 1	29	Day 22 to day 35
Cycle 2 Day 15	43	Day 36 to day 49
Cycle 3 Day 1	57	Day 50 to day 63
Cycle 3 Day 15	71	Day 64 to day 77
Cycle 4 Day 1	85	Day 78 to day 91
Cycle 4 Day 15	99	Day 92 to day 105
Cycle k Day 1 (k≥5)	d=(k-1)*28+1	Day d-14 to day d+13
End of Treatment		Assessment taken at the end of treatment visit
30-day safety follow-up	Post treatment study day 30	Assessment taken at the 30-day safety follow-up visit
DL-1b		
Baseline	1	≤ Day 1
Cycle 1 Day 15	15	Day 2 to 21
Cycle 2 Day 1	29	Day 22 to day 32

Cycle 2 Day 8	36	Day 33 to day 39
Cycle 2 Day 15	43	Day 40 to day 49
Cycle 3 Day 1	57	Day 50 to day 63
Cycle 3 Day 15	71	Day 64 to day 77
Cycle 4 Day 1	85	Day 78 to day 98
Cycle k Day 1 (k≥5)	d=(k-1)*28+1	Day d-14 to day d+13
End of Treatment		Assessment taken at the end of treatment visit
30-day safety follow-up	Post treatment study day 30	Assessment taken at the 30-day safety follow-up visit

Time windows for Laboratory assessments (applies to Part 2)

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1
Cycle 1 Day 15	15	Day 2 to day 21
Cycle 2 Day 1	29	Day 22 to day 35
Cycle 2 Day 15	43	Day 36 to day 49
Cycle 3 Day 1	57	Day 50 to day 70
Cycle 4 Day 1	85	Day 71 to day 98
Cycle k Day 1 (k≥5)	d=(k-1)*28+1	Day d-14 to day d+13
End of Treatment		Assessment taken at the end of treatment visit
30-day safety follow-up	Post treatment study day 30	Assessment taken at the 30-day safety follow-up visit

Last contact date

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:

Table 2-1 Last contact date data sources

Source data	Conditions
Last contact date/last date patient was known to be alive from Survival Follow-up page	- Patient status is reported to be alive, lost to follow-up or unknown.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Tumor (RECIST) assessment date	Evaluation is marked as ‘done’.
Verification for treatment beyond RECIST1.1 PD	At least one non-missing parameter value.

Source data	Conditions
Laboratory/PK collection dates	Sample collection marked as 'done'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term
Biomarker blood sample date	No condition

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring is coming from the 'Survival information' eCRF.

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

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned and who received one dose of any study treatment (i.e. at least one dose of any component of PDR001 (including incomplete infusion), dabrafenib, or trametinib). Patients will be analyzed according to the study treatment they have been assigned to.

All efficacy data will be analyzed using the FAS.

Safety

For non-randomized part 1 and part 2, the FAS and Safety Set are identical. All safety data will be analyzed using the Safety Set.

Dose-determining analysis set

For part 1 (safety run-in) only, the dose-determining set (DDS) includes all patients who received at least one dose of study treatment who either 1) met the minimum exposure criterion and had sufficient safety evaluations, or 2) experienced a DLT during the first 8 weeks (56 days) of PDR001 in combination with dabrafenib and trametinib dosing.

A patient is considered to meet the minimum exposure criterion if the patient receives at least 1 dose of PDR001 and takes at least 50% of the planned cumulative doses (see Table 2-5 and Table 2-6 for details) of dabrafenib and trametinib within the first 8 weeks (56 days) of treatment. Patients who do not experience a DLT during the first 8 weeks are considered to have sufficient safety evaluations if they have been observed for at least 8 weeks following the first

dose of PDR001 in combination with dabrafenib and trametinib and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur. Patients who do not meet the minimum exposure criterion due to an AE will be counted as having a DLT. Patients who do not meet the minimum exposure criterion for reasons other than AE's (e.g. rapid disease progression or non-compliance) will not be included in the DDS.

Note that for patients assigned to DL-1b (4 week run-in of 150 mg BID dabrafenib and 2 mg QD trametinib, followed by 400 mg PDR001 Q4W in combination with 150 mg BID dabrafenib and 2 mg QD trametinib), the 8 week DLT period will start on Day 29.

Pharmacokinetic analysis set

The following analysis sets will be derived separately for part 1 (safety run-in) and part 2 (biomarker cohort).

The **PDR001 pharmacokinetic analysis set** (**PAS-PDR001**) includes all patients who provide at least one evaluable PDR001 PK concentration. For a concentration to be evaluable, patients are required to:

- Receive one of the planned treatments of PDR001 prior to sampling
- For pre-dose samples, prior to dosing on the assessment day and/or collect at approximately 672 hr ± 24 hours after the last dose
- For end-of-infusion samples, have the samples collected within 2 hours post end of infusion

The **dabrafenib and trametinib pharmacokinetic analysis set** (**PAS-D+T**) includes all patients who provide at least one evaluable dabrafenib or trametinib PK concentration. For a concentration to be evaluable, patients are required to:

- Receive a dose of dabrafenib or trametinib prior to sampling
- For pre-dose samples, have the samples collected before the next dose administration
- For post-dose samples,
  - do not vomit within 4 hours after the dosing of dabrafenib and trametinib
  - within window Cycle 2 Day 1: Between 1 and 3 hours post dose
  - within window Cycle 3 Day 1 and Cycle 4 Day 1: Between 2 and 12 hr post-dose
- for dabrafenib and its metabolites, assessments with at least 6 consecutive doses at the protocol planned dose of the respective drug immediately prior to the PK collection are required

  for trametinib, assessments with atleast 14 consecutive doses at the protocol planned dose of the respective drug immediately prior to the PK collection are required

Immunogenicity (IG) analysis sets

The *Immunogenicity prevalence set* includes all subjects in the Full analysis set with a determinant baseline IG sample **or** at least one determinant post-baseline IG sample.

The *Immunogenicity incidence set* includes all subjects in the Immunogenicity prevalence set with a determinant baseline IG sample **and** at least one determinant post-baseline IG sample.

See Section 2.10.1 for the definition of *determinant*.

Patient Classification

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific patient classification rules defined in Table 2-2.

Table 2-2 Patient classification based on protocol deviations and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written informed consent	No dose of any component of study treatment
Safety Set	No written informed consent	No dose of any component of study treatment
DDS (part 1 only)	No written informed consent	No dose of PDR001 and/or < 50% of planned cumulative dabrafenib and trametinib doses
		Didn't experience DLT and not observed for at least 8 weeks following first dose of PDR001 in combination with dabrafenib and trametinib
PDR001 PK Analysis Set (PAS-PDR001)	No written informed consent	No dose of planned treatment of PDR001
		No pre-dose sample collected before the next dose administration
		No end-of-infusion sample collected within 2 hours post end of infusion
Dabrafenib and Trametinib PK Analysis Set (PAS-D+T)	No written informed consent	No dose of dabrafenib or trametinib prior to sampling
		No pre-dose sample collected before the next dose administration
		No post-dose without vomiting within 4 hours after dosing of dabrafenib and trametinib
Immunogenicity Prevalence Set	No written informed consent	No dose of any component of study treatment

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
		No determinant baseline IG sample or at least one determinant post-baseline IG sample
Immunogenicity Incidence Set	No written informed consent	No dose of any component of study treatment
		No determinant baseline IG sample or determinant post-baseline IG sample

Withdrawal of Informed Consent

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

2.2.1 Subgroup of interest

No subgroup analyses will be performed for part 1 (safety run-in).

For part 2 (biomarker cohort), descriptive statistics for efficacy variables will be summarized by the following subgroups (if relevant):

- LDH status: < 1 x ULN, ≥ 1 to < 2 x ULN, ≥ 2 x ULN
- ECOG performance status: 0, 1, 2
- Stage: (IIIC or IVM1a), (IVM1b or IVM1c)

2.3 Patient disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified. For part 1, summaries will be reported overall and by dose cohort. For part 2, summaries will be reported overall. No inferential statistics will be provided.

Baseline demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by dose cohort and overall for part 1, and overall for part 2. Categorical data (e.g. gender, age groups: <65 and ≥ 65 years, race, ethnicity, ECOG performance status groups: 0, 1, and 2, LDH groups: < 1 x ULN, ≥ 1 to < 2 x ULN, and ≥ 2 x ULN, PD-L1 status groups: positive and negative (refer to Section 2.12.4.1), BRAF V600 mutation status conferring eligibility (V600E, V600K, Other), Central BRAF mutation (V600E, V600K, V600E and K negative, missing),, number of metastatic sites: < 3 and ≥ 3) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index) will be summarized by descriptive statistics (N, mean,

median, standard deviation, minimum and maximum). BMI (kg/m2) will be calculated as weight[kg] / (height[m]2) using weight at Baseline.

Baseline stratification factors

Not applicable

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary site of cancer (melanoma), predominant histology/cytology, stage group at initial diagnosis (using AJCC version 7), time since initial diagnosis (in months), time from initial diagnosis to first recurrence/progression (in months), time since most recent relapse/progression to study entry (in months), stage group at time of study entry (AJCC version 7), presence/absence of target and non-target lesions, number and location of metastatic sites involved, stage of tumor (T), lymph nodes (N) and metastases (M) at initial diagnosis, and stage of tumor (T), lymph nodes (N) and metastases (M) at study entry. Note: presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Metastatic sites will be based on diagnosis page.

Number of metastatic sites (< 3 vs ≥ 3) will be derived by summing the total number of "metastatic site" records reported per patient.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on (e)CRF will be summarized and listed by dose cohort for part 1 and overall for part 2. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). For part 1, summaries will be presented overall and by dose cohort. For part 2, summaries will be presented overall. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Other

All data collected at baseline, including child bearing potential, [redacted] informed consent, and treatment beyond progression informed consent will be listed.

2.3.1 Patient disposition

Enrollment by country and center will be summarized for all screened patients and also by dose cohort for part 1 using the FAS. The number (%) of treated patients included in the FAS will be presented overall and by dose cohort for part 1. For part 2, they will be presented overall. The number (%) of screened and not-treated patients and the reasons for screening failure will also be displayed. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by dose cohort for part 1. For part 2, they will be presented overall.

The following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients who are still on-treatment (based on the 'End of Treatment Disposition' page not completed);
- Number (%) of patients who discontinued the study treatment phase (based on the 'End of Treatment Disposition' page);
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Disposition' page);
- Number (%) of patients who have entered the post-treatment follow-up (based on the 'End of Treatment Disposition' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the 'End of Post Treatment Follow-up Disposition' page);
- Reasons for discontinuation from the post-treatment follow-up (based on 'End of Post Treatment Follow-up Disposition' page);
- Number (%) of patients who have entered the survival follow-up (based on the 'End of Treatment Disposition' or 'End of Post Treatment Follow-up Disposition' page).

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan) overall and by dose cohort for part 1. For part 2, they will be tabulated overall. Major protocol deviations leading to exclusion from analysis sets will be tabulated overall and by dose cohort for part 1. For part 2, they will be tabulated overall. All protocol deviations will be listed.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized by dose cohort and overall for part 1. For part 2, they will be summarized overall.

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

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by dose cohort for part 1, separately for each component of study treatment (PDR001, dabrafenib, and trametinib). The duration of treatment will also be presented for the study treatment. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of patients in each interval. The number (%) of patients who have dose reductions or interruptions, and the reasons, will be summarized by dose cohort. For part 2, these summaries will be presented overall.

Patient 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.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to PDR001, dabrafenib, and trametinib:

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 PDR001, dabrafenib, and trametinib (see Table 2-3).

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.

Duration of exposure to PDR001, dabrafenib, and trametinib

Duration of exposure to PDR001 (days) = (last date of exposure to PDR001) – (date of first administration of PDR001) + 1.

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

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

Refer to Table 2-3 for definitions of the last date of exposure to PDR001, dabrafenib, and trametinib.

For part 1 only, to support DDS analysis (refer to Section 2.2 for details):

Duration of exposure to dabrafenib for 8 week DLT period starting from first dose of PDR001 in combination with dabrafenib and trametinib: calculate the duration of exposure to dabrafenib as stated above, using last date of exposure with dabrafenib. Then consider the patient exposed to the drug for 8 weeks if he/she takes at least 50% of planned cumulative dose within the period). Refer to Table 2-5 for details.

Duration of exposure to trametinib for 8 week DLT period starting from first dose of PDR001 in combination with dabrafenib and trametinib: calculate the duration of exposure to trametinib as stated above, using last date of exposure with trametinib. Then consider the patient exposed to the drug for 8 weeks if he/she takes at least 50% of planned cumulative dose within the period). Refer to Table 2-6 for details.

Table 2-3 Definition of last date of exposure of study drug

Scenario	Definition of last date of exposure of study drug	Example
PDR001	The planned end date of the last cycle in which the last non-zero dose of the investigational drug was last administered (i.e. last date of administration + (planned interval duration-1 day))	Example 1: If PDR001 is administered every four weeks, the last date of exposure is the date of administration in the last cycle + 27 days.

Scenario	Definition of last date of exposure of study drug	Example
	Note: If the patient died or was lost to follow-up before the derived last date, the last date of exposure to investigational drug is the date of death or the late of last contact, respectively. If the derived last date of exposure goes beyond the data cut-off date, it should be truncated to the date of data cut-off.	Example 2: If PDR001 is administered every eight weeks, the last date of exposure is the date of administration in the last cycle + 55 days.
Dabrafenib, Trametinib	Date of last administration of a non-zero dose of the study drug.	Example 3: A patient had a permanent discontinuation of the study drug on 06Jan2016 after being put on a temporary interruption since 01Jan2016. In this case the last date of exposure is 31Dec2015.

Summary of duration of exposure of PDR001, dabrafenib and trametinib will include categorical summaries based on 28 day intervals and using descriptive statistics (mean, standard deviation, etc).

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment and will be summarized for each of the study treatment components (PDR001, dabrafenib, trametinib).

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 planned cumulative dose will not be summarized/listed. It will be used for relative dose intensity calculations.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the patient 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 patient is assumed to have taken a non-zero dose 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 (mg / *unit of time*) = Actual Cumulative dose (mg) / 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 (mg */ unit of time)* = Planned Cumulative dose (mg) / Duration of exposure (*unit of time*).

Relative dose intensity (RDI) is defined as follows:

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

For PDR001, the unit of time will be 1 cycle (28 days).

For dabrafenib and trametinib, the unit of time will be 1 day.

DI and RDI will be summarized for combination studies separately for each of the study treatment components, but using the duration of exposure of each of the components.

Note that for the purposes of DI and RDI derivation only for PDR001/Placebo, the last date of exposure for the duration of exposure component of this calculation will simply be the last date of administration in the last cycle + 27 days. i.e. deaths and data cutoff will not be taken into account.

Table 2-4 Examples of PDR001 dose administration and exposure

DAR record number	Start/End Date	Regimen	Dose Administered (mg)	Dose Stopped or Paused, Dose Interrupted?	Dose Permanently Discontinued	Reason
1	01Jan2016	Q4W	400	No	No	
2	28Jan2016	Q4W	200	Yes	No	AE (infusion reaction)

Duration of exposure (days) = (31Jan2016 + 27 days (Q4W)) – (01Jan2016) + 1 = 58 days

Duration of exposure (cycle of 28 days) = 58/28 = 2.07 cycles

Actual cumulative dose (for 58 days, 2.07 cycles) = 600 mg

Dose intensity = 600 mg / 2.07 cycles = 289.95 mg / cycle

Planned dose intensity = = 400 mg / cycle

Relative dose intensity = DI / PDI = (289.95 mg/cycle) / (400 mg/cycle) = 72.5%

Table 2-5 Examples of dabrafenib dose administration and exposure

DAR record number	Start/End Date	Dose Prescribed (mg), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption ?	Dose Permanently Discontinued	Reason
1	01Jan2016 / 05Jan2016	150 mg BID	300	No	No	
2	06Jan2016 / 03Feb2016	150 mg BID	200	Yes	No	AE
3	04Feb2016 / 25Feb2016	150 mg BID	300	No	No	

Duration of exposure (days) = 25Feb2016 – 01Jan2016 + 1 = 56 days

Planned cumulative dose (for 56 days) = 300*56 days = 16800 mg

Actual cumulative dose = 300*5 + 200*29 + 300*22 = 13900 mg

Dose intensity = 13900 mg / 56 days = 248.21 mg/day

Planned dose intensity = 16800 mg / 56 days = 300 mg/day

Relative dose intensity = DI / PDI = (248.21 mg/day) / (300 mg/day) = 0.83

Table 2-6 Examples of trametinib dose administration and exposure

DAR record number	Start/End Date	Dose Prescribed (mg), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption?	Dose Permanently Discontinued	Reason
1	01Jan2016 / 10Jan2016	2 QD	2	No	No	
2	11Jan2016 / 15Jan2016	2 QD	0	Yes	No	AE
3	16Jan2016 / 25Feb2016	1 QD	1	No	No	AE

Duration of exposure = 25Feb2016 – 01Jan2016 + 1 = 56 days

Planned cumulative dose (for 56 days) = 2*56 days = 112 mg

Actual cumulative dose = 2*10 + 0*5 + 1*41 = 61 mg

Dose intensity = 61 mg / 56 days = 1.09 mg/day

Planned dose intensity = 112 mg / 56 days = 2 mg/day

Relative dose intensity = DI / PDI = (1.09 mg/day) / (2 mg/day) = 0.54

Dose reductions, interruptions or permanent discontinuations

The number of patients who have dose reductions, permanent discontinuations, administration stopped/paused during infusion or interruptions, and the reasons, will be summarized separately for each of the study treatment components.

'Dose interrupted', "Was drug administration stopped or paused" and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose reductions, dose interruptions, administration stopped/paused and permanent discontinuations, respectively.

The corresponding fields 'Reason for dose change/dose interrupted', 'Reason for administration stopped or paused' 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/dose administrations with different reasons, separate interruptions will be counted. However, if the reason is the same for multiple entries on consecutive days/dose administrations, then it will be counted as one interruption.

Reduction

No dose reductions are permitted for PDR001 for this study. Therefore, a reduction refers to a dose change where the prescribed dose level of dabrafenib and/or trametinib 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.

Treatment beyond RECIST1.1 progression

The number of patients who continue treatment beyond RECIST1.1 progression according to local investigators assessment based on protocol specified criteria will be summarized. It includes all patients who received any study treatment (i.e. at least one dose of PDR001 (including incomplete infusion), dabrafenib, or trametinib) after RECIST 1.1 progression as assessed by local investigators. Those patients will be identified using the field "Will the patient continue treatment beyond disease progression as per RECIST 1.1?" on the 'Verification for Treatment Beyond RECIST1.1 PD' CRF pages.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic medications, prior checkpoint inhibitor therapy, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized overall and by dose cohort for part 1. For part 2, these will be summarized overall. Prior anti-neoplastic medications will be summarized by therapy type (e.g. chemotherapy, immunotherapy, targeted therapy etc.), setting (e.g. adjuvant neoadjuvant, etc.) and also by lowest ATC class, preferred term and treatment. Summaries will include total number of regimens and time from last treatment to progression for the last therapy. The medication therapy type of any combination therapy will be classified based on the following order: immunotherapy, chemotherapy, biologic therapy (other than immunotherapy), targeted therapy, hormonal therapy. For example, a combination therapy of chemotherapy and immunotherapy will be classified as 'immunotherapy'. For radiotherapy, time since last radiotherapy, locations and setting of last therapy will be summarized. For prior surgery, time since last surgery and procedure will be summarized.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery. Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class, preferred term, overall and by dose cohort for part 1 by means of frequency counts and percentages using FAS. For part 2, they will be summarized overall.

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. Concomitant medications with immunosuppressive intent will be summarized by lowest ATC class and preferred term using frequency counts and percentages. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

Additional summaries will be provided to report medications starting between 31 days and 150 days after last dose of study treatment.

All reported concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 150 days after the last dose of PDR001 or 30 days after last dose of study treatment whichever comes last, will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

2.5 Analysis of the primary objective

Part 1 (safety run-in)

The primary objective of part 1 is to determine the recommended regimen of PDR001 in combination with dabrafenib and trametinib for the randomized part (part 3).

Part 2 (biomarker cohort)

The primary objective of part 2 is to evaluate changes in PD-L1 levels and CD8+ cells upon treatment with PDR001 in combination with dabrafenib and trametinib.

2.5.1 Primary endpoint

Part 1 (safety run-in)

The primary endpoint for part 1 is the incidence of DLTs during the first 8 weeks of treatment for each dose level associated with administration of PDR001 in combination with dabrafenib and trametinib. Estimation of the recommended regimen will be based upon the estimation of the probability of DLT in the first 8 weeks (56 days) for patients in the DDS.

Part 2 (biomarker cohort)

The primary endpoint for part 2 is descriptive statistics of PD-L1 levels and CD8+ cells and changes from baseline by visit. The primary endpoint for part 2 will be assessed using the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

2.5.2.1 Part 1 safety run-in

2.5.2.1.1 Bayesian adaptive model

The dose determination part of this study will be guided by a Bayesian analysis of DLT data for the first 8 weeks (56 days) that patients receive the combination of PDR001, dabrafenib, and trametinib. The Bayesian analysis to assess the triple combination will be based on a separate 10-parameter model for each dose regimen that comprises single-agent toxicity parts and interaction parts to describe both two-way and three-way drug safety interactions. Single agent toxicity is modelled using logistic regression for the probability of a patient experiencing a DLT against log-dose. The odds of a DLT for each dose regimen are then calculated under no interaction for the three single agent toxicities, and interaction is accounted for by adjusting these odds with additional model parameters (odds multipliers). Details of the statistical model are given in Appendix 2 of the protocol.

2.5.2.1.2 Prior distributions

A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent PDR001, dabrafenib, and trametinib model parameters. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data [Spiegelhalter 2004, Neuenschwander 2010, Neuenschwander 2014]. MAP priors are derived from hierarchical models, which take into account possible differences between the studies. For dabrafenib and trametinib, 100% MAP priors will be used. For PDR001, this is then robustified by creating a mixture prior including both a component derived from the MAP prior and a weakly informative robustification component. This robustification allows for the possibility that the dose/toxicity relationship for PDR001 in combination differs substantially from that of the single agent. A full description of the application of the MAP approach to derive the prior distributions of the single agent PDR001, dabrafenib, and trametinib model parameters for each dose regimen is given in Appendix 2 of the protocol.

The prior distributions for the interaction parameters were based upon prior understanding of possible drug safety interactions. These priors allow for the possibility of either synergistic or antagonistic interaction, and are fully described in Appendix 2 of the protocol.

Additional DLT information from completed studies assessing the combination of dabrafenib and trametinib (i.e. Phase I study BRF113220, Phase III study MEK115306 (COMBI-d), and

Phase III study MEK116513 (COMBI-v)) are included using discounted weighting. Full details of the discounted weighting approach are described in Appendix 2 of the protocol.

2.5.2.1.3 Determination of recommended dosing regimen

After each cohort of patients, the posterior distribution for the risk of DLT for new patients at combination doses of interest will be evaluated. The posterior distributions will be summarized, including the mean, median, standard deviation, 95% credible interval, and posterior probability that the risk of DLT for each dose regimen lies within the following intervals:

- Under-dosing: [0, 16%)
- Targeted toxicity: [16%, 33%)
- Excessive toxicity: [33%, 100%]

Dosing regimen decisions are guided by the escalation with overdose control principle [Rogatko 2007]. A dosing regimen may only be used for newly enrolled patients if the risk of excessive toxicity at that dosing regimen is less than 25%.

The starting dosing regimen is 400 mg i.v. Q4W PDR001, 150 mg BID dabrafenib, and 2 mg QD trametinib. For this dosing regimen, the prior risk of excessive toxicity is 12%, which satisfies the EWOC criterion. A full assessment of the prior risk to patients for all dosing regimens is given in Appendix 2 of the protocol.

Data from each cohort, including safety and PK data, will be reviewed by a Dose Level Review Team (DLRT). The final recommended dosing regimen will be based on the recommendation from the BLRM with EWOC criteria as well as clinical judgment of the DLRT. Details on the process for making and communicating dosing regimen decisions are provided in Section 6.2.3 of the protocol. For further details of the BLRM model and results under a variety of scenarios, refer to the Appendix 2 of the protocol for statistical methodology.

The DDS will be used to guide the dosing regimen decision. 6 evaluable patients eligible for the DDS will typically be treated per new cohort until determination of the recommended dosing regimen.

After each dose cohort of patients, the posterior distribution of the model parameters will be updated via simulation with emerging DLT data and will be used to derive the posterior distribution of the probability of a DLT occurring at a given dose level of PDR001 in combination with dabrafenib and trametinib.

Summaries of the posterior distribution of model parameters and posterior distribution of DLT rates based on the DLT data from all patients in the DDS will be produced. DLTs will be listed and their incidence summarized by primary system organ class, worst grade based on the CTCAE version 4.03 and type of AE. The DDS will be used for these summaries.

2.5.2.1.4 General rules for DLT reporting

A DLT is defined as 1) an AE or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 8 weeks (56 days) of treatment with PDR001 in combination with dabrafenib and trametinib and 2) meets any of the pre-defined DLT criteria summarized in Table 6-6 of the protocol. The

National Cancer Institute (NCI) version 4.03 will be used for grading of all DLTs and adverse events in this study.

An AE reported as a DLT by the investigator will be identified on the Adverse event eCRF page as 'AE meets definition of DLT.'

DLTs will be listed by dose level for the DDS.

If the same patient has more than one DLT with the same reported preferred term, the patient will be counted only once with the greatest severity, where applicable. If the same patient has more than one DLT within the same reported primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

2.5.2.2 Part 2 biomarker cohort

Descriptive statistics of PD-L1 levels and CD8+ cell values at baseline, as well as change and percentage change from baseline will be summarized by visit.

Categorical data will be presented as contingency tables (frequencies and percentages). For continuous data, summary statistics of mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25^{th} and 75^{th} percentiles will also be presented.

Graphical presentations of PD-L1 levels and CD8+ cells over time for change and percentage change from baseline will be produced via spaghetti plots and boxplots by visit.

Refer to Section 2.12 for more details on biomarker data.

2.5.3 Handling of missing values/censoring/discontinuations

Part 1 (safety run-in)

Patients who are ineligible for the DDS will be excluded from the primary analysis (incidence of DLTs during first 8 weeks of PDR001 in combination with dabrafenib and trametinib), although their data will be used for all remaining analyses.

Other missing data will be noted as missing on appropriate tables/listings.

Part 2 (biomarker cohort)

Missing data will be noted as missing on appropriate tables/listings.

2.5.4 Supportive analyses

Not applicable.

2.6 Analysis of the key secondary objective

There is no key secondary objective for part 1 or part 2.

2.7 Analysis of secondary efficacy objective(s)

Part 1 (safety run-in) and Part 2 (biomarker cohort)

The other secondary efficacy objective is to:

- Evaluate preliminary anti-tumor activity of PDR001 in combination with dabrafenib and trametinib with respect to descriptive statistics of PFS, ORR, DOR, and DCR (using investigator assessment according to RECIST 1.1) and OS

2.7.1 Secondary endpoints

All secondary efficacy endpoints according to RECIST 1.1 will be based on tumor assessments as per local investigator review. The blinded independent review committee (BIRC) assessments of RECIST 1.1 and immune-related response (i.e.iRECIST) will not be performed for the primary CSR analysis for Part 1 and 2 patients. However, the scans will be kept at the site of the central review vendor in case assessments are required for future analyses.

Progression-free survival (PFS)

PFS is defined as the time from start of treatment to the date of the first documented progression or death due to any cause. PFS will be based on local investigator review of tumor assessments and using RECIST 1.1 criteria (see Appendix 1 of the study protocol). PFS will be based on FAS and will include all data observed up-to the cut-off date.

If a patient has not progressed or died at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date. PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1. documented disease progression or death) will be considered for the primary analysis provided tumor assessments continue after initiation of new cancer therapy (See Section 2.7.3 for additional details regarding censoring rules and determination of date of last adequate tumor assessment).

Discontinuation due to disease progression (collected on the 'End of Treatment Disposition' and 'End of Post Treatment Follow-up Disposition' pages) without supporting objective evidence satisfying progression criteria per RECIST 1.1 will not be considered disease progression for PFS derivation. Clinical deterioration will not be considered as a qualifying event for progression for the primary analysis.

Overall response (ORR)

ORR is defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1 (see Appendix 1 of the study protocol). Complete and partial responses must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met. ORR will be calculated based on the FAS using local investigator review of tumor assessment data. Tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of BOR. Palliative radiotherapy is allowed as per protocol, so this should not be considered in determining anti-neoplastic therapy usage.

Duration of response (DOR)

DOR only applies to patients whose best overall response is complete response (CR) or partial response (PR) according to RECIST 1.1 based on local investigators review of tumor assessment data. The start date is the date of first documented response of CR or PR (i.e., the

start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to any cause. Patients continuing without progression or death due to any cause will be censored at the date of their last adequate tumor assessment using similar censoring rules described in section 2.7.3).

Disease control rate (DCR)

DCR is defined as the proportion of patients with a best overall response (BOR) of CR, PR, or stable disease (SD) lasting 24 weeks or longer according to RECIST 1.1 criteria. A patient will be considered to have SD for 24 weeks or longer if a SD response is recorded at 24 weeks or later from date of first dose of study treatment. DCR will be calculated using the FAS based on the investigators' tumor assessments.

Overall survival (OS)

OS is defined as the time from start of treatment to date of death due to any cause. A cut-off date will be established for each analysis of OS. All deaths occurring on or before the cut-off date in the FAS will be used in the OS analysis.

If a patient is not known to have died at the time of analysis cut-off, OS will be censored at the date of last contact.

2.7.2 Statistical hypothesis, model, and method of analysis

Progression-free survival (PFS)

The distribution of PFS based on local investigators review of tumor assessments and using RECIST 1.1 criteria will be estimated using the Kaplan-Meier method. Censoring reasons will also be summarized. For each part, median PFS along with 95% confidence intervals will be presented for the FAS.

Overall response (ORR)

ORR will be summarized using descriptive statistics (N, %) by dose cohort for part 1 and overall for part 2, along with two-sided exact binomial 95% Cis [Clopper and Pearson 1934].

Duration of response (DOR)

DOR will be listed and summarized by dose cohort for part 1 and overall for part 2, for all patients in the FAS with confirmed BOR of CR or PR. The distribution of duration of response will be estimated using the Kaplan-Meier method and the median duration of response will be presented along with 95% confidence interval only if a sufficient number of responses is observed. A responders-only analysis will also be performed in this case.

Disease control rate (DCR)

DCR will be summarized using descriptive statistics (N, %) by dose cohort for part 1 and overall for part 2, along with two-sided exact binomial 95% CIs [Clopper and Pearson 1934].

Overall survival (OS)

The distribution of OS will be estimated using the Kaplan-Meier method. Censoring reasons will also be summarized. For part 1, OS will be listed for patients by dose cohort. For part 2, median OS along with 95% confidence intervals will be presented for the FAS.

2.7.3 Handling of missing values/censoring/discontinuations

Progression-free survival (PFS)

PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date.

PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1. documented disease progression or death) will be considered for the primary analysis provided tumor assessments continue after initiation of new cancer therapy.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment will be used. If no post-baseline assessments are available (before an event or a censoring reason occurred) then the date of randomization/start date of treatment will be used.

In particular, PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after two or more missing tumor assessments. The term “missing adequate tumor assessment” is defined as a tumor assessment (TA) not performed or tumor assessment with overall lesion response of “UNK”. The rule to determine number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more.

Refer to Table 2-7 for censoring and event date options and outcomes for PFS.

Table 2-7 Outcome and event

Situation	Date	Outcome
No baseline assessment	Date of first dose of study treatment	Censored
Progression or death at or before next scheduled Assessment	Date of progression (or death)	Event
Progression or death after exactly one missing assessment	Date of progression (or death)	Event
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored

Situation	Date	Outcome
Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	Ignore clinical progression and follow situations above	As per above situations
New anticancer therapy given prior to protocol defined progression	Ignore the new anticancer therapy and follow situations above	As per above situations
Death before first PD assessment	Date of death	Event

Overall response rate (ORR)

Patients with unknown or missing best overall response (BOR) will be counted as failures. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the best overall response must be "Unknown" unless progression is reported. For the computation of ORR, these patients will be included in the FAS and will be counted as 'failures'.

Duration of response (DOR)

Patients not experiencing progression or death due to any cause will be censored at the date of their last adequate tumor assessment using similar censoring rules described for PFS analysis with the followingexception. i.e.

- Patients who received new anti-cancer therapy will be censored at the date of their last adequate tumor assessment prior to the therapy.

Overall survival (OS)

If a patient is not known to have died at the time of analysis cut-off, then OS will be censored at the date of last known date patient was alive, i.e., last contact date (see Table 2-1).

2.8 Safety analyses

All safety analyses will be based on the Safety Set. The only exceptions will be the summaries of dose limiting toxicities (DLTs) in part 1 for which the dose-determining set (DDS) will be used and will be presented by treatment group. All listings and tables will be presented overall and by dose cohort for part 1 and overall for part 2.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during the on-treatment period. Additional summaries will be displayed to report all AEs, AEs related to study treatment, all SAEs and SAEs related to study treatment collected up to 150 days after last administration of PDR001. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only

once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the total column.

The following adverse event summaries will be produced overall and by dose cohort for part 1 and overall for part 2: overview of adverse events and deaths (number and % of patients who died, with any AE, any SAE, any dose reductions/interruptions), AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose interruption, reductions (for dabrafenib and/or trametinib only), requiring additional therapy, requiring immunosuppressive medication, and leading to fatal outcome. In addition, a summary of serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term). 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.

If the same patient has more than one AE (irrespective of study treatment causality, seriousness and severity) 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 legal requirements of clinicaltrials.gov and EudraCT, two required tables for on-treatment adverse events which are not SAE's with an incidence greater than and equal to 5% and on-treatment SAE's and SAE's suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

For part 1, a summary of AE's reported as a DLT by SOC and PT will be produced by dose cohort for the DDS. If the same patient has more than one DLT with the same reported PT, the patient will be counted only once with the greatest severity, where applicable. If the same patient has more than one DLT within the same reported SOC, the patient will be counted only once with the greatest severity at the SOC level.

2.8.1.1 Adverse events of special interest / grouping of AEs

All AE groupings for a clinical program are stored in the Compound Case Retrieval Strategy sheet (CRS) with clear versioning and reference to the MedDRA version used. The main responsibility of the risk definitions are with Brand Safety Leader(s) and the Safety Management Team (SMT). All AESIs should exclusively be based on adverse events only. The CRS contains all MedDRA terms which need to be considered for case retrieval (NMQs, HLGTs, PTs, etc.). MedDRA terms should NOT be given in the MAP/RAP since it can become outdated with the next MedDRA version.

All AESI definitions or AE grouping need to be specified in the CRS. If a CRS update is necessary, the final version needs to be available in a reasonable time ahead of the DBL. The CRS version should be included in a footnote of the AESI tables.

Data analysis of AESIs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to PDR001, and the combination of 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. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

AESI for PDR001 are:

- Endocrinopathies
- Pneumonitis
- Colitis
- Hepatitis
- Nephritis
- Encephalitis
- Rash
- Infusion reaction
- Other immune disorders

AESI for dabrafenib are:

- Hypersensitivity
- Pyrexia
- Cutaneus squamous cell carcinoma (cuSCC) including keratoacanthoma
- Non-cutaneous treatment emergent malignancies
- New primary melanoma
- Pre-renal and intrinsic renal failure
- Uveitis
- Hyperglycemia
- Pancreatitis

AESI for trametinib are:

- Skin related toxicities

- Ocular events
- Cardiac related events
- Hepatic disorders
- Pneumonitis/interstitial lung disease
- Bleeding events
- Diarrhea
- Hypertension
- Edema
- Hypersensitivity
- Deep vein thrombosis/pulmonary embolism

AESI for combination of dabrafenib and trametinib are:

- Neutropenia

Summaries of these AESIs will be provided overall and by dose cohort for part 1 and overall for part 2 (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death, requiring immunosuppressive medication etc.). If sufficient number of events occurred, analysis of time to first occurrence will be applied.

Additional summaries will be provided to report all AESIs, AESIs related to study treatment, all serious AESIs and serious AESIs related to study treatment collected up to 150 days after last administration of PDR001.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced overall and by dose cohort for part 1 and overall for part 2, by system organ class and preferred term. Additional summary will be displayed to report all deaths up to 150 days after last administration of PDR001.

If study indication is primary reason for death (and not coded accordingly in the database) it must be included in the summary table. All deaths will be listed; post treatment deaths will be flagged. The death summaries cover patients from the Safety Set. A separate listing of deaths prior to starting treatment will be provided for all screened patients.

2.8.3 Laboratory data

Laboratory data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.1). All laboratory assessments will be listed and those collected later than 30 days after the last study treatment/exposure date will be flagged in the listings.

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high (low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTCAE grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTCAE grade 3 or 4 laboratory toxicities

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
    - TBL > 2xULN
    - TBL > 3xULN
    - ALT or AST > 3xULN & TBL > 2xULN
    - ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN (potential Hy's law)

Potential Hy's Law events are defined as those patients with occurrence of AST or ALT > 3xULN and TBL > 2xULN, and ALP < 2xULN at initial presentation during the on-treatment period. Note that the criteria relating to combined elevations of AST (or ALT) and TBL are based on the peak values at any post-baseline time for a subject.

For patients with abnormal ALT or AST baseline values, a clinically significant liver safety signal corresponding to Hy's law is defined by : [ALT or AST > 3*baseline] OR [ALT or AST >8*ULN], whichever is lower, combined with [TBIL >2*baseline AND >2*ULN]

Further medical review has to be conducted to assess potential confounding factor such as, liver metastates, liver function at baseline etc.

A figure displaying time course of hepatic function tests (ALT, AST, TBL, ALP) in patients with Hy's law will be displayed in the Safety Set.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

At scheduled visits, single 12-lead ECG's will be performed. ECG machines will automatically calculate heart rate and measures of PR, QRS, QT, and QTcF intervals. All ECG assessments will be read and interpreted locally.

Unscheduled safety ECG's may be performed at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECG's with clinically significant findings should be collected in triplicate.

ECHO/MUGAs will be performed to assess cardiac ejection fraction. The same procedure (either ECHO or MUGA) should be performed at baseline and follow-up visits. All ECG assessments will be read and interpreted locally.

Data handling

In case of unscheduled triplet ECG assessments, the average of the ECG parameters at that assessment should be used in the analyses.

Data analysis

The number and percentage of patients with notable ECG values will be presented overall and dose cohort for part 1 and overall for part 2.

- QT and QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS

- Increase from baseline >25% and to a value > 120 ms
- New values of QRS > 120 ms

For each of the ECG parameters (QT, QTc, QRS, HR and PR intervals), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point will be summarized.

Patients with notable ECG interval values will be listed and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG values.

A listing of all ECG assessments will be produced by treatment group and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

For left ventricular ejection fraction (LVEF), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point will be summarized overall and by dose cohort for part 1. For part 2, they will be summarized overall.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-8 below.

Table 2-8 Clinically notable changes in vital signs

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

Vital sign (unit)	Clinically notable criteria	
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 overall and by dose cohort for part 1 and overall for part 2. Descriptive statistics will be tabulated for baseline, at each post-baseline time point and changes from baseline at each post-baseline time point for each vital sign measure.

A listing of all vital sign assessments will be produced by dose cohort for part 1 and overall for part 2, and notable values will be flagged. A separate listing of only the patients with notable vital sign values may also be produced. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.3 ECOG performance status

The ECOG performance status will be used to assess physical health of patients, ranging from 0 (most active) to 5 (least active):

Table 2-9 ECOG performance scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Shift tables of ECOG performance status at baseline to worst post-baseline ECOG status by score will be provided. Shift tables of ECOG performance status at baseline to best post-baseline ECOG status by score will also be provided. ECOG performance status at each time point will be listed.

2.8.4.4 Ophthalmic examinations

A listing of all ophthalmic examinations will be produced by dose cohort for part 1 and overall for part 2. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.5 Additional analyses

Time to first occurrence

Time to first occurrence of first AESI (considering the PT that occurs first only) is defined as time from start of study treatment to the date of first occurrence of an AESI, i.e. time in days is calculated as (start date of first occurrence of event) – (start of study treatment) +1. Refer to Section 2.8.1.1 for the definition of AESI's.

In the absence of an event during the on-treatment period, the censoring date applied will be **the earliest** of the following dates:

- death date
- new anticancer antineoplastic therapy start date,
- end date of on-treatment period
- data cut-off date
- withdrawal of informed consent date.

Failure curves (ascending Kaplan-Meier curves) will be constructed for the SAF by dose cohort for part 1 and overall for part 2. Median together with 95% confidence interval as well as 25th percentile and 75th percentile will be presented.

In addition, the median time to occurrence for the subset of patients who experienced the event of interest will be calculated. Simple descriptive statistics, median, min and max as well as 25th percentile and 75th percentile, will be presented.

2.9 Pharmacokinetic endpoints

PK concentrations

Descriptive statistics (n, m (number of non-zero concentrations), mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for PDR001, dabrafenib, and trametinib concentrations will be presented at each scheduled time point by treatment for the PAS-PDR001 and PAS-D+T, respectively.

The mean (+/- SD) and geometric mean concentration-time profiles for PDR001, dabrafenib, and trametinib concentrations by treatment over time will be displayed graphically for the PAS-PDR001 and PAS-D+T, respectively, on the linear view.

All individual serum PDR001, and plasma dabrafenib, and trametinib concentration data will be listed by treatment group (for part 1) and overall (part 2) for the Full analysis set.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) (i.e. < 0.25 µg/mL for PDR001, < 1 ng/mL for dabrafenib, (GSK2118436), < 1 ng/mL for hydroxy-dabrafenib (GSK2285403), < 1 ng/mL for desmethyl-dabrafenib (GSK2167542), < 5 ng/mL for carboxy-dabrafenib (GSK2298683) and < 0.250 ng/mL for trametinib (GSK1120212)) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the

calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

2.10 PD and PK/PD analyses

2.10.1 Immunogenicity

2.10.1.1 Sample ADA status

Each IG sample is assessed in a three tiered anti-drug anti-body (ADA) testing approach. All IG samples are analyzed in the initial screening assay (first tier). Samples testing positive in the screening assay are then subjected to a confirmatory assay to demonstrate that ADA are specific for the therapeutic protein product (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier). Samples identified as positive in the confirmatory assay are considered ADA positive and are further characterized in the neutralization assay to indicate the presence of neutralizing antibodies (NAb). Samples can test negative in either the screening or confirmatory assay but for analysis purposes they are not differentiated. The following properties of each sample will be provided in the source data:

- Result of assay according to pre-specified confirmatory cut point: ADA positive (yes) or ADA negative (no)
- Titer (for positive samples): numerical representation of the magnitude of ADA response
- Presence of NAb (for positive samples, if NAb assay results are available): yes or no
- Drug tolerance level: highest drug concentration that does not interfere in the ADA detection method
- Fold titer change (i.e. x-fold): threshold for determining treatment boosted

Sample ADA status is determined based on the following definitions:

- *ADA-inconclusive sample*: Sample where assay is ADA negative and PDR001 PK concentration at the time of IG sample collection is greater than or equal to the drug tolerance level or missing.
- *Unevaluable sample*: Sample where assay is not available.
- *Determinant sample:* Sample that is neither ADA-inconclusive nor unevaluable.

The following definitions apply only to determinant samples:

  - *ADA-negative sample*: Determinant sample where assay is ADA negative and PDR001 PK concentration at the time of IG sample collection is less than the drug tolerance level.
  - *ADA-positive sample*: Determinant sample where assay is ADA positive.
  - *ADA-positive NAb sample*: Determinant sample where assay is ADA positive and presence of NAb = yes.

The following definitions apply only to post-baseline ADA-positive samples with a corresponding determinant baseline sample: To be classified as *treatment-boosted* or *treatment-unaffected*, both the post-baseline and baseline titer must be non-missing:

- *treatment-induced ADA-positive sample:* ADA-positive sample post-baseline with ADA-negative sample at baseline.
- *treatment-boosted ADA-positive sample:* ADA-positive sample post-baseline with titer that is at least *the fold titer change* greater than the ADA-positive baseline titer.
- *treatment-unaffected ADA-positive sample*: ADA-positive sample post-baseline with titer that is less than *the fold titer change* greater than the ADA-positive baseline titer.

NOTE: PK concentrations which are flagged for exclusion will still be used to determine ADA-inconclusive and ADA-negative samples.

The following summaries of ADA sample status (n and %) will be provided using *Immunogenicity prevalence set*:

- ADA-positive samples (i.e. ADA prevalence) and ADA-positive NAb samples, both overall and by time point (including baseline). For summaries by time point, the denominator is the number of subjects at that time point with a determinant sample.

Listings will be provided of sample ADA status (including titer for positive samples).

2.10.1.2 Subject ADA status

Any IG sample collected after 150 days of the last dose of PDR001 will not be used for summaries or derivations and will only be included in the listing.

Subject ADA status is defined as follows:

- *Treatment-induced ADA-positive subject*: subject with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample.
- *Treatment-boosted ADA-positive subject*: subject with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample.
- *Treatment-unaffected ADA-positive subject*: subject with ADA-positive sample at baseline, no treatment-boosted ADA-positive samples, and at least one treatment-unaffected ADA-positive sample.
- *Treatment-reduced ADA-positive subject*: subject with ADA-positive sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- *ADA-negative subject*: subject with ADA-negative sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.

- *Inconclusive subject*: subject who does not qualify as treatment-induced ADA-positive, treatment-boosted ADA-positive, treatment-unaffected ADA-positive, treatment-reduced ADA-positive, or ADA-negative

The following overall summaries of ADA subject status (n and %) will be provided using the *Immunogenicity incidence set*:

- Treatment-boosted ADA-positive subjects;: denominator is the number of subjects with an ADA-positive sample at baseline.
- Treatment-induced ADA-positive subjects;: denominator is the number of subjects with an ADA-negative sample at baseline.
- ADA-negative subjects;: denominator is the number of subjects with an ADA-negative sample at baseline.
-
- ADA-positive subjects (i.e. ADA incidence): calculated as the number of treatment-boosted ADA-positive and treatment-induced ADA-positive subjects; denominator is the number of subjects in *Immunogenicity incidence set*.

Listings will be provided of subject ADA status

[redacted]

2.11 Patient-reported outcomes

Not applicable.

2.12 Biomarkers

Biomarker data will be collected for parts 1 and 2.

For part 2 (biomarker cohort), refer to Section 2.5.1 and Section 2.5.2.2 for more details on primary endpoints of PD-L1 levels and CD8+ cells.

2.12.1 Introduction

As a project standard, Novartis Oncology Biostatistics will analyze only biomarkers collected in the clinical database. [redacted]

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue their analysis due to either practical or strategic reasons. Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

2.12.2 Biomarker data

The Full Analysis Set will be used for all biomarker analysis for part 1 and part 2. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

Assessment of associations between biomarker and safety data will be conducted using the Safety Set.

Table 2-10 summarizes the biomarker collection schedules and sample types.

Table 2-10 Sample biomarker summary table

Biomarker	Part of study	Time point	Sample	Method
PD-L1 levels, CD8+ cells	Part 1 (safety run-in)	Screening	Archival or new tumor biopsy	IHC
		Cycle 1 Day 15	Optional new tumor biopsy	
		Any time during Cycle 3	Optional new tumor biopsy	
		At disease progression	Optional new tumor biopsy	
PD-L1 levels, CD8+ cells	Part 2 (biomarker cohort)	Screening	New tumor biopsy	IHC
		Cycle 1 Day 15	New tumor biopsy	
		Any time during Cycle 3	New tumor biopsy	
		At disease progression	New tumor biopsy	
		Any time on treatment	Optional new tumor biopsy	

2.12.3 General data handling and preprocessing

The last (pre-dose) assessment performed closest to treatment dose will be used as the baseline value.

For assessments performed in tumor biopsies, fresh biopsy results will be used for baseline when both archived and fresh tumor samples are available for the same time point.

When more than one biomarker data value are available for a patient at any time point, the mean of the replicate values will be used for all statistical analyses.

For CD8, the following variables are provided in the raw data:

- Percent Marker Area
- Intraepithelial density 0 (% of cells containing no CD8)
- Intraepithelial density 1 (% of cells containing 1 to <5% of CD8)

- Intraepithelial density 2 (% of cells containing 5 to <10% of CD8)
- Intraepithelial density 3 (% of cells containing ≥10% of CD8)
- Intratumoral stroma density 0 (% of cells containing no CD8)
- Intratumoral stroma density 1 (% of cells containing 1 to <5% of CD8)
- Intratumoral stroma density 2 (% of cells containing 5 to <10% of CD8)
- Intratumoral stroma density 3 (% of cells containing ≥10% of CD8)

In addition the following variables will be derived:

- Intraepithelial "H-Score"
- Intratumoral stroma "H-Score"

Percent Marker Area, Intraepithelial H-Score and Intratumoral Stroma H-Score will be summarized.

For the calculation of H-Scores:

Let X1, X2, X3, and X4 be the CD8 intraepithelial densities for levels (or bins) 0, 1, 2, and 3. Similarly, let X5, X6, X7, and X8 be the CD8 intratumoral stroma densities for levels (or bins) 0, 1, 2, and 3.

Let Intraepithelial H-Score = (1*X2) + (2*X3) + (3*X4)

Let Intratumoral Stroma H-Score = (1*X6) + (2*X7) + (3*X8)

Note that 0*X1 (for intraepithelial) and 0*X5 (for intratumoral stroma) are intentionally left out, since these will always equal 0.

2.12.4 Biomarker data analysis

*PD-L1 levels and CD8+ variables (*Percent Marker Area, Intraepithelial H-Score and Intratumoral Stroma H-Score) as measured by Immunohistochemistry (IHC), which are considered as core exploratory biomarkers in trials with immunotherapy, will be summarized. [redacted]

2.12.4.1 Categorization of IHC biomarker data

The PD-L1 expression status by the selected thresholds will be tabulated for all treated patients as described in Table 2-11.

Table 2-11 PD-L1 expression status definitions

Analyte	Parameter	Negative	Positive
PD-L1	Percent positive tumor	<1 % tumor cell staining	≥ 1% tumor cell staining

A Melanoma (MEL) score for PD-L1 expression [Daud 2016] will be derived and tabulated for all treated patients as described in Table 2-12. A MEL score ≥ 2 is considered PD-L1 positive.

Table 2-12 PD-L1 Melanoma (MEL) score definitions

Analyte	MEL score	Definition
PD-L1	0	No membrane staining
	1	Membrane staining in tumor and tumor-associated immune cells range of > 0% to < 1%
	2	Membrane staining in tumor and tumor-associated immune cells range of ≥ 1% to < 10%
	3	Membrane staining in tumor and tumor-associated immune cells range of ≥ 10% to < 33%
	4	Membrane staining in tumor and tumor-associated immune cells range of ≥ 33% to < 66%
	5	Membrane staining in tumor and tumor-associated immune cells range of ≥ 66%

2.12.4.2 Listing and summary statistics of IHC data

For Part 1 biomarker data will be summarized at baseline only whereas post-baseline summaries will also be provided for Part 2 data.

For each quantitative measurement of the IHC assay, the mean, standard deviation, %CV, median, minimum, maximum, inter-quartile range and number at each time point will be reported. Interquartile range is the number of data points between the 25th and 75th percentile. For part 1, data will be summarized by dose cohort and overall.

For part 2, data will be summarized overall and the following analysies will be performed.

Absolute and relative change (percent change) from baseline will be calculated for each patient.

Percent change is computed as ((visit i – baseline) / baseline) * 100. To compute the average percent change from baseline is to compute the average expression level at each time point and then compute the percent change using the average values. Please note that the number of patients for the average of percent change from baseline might vary due to potential missing values at respective time points.

Absolute and relative change (percent change) from baseline will be calculated and summarized for each patient.

Graphical presentations of the PD-L1 and CD8+ quantitative biomarker variables over time as well as change and percentage change from baseline will be produced via spaghetti plots and boxplots by visit (Part 2 only).

2.12.4.3 Association between biomarkers and clinical outcome

For the purposes of the CSR no analyses examining the relationshiop between biomarkers and clinical outcome will performed for Part 1 and 2 patients. Additional analyses related to this aspect that may be performed after the completion of the end-of-study CSR will be

documented in separate reports. The data analysis will be described in a stand-alone analysis plan document.

[redacted]

2.14 Interim analysis

Part 1 (safety run-in)

No formal interim analysis is planned. However, the safety run-in design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort of patients, the next dose will be chosen depending on the observed data (based on safety, PK, tolerability data, guided by the recommendations from the BLRM of DLT using EWOC, and recommendations from participating investigators). Details of this procedure and the process for communication with Investigators are provided in Section 6.2.3 of the protocol. In order to make timely dose decisions the investigators should make sure to enter the data required by the protocol into the eCRF in time.

Part 2 (biomarker cohort)

No formal interim analysis is planned.

3 Sample size calculation

3.1 Primary analysis

Part 1 (safety run-in)

No formal statistical power calculations to determine sample size were performed for this part of the study. In the case that the starting dose (PDR001 400 mg i.v. every 4 weeks with the fixed dose combination of 150 mg BID dabrafenib and 2 mg QD trametinib) is confirmed to be safe and tolerated, the safety run-in part is expected to enroll 6 evaluable patients (i.e. who met the minimum exposure criterion and had sufficient safety evaluations during the first 8 weeks of PDR001 in combination with dabrafenib and trametinib dosing). Otherwise, up to 18 additional patients are foreseen to be enrolled to assess additional cohorts.

Part 2 (biomarker cohort)

No formal statistical power calculations to determine sample size were performed for this part of the study. Up to 20 evaluable patients (i.e. who have at least one tumor biopsy at screening and at least two during triple combination therapy) will be enrolled in this cohort.

3.2 Power for analysis of key secondary variables

There are no key secondary variables for part 1 or part 2.

4 Change to protocol specified analyses

The changes summarized in Table 4-1 were made between the protocol statistical section (Amendment 5) and the SAP.

Table 4-1 Summary of changes to protocol specified analyses

Protocol section	SAP section	Change and reason
Section 10.5.2	Section 2.7.1 and 2.13	The protocol mentions that data from central review (RECIST and irRECIST) will be summarized as a supportive analysis for Part 1 and 2. However,for the main CSR analysis the Part 1 and 2 scans will not be read via central review and therefore the SAP text is changed to reflect this...
Section 10.5.2	Section 2.7.3	DOR definition clarified i.e. to emphasize that deaths due to any cause will be regarded as an event and new anti-cancer therapy will lead to censoring at last adequate assessment.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 1 should not be applicable for final CSR. All patients should have EOT page complete before the Database lock for Final CSR

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date: **Use Dec31yyyy**

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date: **Use EOT date**

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date: **Use last day of the Month (mm)**

Case 5: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm = the month of EOT date: **Use EOT date**

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment: **Use the treatment start date**

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  o Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

day	• If available month and year = month and year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  o Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month and year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	**Rule** (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawl of consent date))
day, month, and year	Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

The above imputations are only used for analyses of time to and duration of AEs and concomitant medications.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date, then the evaluation is considered post-cut-off date and will be excluded from analysis.

5.2 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 should be specified in the footnote of relevant tables.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

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).

5.3 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. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used (refer to Table 5-3).

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high 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. Grade 5 will not be used. 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.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

Table 5-3 CTC grades for laboratory values in Novartis Oncology (based on CTCAE v4.03 – June 2010

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Hematology								
WBC ↓	10^9/L	WBC	**3.9 – 10.7 x 10^9/L**	≥ LLN	< LLN - 3.0 x 10^9 /L	< 3 0 – 2 0 x 10^9 /L	< 2.0 – 1.0 x 10^9 /L	< 1.0 x 10^9 /L
WBC [2] (Leukocytosis)	10^9/L	WBC			-	-	> 100 x 10^9 /L	-
Hemoglobin [2] (Anemia)	g/L	HGB	**120 - 160 g/L** or 7.4 - 9.9 mmol/L (F) **140 - 170 g/L** or 8.7 – 10 6 mmol/L (M)	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L	< 100 - 80 g/L < 6 2 - 4.9 mmol/L	< 80 g/L < 4.9 mmol/L	-
Hemoglobin ↑	g/L	HGB	*(16.113 x mmol/L = g/L)*		Increase >0-20 g/L above ULN	Increase >20-40 g/L above ULN	Increase >40 g/L above ULN	-
Platelets ↓	10^9/L	PLAT	**150 - 350 x 10^9/L**	≥ LLN	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9 L	< 50.0 - 25 0 x 10^9/L	< 25.0 x 10^9 /L
Neutrophils [3]↓	10^9/L	NEUT		≥2x10^9 /L	< 2 0 - 1.5 x 10^9 /L	< 1 5 - 1.0 x 10^9 /L	< 1.0 - 0.5 x 10^9 /L	< 0.5 x 10^9 /L
Lymphocytes [3]↓	10^9/L	LYM		≥1.5x10^9 /L	< 1 5 - 0.8 x 10^9 /L	< 0 8 - 0.5 x 10^9 /L	< 0.5 - 0.2 x 10^9 /L	< 0.2 x 10^9 /L
Lymphocytes ↑	10^9/L	LYM			-	> 4 - 20 x 10^9 /L	> 20 x 10^9 /L	-
Biochemistry								
AST ↑	U/L	AST	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3 0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3 0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin ↑	umol/L	B LI	**5.1 – 20.5 umol/L** or 0 3 – 1.2 mg/dL *(17.1 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1 5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	**36 - 92 U/L** or 0.5 - 1 5 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2 5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine [4]↑	umol/L	CREAT	**61.9 - 115 umol/L** or 0.7 – 1 3 mg/dL *(88.4 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1 5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase [4]↑	U/L	CK	**30 - 170 U/L** or 0.5 – 2 83 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2 5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Albumin [2] (Hypoalbuminemia)	g/L	ALB	**35 - 55 g/L** or 3 5 to 5 5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-
Total Cholesterol ↑	mmol/L	CHOL	**3.88 – 5.15 mmol**/L or 150 - 199 mg/dL *(38.67 x mg/dL = mmol/L)*	≤ ULN	> ULN - 7.75 mmol/L > ULN - 300 mg/dL	> 7.75 -10.34 mmol/L > 300 – 400 mg/dL	>10 34-12.92 mmol/L > 400 – 500 mg/dL	>12 92 mmol/L > 500 mg/dL
Lipase ↑	U/L	LIPASE	**<95 U/L** or <1.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1 5 x ULN	> 1 5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	**0 - 130 U/L** or 0 – 2.17 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1 5 x ULN	> 1 5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Uric acid [2] (Hyperuricemia)	umol/L	URATE	**150 - 470 umol/L** or 2.5 – 8 mg/dL *(59.48 x mg/dL = umol/L)*	≤ ULN	> ULN – 10 mg/dL > ULN – 595 umol/L	-	-	> 10 mg/dL > 595 umol/L
ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range								

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Phosphorus[2] (Hypophosphatemia)	mmol/L	PHOS	**0.97 – 1.45 mmol/L** or 3 0 - 4.5 mg/dL *(0.32 x mg/dL = mmol/L)*	≥ LLN	< LLN - 2.5 mg/dL < LLN - 0.8 mmol/L	< 2 5 - 2.0 mg/dL < 0 8 - 0.6 mmol/L	< 2 0 - 1 0 mg/dL < 0 6 - 0 3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L
Calcium (corrected) [2] (Hypercalcemia)	mmol/L	CACALC	**2.2 - 2.6 mmol/L** or 9 - 10.5 mg/dL *(0.2495 x mg/dL = mmol/L)*	≤ ULN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L	> 11.5 - 12 5 mg/dL > 2 9 - 3.1 mmol/L	> 12.5 - 13 5 mg/dL > 3.1 - 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Calcium (corrected) [2] (Hypocalcemia)	mmol/L	CACALC		≥ LLN	< LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	< 8 0 - 7.0 mg/dL < 2 0 - 1.75 mmol/L	< 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Magnesium [2] (Hypermagnesemia)	mmol/L	MG	**0.62 – 0.99 mmol/L** or 1 5 – 2.4 mg/dL *(0.4114 x mg/dL = mmol/L)*	≤ ULN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3 3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L
Magnesium [2] (Hypomagnesemia)	mmol/L	MG		≥ LLN	< LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	< 1 2 - 0.9 mg/dL < 0 5 - 0.4 mmol/L	< 0.9 - 0.7 mg/dL < 0.4 - 0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L
Glucose (non-fasting) [2] (Hyperglycemia)	mmol/L	GLUCSN	**<7.8 mmol/L** or <140 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	-	> ULN - 250 mg/dL > ULN - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27 8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose (fasting) [2] (Hyperglycemia)	mmol/L	GLUCSF	**3.9 – 5.8 mmol/L** or 70 - 105 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	> ULN - 160 mg/dL > ULN - 8.9 mmol/L	> 160 - 250 mg/dL > 8 9 - 13 9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27 8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose [2] (Hypoglycemia)	mmol/L	GLUCSN/GLUCSF		≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3 0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium [2] (Hyperkalemia)	mmol/L	K	**3.5 - 5.0 mmol/L** *(0.2558 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 5.5 mmol/L	> 5 5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium [2] (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium [2] (Hypernatremia)	mmol/L	SODIUM	**136 - 145 mmol/L** *(0.435 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium [2] (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	-	< 130 - 120 mmol/L	< 120 mmol/L
Triglyceride [2] ↑	mmol/L	TRIG	**< 2.82 mmol/L** or < 250 mg/dL *(0.01129 x mg/dL = umol/L)*	< 150 < 1.71	≥ 150 - 300 mg/dL ≥ 1.71 – 3.42 mmol/L	> 300 - 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 - 1000 mg/dL > 5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L
Coagulation								
INR [2]↑	1	NR	**0.8 – 1.2**	≤ ULN	> ULN - 1.5 x ULN	> 1 5 - 2.5 x ULN	> 2.5 x ULN	-
Activated partial thromboplastin time[2]↑	sec	APTT	**25 - 35 sec**	≤ ULN	> ULN - 1.5 x ULN	> 1 5 - 2.5 x ULN	> 2.5 x ULN	-
Fibrinogen [4]↓	g/L	FIBRINO	**1.5 – 3.5 g/L** or 150 – 350 mg/dL *(0.01 x mg/dL = g/L)*	≥ LLN	< LLN - 0.75 x LLN	< 0.75 - 0 5 x LLN	< 0.5 - 0.25 x LLN	< 0.25 x LLN

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

(1) = **LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria**, e.g. if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≤ ULN.

(2) = **Life-threatening consequences and/or hospitalization are <u>not</u> considered** for determination of LAB CTC grades 3 and 4. Concomitant usage of anticoagulation therapy (for INR and Fibrinogen) is not considered either.

(3) = Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, **≥ 1.5 x 10^9 /L (lymphocytes) and ≥ 2 x 10^9 /L (neutrophils) are considered as LAB CTC grade 0**

(4) = For Creatinine and Fibrinogen, the **comparison with baseline is <u>not</u> considered** for derivation of LAB CTC grades

5.4 Statistical models

5.4.1 Primary analysis

For part 1, please refer to the Section 10 and Appendix 2 of the protocol.

For part 2, not applicable due to lack of hypothesis testing.

5.4.2 Key secondary analysis

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

Not applicable.

6 Reference

1. Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 26, 404-413.
2. Daud A, Wolchok J, Robert C, et al (2016). Programmed death ligand 1 expression and response to the anti-programmed death 1 antibody pembrolizumab in melanoma. J Clin Oncol, 34:4102-4109.
3. Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ (2010). Summarizing information on historical controls in clinical trials. Clinical Trials; 7:5-18.
4. Neuenschwander B, Matano A, Tang Z, Roychoudhury S, Wandel S, Bailey S (2014). A Bayesian industry approach to phase 1 combination trials in oncology statistical methods in drug combination studies, CRC Press; Chapter 6.
5. Nishino M, Gargano M, Suda M, et al (2014). Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab? J Immunother Cancer; 2:17
6. Nishino M, Giobbie-Hurder A, Gargano M, et al (2013). Developing a Common Language for Tumor Response to Immunotherapy: Immune-Related Response Criteria Using Unidimensional Measurements. Clin Cancer Res; 19:3936-3943
7. Rogatko A, Schoeneck D, Jonas W, et al (2007). Translations of innovative designs into phase 1 trials. J Clin Oncol; 25(31): 4982-6.
8. Spiegelhalter DJ, Abrams KR and Myles JP (2004). Bayesian Approaches to Clinical Trials and Health-care Evaluation. Chichester, Wiley.

NOVARTIS

Clinical Development

PDR001, dabrafenib, trametinib

CPDR001F2301 / NCT02967692

A randomized, double-blind, placebo-controlled phase III study comparing the combination of PDR001, dabrafenib and trametinib versus placebo, dabrafenib and trametinib in previously untreated patients with unresectable or metastatic *BRAF* V600 mutant melanoma

Statistical Analysis Plan (SAP) for Part 3 Amendment 3

Author:	Trial Statistician [redacted]

Document type:	SAP Documentation
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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
16-Aug-2019	Prior to IA DB lock	Incorporate changes as per protocol Amendment #5 and to implement changes to PRO and Biomarker analyses (Am1)	The sample size and interim analysis sections were updated to incorporate an additional PFS interim analysis and change to required number of events for both PFS and OS. PRO section PRO analysis section updated to incorporate FDA feedback. Biomarker section updated to meet needs of Biomarker team for CSR analysis and to add threshold levels for specific biomarker subgroups. DOR/iDOR and iDCR/DCR definition and censoring rules were clarified. Notation of immune-related response endpoints changed to be consistent with Novartis iRECIST guidance document and Seymour paper. Additional analyses of PFS and OS were added related to RMST and Milestone Survival.	Extensive updates to section 2.14 Interim analysis and section 3 (Sample Size calculation) as well as minor updates to sections 1.1 and 2.1. 2.2.1 Subgroup of interest 2.5.3 Handling of missing values/censoring/discontinuations 2.5.4 Supportive Analyses 2.6.2 Statistical hypothesis, model, and method of analysis 2.7.1 Secondary endpoints 2.10.1 Immunogenicity Section 2.11 PRO Sections 2.12.3 and 2.12.5 related to Biomarker analyses [redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Additional PFS sensitivity analysis to address possible bias from change in schedule following treatment withdrawal. Corrected error in PFS censoring/event rule table (Table 2-12) Immunogenecity section updated to incorporate updates to standard text.	
4-May 2020	Prior to Final DBL	Changes needed for final PFS analysis including analyses to describe and assess impact of COVID-19 (Am2)	Change to derivation of RDI/DI for PDR001/Placebo to align with other project trials. This is a more accurate representation of drug intensity. Update to Hy's Law criteria based on updated Novartis guidance document Update on handling of pk data below LLOQ (e.g. to include metabolytes) Alignment of Immunogenicity text with standard IG SAP and TFLs. Update to PRO analysis text e.g. clarifications to responder analysis [redacted]	2.4.1 Study Treatment Compliance 2.2.1 Subgroup of Interest 2.5.4 Supportive Analysis (for primary objective) 2.6.2 statistical hypothesis, model and method of analysis (for secondary objectives) 2.8.3 Laboratory data 2.9 Pharmacokinetic endpoints 2.10.1 Immunogenicity 2.11.3 Details of Statistical Methods (PROs) 2.12.5.3 Association between biomarkers and clinical outcome 2.13.1 Duration of Follow-up 2.13.3 Analyses incorporating Post-treatment new anti-neoplastic (ANP) therapies. 2.13.4 Impact of COVID-19

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			[redacted] Change of threshold level for TMB subgroups to align with competitor definition. Clarification that OS Forest plot for biomarker subgroups is required. Text on Duration of follow-up is aligned with shell outputs. Addition of analyses related to outcome after study treatment withdrawal incorporating Anti-neoplastic data. [redacted]	
30 July 2020	Prior to Final DBL	To incorporate health authority feedback and fix some minor inconsistencies in document (Am3)	Change to DOR/iDOR definitions to count deaths due to any cause as an event. Clarification of definition of "backdating PFS sensitivity analysis". Minor changes to fix some inconsistencies related to biomarker related analyses.	1.2 Study Objectives and endpoints 2.2.1 Subgroup of Interest 2.3 Patient disposition , demographics and other baseline characteristics 2.5.4 Supportive Analysis (for primary objective) 2.7.1 Secondary endpoints 2.9 Pharmacokinetic endpoints

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			In pk section change "plasma" to "serum" for PDR001.	2.13.2 Efficacy endpoints according to response criteria for immunotherapy [redacted]

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List of abbreviations

AE	Adverse event
AESI	Adverse Events of Special Interest
ADA	Anti-Drug Antibodies
AJCC	American Joint Committee on Cancer
ALB	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area-under-the-curve
bid	bis in diem/twice a day
BIRC	Blinded Independent Review Committee
BMI	Body Mass Index
BOR	Best Overall Response
CD8	Cluster of Differentiation 8
CI	Confidence Interval
CTLA-4	Cytotoxic T-lymphocyte-associated Protein 4
CR	Complete Response
CRO	Contract Research Organization
CRS	Case Retrieval Strategy
CSP	Clinical Study Protocol
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Measured concentration at end of dosing interval
$C_{trough,ss}$	Measured concentration at end of dosing interval at steady state
DAR	Dose Administration Record
DCR	Disease Control Rate
DI	Dose Intensity
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DOR	Duration of Response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
eDISH	Evaluation of Drug-induced Serious Hepatotoxicity
EORTC QLQ-30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core
EOT	End of Treatment
EQ-5D	Quality of life questionnaire consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) offered by EuroQoL group
FACT-M	Functional Assessment of Cancer Therapy–Melanoma

FAS	Full Analysis Set
FH	Fleming-Harrington
GLMM	Generalized Linear Mixed Model
HGLT	High Level Group Term
HLT	High Level Term
HR	Hazard Ratio
ICPW	Inverse Probability of Censoring Weighted
IHC	Immunohistochemistry
irCR	Immune Related Complete Response
irDCR	Immune Related Disease Control Rate
irDOR	Immune Related Duration of Response
IG	Immunogenicity
INR	International Normalized Ratio
irORR	Immune Related Overall Response Rate
irPD	Immune Related Progressive Disease
irPFS	Immune Related Progression-Free survival
irPR	Immune Related Partial Response
K-M	Kaplan-Meier
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MEL	Melanoma scoring system for PD-L1 expression
MID	Minimal Important Difference
MUGA	Multigated Acquisition
Mut/MB	Mutations per Megabase
NCI	National Cancer Institute
NMQ	Novartis MedDRA Query
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamics
PD-1	Programmed Death 1
PDI	Planned Dose Intensity
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial Response
PRO	Patient-reported Outcomes
PT	Preferred Term
qd	Qua'que di'e / once a day
Q4W	Every 4 weeks
Q8W	Every 8 weeks

QoL	Quality of Life
RAP	Report and Analysis Process
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP3R	Recommend Part 3 Regimen
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Stable Disease
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOD	Sum of Diameters
SSD	Study Specific Document
TA	Tumor Assessment
TBL	Total Bilirubin
TFLs	Tables, Figures, Listings
ULN	Upper Limit of Normal
UNK	Unknown
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for **part 3 (randomized part)** of the clinical study report (CSR) of study CPDR001F2301, a randomized, double-blind, placebo-controlled, phase III study comparing the combination of PDR001, dabrafenib and trametinib versus placebo, dabrafenib and trametinib in previously untreated patients with unresectable or metastatic *BRAF* V600 mutant melanoma. All planned analyses for **part 1 (safety run-in) and part 2 (biomarker cohort)** are described in a separate analysis plan.

The content of this SAP is based on protocol CPDR001F2301 version 05 (Amendment 5). All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

This study has been designed as a phase III, multi-center study consisting of 3 parts:

- Part 1: Safety run-in part
- Part 2: Biomarker cohort
- Part 3: Double-blind, randomized, placebo-controlled part

Part 1 of this study is an open-label, multi-center safety run-in part investigating the safety and tolerability, pharmacokinetics (PK) / pharmacodynamics (PD), and preliminary efficacy of PDR001 in combination with dabrafenib and trametinib in previously untreated patients with BRAF V600 mutant unresectable or metastatic melanoma (AJCC edition 7 stage IIIC/IV). The primary objective of the safety run-in is to determine the recommended regimen of PDR001 in combination with dabrafenib and trametinib to be used in part 3 of the study.

Part 2 of this study is an open-label, multi-center biomarker cohort investigating the safety and tolerability, PK/PD, biomarker data, and preliminary efficacy of PDR001 in combination with dabrafenib and trametinib in previously untreated patients with BRAF V600 mutant unresectable or metastatic melanoma (AJCC edition 7 stage IIIC/IV). The primary objective of the biomarker cohort is to evaluate changes in PD-L1 levels and CD8+ cells upon treatment with PDR001 in combination with dabrafenib and trametinib.

For more details on the design of part 1 and part 2, refer to the protocol or part 1/2 SAP.

Part 3 of this study is a randomized, double-blind, placebo-controlled part comparing safety and efficacy of PDR001 in combination with dabrafenib and trametinib to placebo in combination with dabrafenib and trametinib in previously untreated patients with BRAF V600 mutant unresectable or metastatic melanoma (AJCC edition 7 stage IIIC/IV). After the recommended dosing regimen for the combination of PDR001 with dabrafenib and trametinib has been identified in part 1 of the study, approximately 500 patients will be randomized to one of the following treatment arms in 1:1 ratio:

- PDR001 in combination with dabrafenib and trametinib
- Placebo in combination with dabrafenib and trametinib

Randomization will be stratified by the following factors:

- LDH level (< 1 x ULN vs ≥ 1 to < 2 x ULN vs ≥ 2 x ULN)
- ECOG performance status (0 vs 1 vs 2)

Progression-free survival (PFS) as assessed by local investigators review of tumor assessments and using RECIST 1.1 criteria is the primary endpoint for this part of the study. Overall survival (OS) is the key secondary endpoint.

A maximum of two analyses (one interim and one final) is planned for PFS. An interim analysis is planned after approximately 260 PFS events have been observed and a final analysis is planned after approximately 352 events or at approximately 24 months after the last patient has been randomized whichever occurs first.

A maximum of three analyses (two interim and one final) is planned for OS;

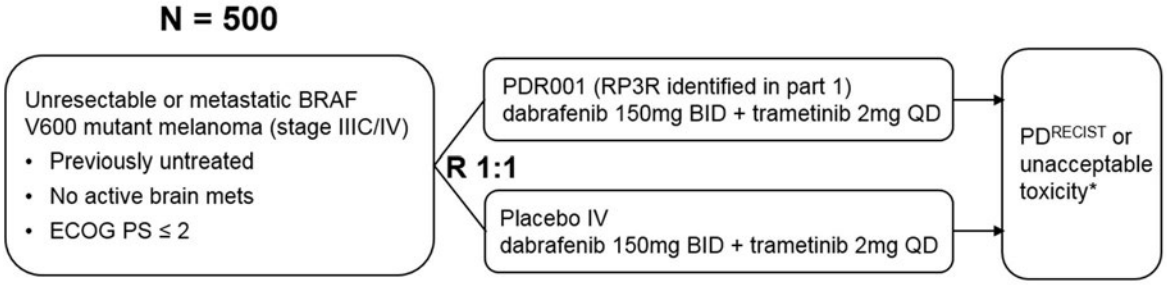
- at the time of the interim analysis for PFS (provided PFS is significant)..
- at the time of the final analysis for PFS (provided interim or final PFS is significant)
- and a final analysis for OS when approximately 245 deaths are observed. The final OS analysis is expected approximately 36 months from date the first patient was randomized according to a Novartis prediction analysis using actual study data This prediction is uncertain and maybe subject to change. The final OS analysis may be performed prior to 245 deaths being observed at the specific request of health authorities following a significant primary PFS outcome.

Addition details are described in Section 4 and Section 10 of the protocol.

An independent Data Monitoring Committee (DMC) will monitor unblinded safety data approximately every 3 to 6 months during the conduct of part 3. In addition the DMC will review the primary PFS results along with other key efficacy (e.g. OS, ORR, DOR, DCR) and safety data at the time of the interim PFS analysis. Full details of the analyses required for DMC review will be described in a separate analysis plan.

Refer to Figure1-1 for a study design diagram for part 3.

Figure 1-1 Part 3: Double-blind, randomized, placebo-controlled part overview of study design



Randomization Stratification
- ECOG PS (0 vs 1 vs 2)
- LDH (< 1 x ULN vs ≥ 1 to < 2 x ULN vs ≥ 2 x ULN)

Primary endpoints: PFS^{RECIST}
Key Secondary: OS
Other Secondary: ORR, DOR, DCR, Safety, PROs, PK

*Treatment beyond PD^{Recist} is permitted if all of the following criteria are met: (1) subject has irSD, irPR or unconfirmed irPD according irRECIST, (2) the treatment will not delay an imminent intervention to prevent serious complications, (3) tolerance of study treatment, and (4) stable performance status

NOTE: PDR001 RP3R identified in Part 1 was 400mg Q4W

1.2 Study objectives and endpoints

Objectives and related endpoints for part 3 are described in Table 1-1 below. For objectives pertaining to part 1 and part 2, refer to the protocol or the part 1/2 SAP.

Table 1-1 Part 3 objectives and related endpoints

Objective	Endpoint
Primary	
• To compare the anti-tumor activity of PDR001 in combination with dabrafenib and trametinib versus placebo plus dabrafenib and trametinib as measured by PFS per investigator's assessment according to RECIST 1.1	• Investigator assessed PFS (according to RECIST 1.1)
Key secondary	
• To compare overall survival of PDR001 in combination with dabrafenib and trametinib versus placebo plus dabrafenib and trametinib	• Overall survival
Other secondary	
• To compare the anti-tumor activity of PDR001 in combination with dabrafenib and trametinib versus placebo plus dabrafenib and trametinib as measured by ORR, DCR, DOR per investigator's assessment according to RECIST 1.1	• ORR, DCR, and DOR by investigators's assessment according to RECIST 1.1
• To evaluate safety and tolerability of PDR001 in combination with dabrafenib and trametinib versus placebo plus dabrafenib and trametinib	• Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, ECOG PS, vital signs, liver assessments and cardiac assessments • Tolerability: Dose interruptions, reductions, and dose intensity
• To evaluate patient reported outcomes of PDR001 in combination with dabrafenib and trametinib versus placebo plus dabrafenib and trametinib	• Change from baseline in EORTC QLQ-C30, EQ-5D, and FACT-M melanoma subscale • Time to 10 point definitive deterioration in overall quality of life score from EORTC QLQ-30
• To characterize PK of PDR001, dabrafenib and trametinib when administered in combination	• PK parameters such as but not limited to Ctrough and $Ctrough_{ss}$ for PDR001, dabrafenib and trametinib
• To evaluate the prevalence and incidence of immunogenicity	• ADA prevalence at baseline and ADA incidence on-treatment
• To characterize the potential for PD-L1 expression to identify subjects with an enhanced response to PDR001 in combination with dabrafenib and	

Objective	Endpoint
trametinib versus placebo plus dabrafenib and trametinib	• PFS by investigator's assessment according to RECIST 1.1 and OS by centrally assessed PD-L1 status

[redacted]

Objective	Endpoint
[redacted]	

2 Statistical methods

2.1 Data analysis general information

All analyses will be performed by Novartis and/or a designated CRO. SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures, and listings.

Data included in the analysis

For **part 3**, there is one interim and one final analysis planned for the primary efficacy endpoint (PFS). Up to two interim and one final analysis may be performed for the key secondary endpoint (OS). A unique cut-off date will be established after the targeted number of events for each of the planned interim and final analyses has been documented.

For each of the analyses, 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 events, the end date will not be imputed and therefore will not appear in the listings.

The analysis cut-off date for the final OS analysis will be established when approximately 245 deaths have occurred, or if statistical significance is reached at the interim OS analysis. If the primary analysis of PFS does not demonstrate treatment benefit, then follow-up for OS will end.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, rate, etc.) will be summarized by means of contingency tables by treatment group; a missing category will be included as applicable. Percentages will be

calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment group.

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug will refer to PDR001 only. Whereas, ***study treatment*** will refer to PDR001 + dabrafenib and trametinib and placebo + dabrafenib and trametinib.

The term investigational treatment may also be referred to as ***study treatment*** which is used throughout this document.

Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when a non-zero dose of investigational drug is administered and recorded on the Dosage Administration Record (DAR) (e)CRF. The date of first administration of study drug will also be referred as start of investigational drug.

Date of last administration of investigational drug

The date of last administration of investigational drug is defined as the last date when a non-zero dose of investigational drug is administered and recorded on DAR eCRF. The date of last administration of investigational drug will also be referred as end of investigational drug.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of any component of study treatment was administered as per the Dosage Administration (e)CRF. (Example: if 1st dose of PDR001 or placebo is administered on 05-Jan-2016, and 1st dose of dabrafenib and trametinib is administered on 03-Jan-2016, then the date of first administration of study treatment is on 03-Jan-2016). The date of first administration of study treatment will also be referred as ***start of study treatment***.

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of study treatment was administered as per Dose Administration (e)CRF. (Example: if the last PDR001 or placebo dose is administered on 15-Apr-2016, and the last dose of dabrafenib and trametinib is administered on 17-Apr-2016, then the date of last administration of study treatment is on 17-Apr-2016).

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date. The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) – reference start date + 1 if event is on or after the reference date;
- The date of the event (visit date, onset date of an event, assessment date etc.) – reference start date if event precedes the reference date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, PK etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (i.e., tumor assessment, survival time, disease progression, tumor response, ECOG performance status, and patient reported outcomes (PRO)) is the date of randomization.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is defined as "baseline" value or "baseline" assessment. In the context of baseline definition, the efficacy evaluations also include PRO and performance status.

For safety evaluations, the last available assessment on or before the date of start of study treatment is defined as ''baseline" assessment. For cases where time of assessment and time of treatment start is captured (e.g. pre-dose ECG, laboratory assessments), the last available assessment before the treatment start date/time is used for baseline.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or collected for ECGs or vital signs, then the last value should be considered as baseline.

If patients have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of patient's informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date)

3. ***post-treatment period***: starting at day 31 after last administration of study treatment.

For cases where time of assessment and time of treatment start/stop is captured (e.g. ECG's, laboratory assessments), the last available assessment before the treatment period start/stop date/time will be used.

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period. Refer to Section 5.1.2 for imputation rules concerning AE start and stop dates.

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). However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Additional summaries will be displayed to report deaths, all AEs, AEs related to study treatment, all SAEs and SAEs related to study treatment collected up to 150 days after last administration of PDR001/placebo.

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Windows for multiple assessments

In order to summarize PRO measures, performance status (ECOG), physical exam, vital sign, ECG, ECHO, laboratory, and biomarker data collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used. If multiple assessments on the same date then the worst case will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed. Assessments included in the EOT assessment will also be available for inclusion in the other time assessment windows.

Table 2-1 Time windows for ECOG PS assessments for Part 3

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1
Cycle 2 Day 1	29	Day 15 to day 42
Cycle 3 Day 1	57	Day 43 to day 70
Cycle 4 Day 1	85	Day 71 to day 98
Cycle k Day 1 (k≥4)	d=(k-1)*28+1	Day d-14 to day d+13
End of Treatment		Assessment taken at the end of treatment visit

30-day safety follow-up	Post treatment study day 30	Assessment taken at the 30-day safety follow-up visit

Table 2-2 Time windows for Laboratory assessments for Part 3

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1
Cycle 1 Day 15	15	Day 2 to day 21
Cycle 2 Day 1	29	Day 22 to day 35
Cycle 2 Day 15	43	Day 36 to day 49
Cycle 3 Day 1	57	Day 50 to day 70
Cycle 4 Day 1	85	Day 71 to day 98
Cycle k Day 1 (k≥5)	d=(k-1)*28+1	Day d-14 to day d+13
End of Treatment		Assessment taken at the end of treatment visit
30-day safety follow-up	Post treatment study day 30	Assessment taken at the 30-day safety follow-up visit

Time windows will be defined for descriptive summary of PRO data by visit and longitudinal data analysis. If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment obtained prior to visit will be considered. Data obtained at the end of treatment will be classified as other assessment in the corresponding time window. Time to definitive deterioration and longitudinal model analysis (refer to Section 2.11) will be conducted in two ways; once where only data collected under treatment (i.e. while the patient is treated) is included, and once where post-treatment data will also be included. The end of treatment assessment will be included if collected within 14 days of the last dose intake.

Table 2-3 Time windows for PRO for Part 3

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline	On or before Study Day 1*	≤ Study Day 1
Cycle 4 Day 1	Study Day 85	Study Days 2 – 113
Cycle 6 Day 1	Study Day 141	Study Days 114 – 169
…	…	…
Every 2 cycles until Cycle 22 Day 1 Every 3 cycles thereafter	Study Day 589	Study Days 562 - 631
Cycle y=22+3*k (with k = 1, 2, …)	Study Day (22+3*k-1)*28+1	Study Days (22+3*k-1)*28+1-41 to (22+3*k-1)*28+42 Note: data from EOT visit will only be included if obtained within 14 days of last non-zero dose intake.

Post treatment		
30 days post disease progression per RECIST 1.1	Unplanned (post progression day 30)	Post disease progression days 15 – 45
60 days post disease progression per RECIST 1.1	Unplanned (post progression day 60)	Post disease progression days 46 – 75
Study Day 1 = randomization date		
Post disease progression day 1= date of disease progression per RECISIT 1.1 + 1 day		

Last contact date

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:

Table 2-4 Last contact date data sources

Source data	Conditions
Last contact date/last date patient was known to be alive from Survival Follow-up page	Patient status is reported to be alive, lost to follow-up or unknown.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Tumor (RECIST) assessment date	Evaluation is marked as ‘done’.
Verification for treatment beyond RECIST1.1 PD	At least one non-missing parameter value.
Laboratory/PK collection dates	Sample collection marked as ‘done’.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term
Biomarker blood sample date	No condition
PRO patient completed questionnaire	No condition

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date

imputation is allowed for event (death)/censoring is coming from the 'Survival information' eCRF.

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

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure. This population will be the primary population for efficacy analyses.

Per Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the clinical study protocol (CSP).

The PPS will only be used for sensitivity analyses of the primary and key secondary endpoint.

The following list of protocol deviations that could potentially impact the scientific integrity of the primary efficacy endpoint will lead to exclusion of the patient from the Per-Protocol Set:

- type of indication is different from what is required in CSP:
  - disease is different from unresectable or metastatic melanoma (AJCC staging edition 7: stage IIIC and IV) (INCL08)
  - not BRAF V600 mutation positive (local assessment or central if local not available) (INCL09)
  - ECOG performance status is > 2 (INCL04)
  - no measurable lesions at baseline according to RECIST 1.1 (INCL10)
  - clinically active cerebral melanoma metastasis at baseline (EXCL02)
  - uveal or mucosal melanoma (EXCL03)
  - malignant disease, other than that being treated in this study (not including curatively treated and not recurred within 2 years prior to study treatment start) (EXCL16)
- not able to swallow or retain oral medication or has clinically significant gastrointestinal abnormalities (INCL23)
- prior therapy does not match in terms of time, duration, treatment modality, and/or washout period :
  - received prior systemic anti-cancer treatment for unresectable or metastatic melanoma (EXCL04)
  - received prior loco-regional with inralesional therapy for unresectable or metastatic melanoma in last 6 months (EXCL05)

- received prior neoadjuvant or adjuvant therapy for melanoma less than 6 months prior to study treatment (EXCL06)
- received radiation therapy ≤ 4 weeks before study treatment (EXCL07)
- had major surgery, open biopsy or traumatic injury ≤ 2 weeks before study treatment (EXCL08)
- received systemic chronic steroid therapy (≥ 10mg/day prednisone or equivalent) ≤ 7 days prior to study treatment (EXCL10)
- history of organ transplant requiring use of immunosuppressive medication (EXCL12)
- received prohibited medication prior to the start of study treatment (EXCL15)

- study treatment received different from treatment assigned by randomization (TRT12)
- written informed consent not obtained (INCL07)

Full specifications of deviations leading to exclusion will be described in the Study Specific Document (SSD).

Safety set

The Safety Set includes all patients who received any study treatment (i.e. at least one dose of any component of PDR001 or placebo (including incomplete infusion), dabrafenib, or trametinib). Subjects will be analyzed according to the study treatment they actually received.

The actual treatment received corresponds to:

- the randomized treatment if patients took at least one dose of that treatment
- the first treatment received if the randomized treatment was never received

Pharmacokinetic analysis set

The **PDR001 pharmacokinetic analysis set** (**PAS-PDR001**) includes all patients who provide at least one evaluable PDR001 PK concentration. For a concentration to be evaluable, patients are required to:

- Receive one of the planned treatments of PDR001 prior to sampling
- For pre-dose samples, prior to dosing on the assessment day and/or collect at approximately 672 hr ± 24 hours after the last dose.
- For end-of-infusion samples, have the samples collected within 2 hours post end of infusion

The **dabrafenib and trametinib pharmacokinetic analysis set** (**PAS-D+T**) includes all patients who provide at least one evaluable dabrafenib or trametinib PK concentration. For a concentration to be evaluable, patients are required to:

- Receive a dose of dabrafenib or trametinib prior to sampling
- For pre-dose samples, have the samples collected before the next dose administration
- For post-dose samples,
  - do not vomit within 4 hours after the dosing of dabrafenib and trametinib

  - within window Cycle 2 Day 1: Between 1 and 3 hours post dose
  - within window Cycle 3 Day 1 and Cycle 4 Day 1: Between 2 and 12 hr post-dose
- For dabrafenib and its metabolites, assessments with at least 6 consecutive doses at the protocol planned dose of the respective drug immediately prior to the PK collection are required

  for trametinib, assessments with at least 14 consecutive doses at the protocol planned dose of the respective drug immediately prior to the PK collection are required

Immunogenicity (IG) analysis sets

The *Immunogenicity prevalence set* includes all subjects in the Full analysis set with a determinant baseline IG sample **or** at least one determinant post-baseline IG sample.

The *Immunogenicity incidence set* includes all subjects in the Immunogenicity prevalence set with a determinant baseline IG sample **and** at least one determinant post-baseline IG sample.

See Section 2.10.1 for the definition of *determinant*.

Patient Classification

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific patient classification rules defined in Table 2-5.

Table 2-5 Patient classification based on protocol deviations and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written informed consent	Not applicable
Per-Protocol Set	See definition of PP set	Not applicable
Safety Set	No written informed consent	No dose of any component of study treatment
PDR001 PK Analysis Set (PAS-PDR001)	No written informed consent	Not meeting the definition for inclusion in the PAS-PDR001 analysis set
Dabrafenib and Trametinib PK Analysis Set (PAS-D+T)	No written informed consent	Not meeting the definition for inclusion in the PAS-D+T analysis set
Immunogenicity Prevalence Set	No written informed consent	Not meeting the definition for inclusion in the Immunogenicity Prevalance Set

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
Immunogenicity Incidence Set	No written informed consent	Not meeting the definition for inclusion in the Immunogenicity Incidence Set

Withdrawal of Informed Consent

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

Death events may be used in the analysis if captured from public records (registers), local law and subject informed consent permitting.

Additional data for which there is a separate informed consent (optional biomarker, pharmacogenomix, etc) collected in the clinical database without having obtained the consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.2.1 Subgroup of interest

Efficacy

The primary efficacy and key secondary endpoint (PFS and OS) will be summarized by the following subgroups ***to examine the homogeneity of treatment effect*** provided that the primary efficacy analysis based on the FAS is statistically significant:

- Stratification factors of LDH group (< 1 x ULN, ≥ 1 to < 2 x ULN, ≥2 x ULN) and ECOG PS (0, 1, 2) (based on randomization data from IRT)
- Sex
- Race
- Ethnicity
- Age category (< 65 years, ≥ 65 years)
- Number of metastatic organs at baseline (< 3, ≥ 3)
- Stage at study entry ([IIIC], [IVM1a, IVM1b or IVM1c]) – AJCC 7
- Central BRAF mutation (V600E, V600K)
- BRAF mutation (V600E, V600K, Other) (Note: If local BRAF mutation data is missing for a subject the central BRAF mutation result will be used here for completeness of the analysis set)
- Prior adjuvant checkpoint inhibitor therapy (yes, no)

- PD-L1 status (positive, negative), where a positive status is defined as having ≥ 1% tumor cell staining and negative is defined as having <1% tumor cell staining
- Geographic region (Europe, North America, Latin America, Asia Pacific)
- Sum of diameters at baseline (<66mm , > =66 mm : as per a previous pooled analysis of dabrafenib plus trametinib)
- Cold tumors with lack of immunogenicity as defined by low TMB (tumor mutation burden; < 10 Mut/MB) and low PD-L1 (<1% tumor cell staining) vs. all others
- Cold tumors with lack of immunogenicity as defined by low TMB (tumor mutation burden; < 10 Mut/MB) and low T-cell inflamed signature levels (< 6.29) vs. all others
- Elevated LDH (<ULN, >=ULN)

Additionally, PFS and OS will be summarized by the following PD-L1 subgroups to support secondary efficacy objective (refer to Table 1-1 and Section 2.7.1).

- PD-L1 status (positive, negative), where a positive status is defined as having ≥ 5% tumor cell staining and negative is defined as having <5% tumor cell staining
- PD-L1 status (positive, negative), where a positive status is defined as having ≥ 10% tumor cell staining and negative is defined as having <10% tumor cell staining

No formal statistical test of hypotheses will be performed for the subgroups, only point estimates of the treatment effect and 95% confidence intervals will be provided (see Section 2.5.4 and Section 2.6.2 for further analysis details). The objective of the efficacy subgroup analysis is to demonstrate homogeneity of treatment effect in the above subgroups.

Safety

Safety subgroup analyses will use the same method as for the analysis in the overall analysis set. Key safety analyses *(*AEs, related AEs, SAEs, related SAEs, AESIs, AEs leading to treatment discontinuation, and deaths*)* will be repeated on safety set in the following subgroups:

- Sex
- Race

- Ethnicity
- Age category (< 65 years, ≥ 65 years)
- Geographic region (Europe, North America, Latin America, Asia Pacific)

The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of patients, or safety issues that are more commonly observed in a subgroup of patients.

2.3 Patient disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment group and for all patients, and listings will be reported by treatment group to assess baseline comparability. No inferential statistics will be provided.

Baseline demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment group. Categorical data (e.g. gender, age groups: <65 and ≥ 65 years, race, ethnicity, ECOG performance status groups: 0, 1, and 2, LDH group: < 1 x ULN, ≥ 1 to < 2 x ULN, and ≥ 2 x ULN, PD-L1 status groups: positive and negative based on 1%, 5%, and 10% tumor cell staining cut-off (refer to Section 2.7.1), T-cell inflamed signature subgroups, TMB, BRAF V600 mutation groups (V600 status conferring eligibility): V600E, V600K, others; and central BRAF V600 mutation groups: V600E, V600K, V600E and K negative, missing will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum). BMI (kg/m2) will be calculated as weight[kg] / (height[m]2) using weight at Baseline.

Baseline stratification factors

The number (%) of patients in each stratum (LDH group: < 1 x ULN, ≥ 1 to < 2 x ULN, ≥ 2 x ULN and ECOG PS: 0, 1, 2) based on data obtained from the IRT system will be summarized overall and by treatment group for the FAS. Discordances between the stratum recorded in IRT at the time of randomization and the actual stratum recorded in the clinical database through the data collected on eCRF will be cross-tabulated and listed.

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary site of cancer at intitial diagnosis (melanoma), predominant histology/cytology, stage group at initial diagnosis (using AJCC edition 7), time since initial diagnosis of melanoma (in months), time from initial diagnosis to first recurrence/progression (in months), time since most recent relapse/progression to study entry (in months), stage group at time of study entry (AJCC edition 7 and edition 8), presence/absence of target and non-target

lesions, sum of diameters (SOD) (in mm), location of metastatic sites involved, number of organs of disease. Note: presence/absence of target and non-target lesions and SOD will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Metastatic sites will be based on diagnosis page.

Sum of diameters will be derived by summing all target lesions diameters reported on target lesion RECIST page at baseline.

Number of organs of disease at baseline (< 3 vs ≥ 3) will be derived by summing the total number of "unique organs records reported per patient on the diagnosis and extent of cancer page.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on (e)CRF will be summarized and listed by treatment group. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Other

All data collected at baseline, including history of smoking and alcohol use, [redacted] informed consent, and treatment beyond progression informed consent will be listed.

2.3.1 Patient disposition

Enrollment by country and center will be summarized for all screened patients and also by treatment group using the FAS. The number (%) of randomized patients included in the FAS will be presented overall and by treatment group. The number (%) of screened and not-randomized patients and the reasons for not completing will also be displayed. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

The following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients who were randomized (based on data from IRT system);
- Number (%) of patients who were randomized but not treated (based on 'DAR' eCRF page not completed for any study treatment component);
- Primary reason for not being treated (based on 'End of Treatment Disposition' eCRF page);
- Number (%) of patients who were treated (based on 'DAR' eCRF pages of each study treatment component completed with non-zero dose administered);
- Number (%) of patients who are still on-treatment (based on the 'End of Treatment Disposition' page not completed);

- Number (%) of patients who discontinued the study treatment phase (based on the 'End of Treatment Disposition' page);
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Disposition' page);
- Number (%) of patients who have entered the post-treatment follow-up (based on the 'End of Treatment Disposition' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the 'End of Post Treatment Follow-up Disposition' page);
- Reasons for discontinuation from the post-treatment follow-up (based on 'End of Post Treatment Follow-up Disposition' page);
- Number (%) of patients who have entered the survival follow-up (based on the 'End of Treatment Disposition' or 'End of Post Treatment Follow-up Disposition' page).

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan) overall and by treatment group. Major protocol deviations leading to exclusion from analysis sets will be tabulated separately overall and by treatment group. All protocol deviations will be listed.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized by treatment group and stratum (LDH group and ECOG PS).

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

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment group, separately for each component of study treatment (PDR001, placebo, dabrafenib, and trametinib). The duration of treatment will also be presented for the study treatment. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of patients in each interval. The number (%) of patients who have dose reductions or interruptions, and the reasons, will be summarized by treatment group.

Patient 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.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to PDR001 or placebo, dabrafenib, and trametinib:

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 PDR001 or placebo, dabrafenib, and trametinib (see Table 2-6).

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.

Duration of exposure to PDR001 or placebo, dabrafenib, and trametinib

Duration of exposure to PDR001 or placebo (days) = (last date of exposure to PDR001 or placebo) – (date of first administration of PDR001 or placebo) + 1.

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

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

Refer to Table 2-6 for definitions of the last date of exposure to PDR001 or placebo, dabrafenib, and trametinib.

Table 2-6 Definition of last date of exposure of study drug

Scenario	Definition of last date of exposure of study drug	Example
PDR001 or placebo	The planned end date of the last cycle in which the last non-zero dose of the investigational drug was last administered (i.e. last date of administration + (planned interval duration-1 day)) Note: If the patient died or was lost to follow-up before the derived last date, the last date of exposure to investigational drug is the date of death or the date of last contact, respectively. If the derived last date of exposure goes beyond the data cut-off date, it should be truncated to the date of data cut-off.	Example 1: If PDR001 or placebo is administered every four weeks, the last date of exposure is the date of administration in the last cycle + 27 days. Example 2: If PDR001 or placebo is administered every eight weeks, the last date of exposure is the date of administration in the last cycle + 55 days.
Dabrafenib, Trametinib	Date of last administration of a non-zero dose of the study drug.	Example 3: A patient had a permanent discontinuation of the study drug on 06Jan2016 after being put on a temporary interruption since 01Jan2016. In this case the last date of exposure is 31Dec2015.

Summary of duration of exposure of PDR001 or placebo, dabrafenib and trametinib will include categorical summaries based on 28 day intervals and using descriptive statistics (mean, standard deviation, etc).

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment and will be summarized for each of the study treatment components (PDR001 or placebo, dabrafenib, trametinib).

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 planned cumulative dose will not be summarized/listed. It will be used for relative dose intensity calculations.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the patient 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 patient is assumed to have taken a non-zero dose 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 (mg */ unit of time*) = Actual Cumulative dose (mg) / 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 (mg */ unit of time)* = Planned Cumulative dose (mg) / Duration of exposure (*unit of time*).

Relative dose intensity (RDI) is defined as follows:

RDI (%) = [DI (mg */ unit of time*) / PDI (mg */ unit of time*)] x 100.

For PDR001 or placebo, the unit of time will be 1 cycle (28 days).

For dabrafenib and trametinib, the unit of time will be 1 day.

DI and RDI will be summarized for combination studies separately for each of the study treatment components, but using the duration of exposure of each of the components.

Note that for the purposes of DI and RDI derivation only for PDR001/Placebo, the last date of exposure for the duration of exposure component of this calculation will simply be the last date of administration in the last cycle + 27 days. i.e. deaths and data cutoff will not be taken into account.

Table 2-7 Examples of PDR001 or placebo dose administration and exposure

DAR record number	Start/End Date	Regimen	Dose Administered (mg)	Dose Stopped or Paused, Dose Interrupted?	Dose Permanently Discontinued	Reason
1	01Jan2016	Q4W	400	No	No	
2	29Jan2016	Q4W	200	Yes	No	AE (infusion reaction)

Duration of exposure (days) = (31Jan2016 + 27 days (Q4W)) – (01Jan2016) + 1 = 58 days

Duration of exposure (cycle of 28 days) = 58/28 = 2.07 cycles

Actual cumulative dose (for 58 days, 2.07 cycles) = 600 mg

Dose intensity = 600 mg / 2.07 cycles = 289.95 mg / cycle

Planned dose intensity = 400 mg / cycle

Relative dose intensity = DI / PDI = (289.95 mg/cycle) / (400 mg/cycle) = 72.5%

Table 2-8 Examples of dabrafenib dose administration and exposure

DAR record number	Start/End Date	Dose Prescribed (mg), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption ?	Dose Permanently Discontinued	Reason
1	01Jan2016 / 05Jan2016	150 mg BID	300	No	No	
2	06Jan2016 / 03Feb2016	150 mg BID	200	Yes	No	AE
3	04Feb2016 / 25Feb2016	150 mg BID	300	No	No	

Duration of exposure (days) = 25Feb2016 – 01Jan2016 + 1 = 56 days

Planned cumulative dose (for 56 days) = 300*56 days = 16800 mg

Actual cumulative dose = 300*5 + 200*29 + 300*22 = 13900 mg

Dose intensity = 13900 mg / 56 days = 248.21 mg/day

Planned dose intensity = 16800 mg / 56 days = 300 mg/day

Relative dose intensity = DI / PDI = (248.21 mg/day) / (300 mg/day) = 83%

Table 2-9 Examples of trametinib dose administration and exposure

DAR record number	Start/End Date	Dose Prescribed (mg), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption?	Dose Permanently Discontinued	Reason
1	01Jan2016 / 10Jan2016	2 QD	2	No	No	
2	11Jan2016 / 15Jan2016	2 QD	0	Yes	No	AE
3	16Jan2016 / 25Feb2016	1 QD	1	No	No	AE

Duration of exposure = 25Feb2016 – 01Jan2016 + 1 = 56 days

Planned cumulative dose (for 56 days) = 2*56 days = 112 mg

Actual cumulative dose = 2*10 + 0*5 + 1*41 = 61 mg

Dose intensity = 61 mg / 56 days = 1.09 mg/day

Planned dose intensity = 112 mg / 56 days = 2 mg/day

Relative dose intensity = DI / PDI = (1.09 mg/day) / (2 mg/day) = 54%

Dose reductions, re-escalations, interruptions or permanent discontinuations

The number of patients who have dose reductions, dose re-escalations, permanent discontinuations, administration stopped/paused during infusion or interruptions, and the reasons, will be summarized separately for each of the study treatment components.

'Dose interrupted', "Was drug administration stopped or paused" and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose reductions, dose interruptions, administration stopped/paused and permanent discontinuations, respectively.

The corresponding fields 'Reason for dose change/dose interrupted', 'Reason for administration stopped or paused' 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/dose administrations with different reasons, separate interruptions will be counted. However, if the reason is the same for multiple entries on consecutive days/dose administrations, then it will be counted as one interruption.

Reduction

No dose reductions are permitted for PDR001 or placebo for this study. Therefore, a reduction refers to a dose change where the prescribed dose level of dabrafenib and/or trametinib 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.

Treatment beyond RECIST1.1 progression

The number of patients who continue treatment beyond RECIST 1.1 progression according to local investigators assessment based on protocol specified criteria will be summarized. It includes all patients who received any study treatment (i.e. at least one dose of PDR001 or placebo (including incomplete infusion), dabrafenib, or trametinib) after RECIST 1.1 progression as assessed by local investigators. Those patients will be identified using the field "Will the patient continue treatment beyond disease progression as per RECIST 1.1?" on the 'Verification for Treatment Beyond RECIST1.1 PD' CRF pages.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic medications, prior adjuvant checkpoint inhibitor therapy, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized by treatment group. Note that biopsies will not be regarded as an anti-neoplastic surgery for the purposes of this analysis. Prior anti-neoplastic medications will be summarized by therapy type (e.g. chemotherapy, immunotherapy, targeted therapy etc.), setting (e.g. adjuvant neoadjuvant, etc.) and also by lowest anatomical therapeutic classification (ATC) class, preferred term and treatment. Summaries will include total number of regimens and time from last treatment to progression for the last therapy. The medication

therapy type of any combination therapy will be classified based on the following order: immunotherapy, chemotherapy, biologic therapy (other than immunotherapy), targeted therapy, hormonal therapy. For example, a combination therapy of chemotherapy and immunotherapy will be classified as 'immunotherapy'. For radiotherapy, time since last radiotherapy, locations and setting of last therapy will be summarized. For prior surgery, time since last surgery and procedure will be summarized.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery. Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class, preferred term, overall and by treatment group by means of frequency counts and percentages using FAS. Note that biopsies will not be regarded as an anti-neoplastic surgery for the purposes of this analysis.

The number and percentage of patients who reported taking at least one anti-neoplastic therapy since discontinuation of study treatment by category (see Table 2-10) will be summarized by treatment group. The analysis will also be repeated for patients who discontinued therapy following progression.

Table 2-10 Categories of anti-neoplastic therapies since discontinuation

Category	Sub-category
Chemotherapy	
Immunotherapy	IL2 and similar cytokines, TVEC and other intratumoral immune stimulants
Biologic therapy	Antibodies targeting EGFR etc (excluding checkpoints inhibitors)
Small molecule targeted therapy	MEK, BRAF etc
Checkpoint inhibitors	PD-1, PD-L1, CTLA4, LAG3 etc
Surgery	Excluding biopsies
Radiotherapy	
Other or investigational	

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. Concomitant medications with immunosuppressive intent will be summarized by lowest ATC class and preferred term using frequency counts and percentages.

All reported systemic steroids will be summarized by lowest ATC class and preferred term using frequency counts and percentages. Reported cumulative dose and maximum cumulative dose, adjusted for relative anti-inflammatory potency [Schimmer and Parker 2007], will also be summarized along with route of administration.

Table 2-11 Systemic steroid anti-inflammatory potency relative to Hydrocortisone

Steroid Name	Anti-inflammatory potency, relative to Hydrocortisone
Hydrocortisone	1
Cortisone acetate	0.8
Prednisone	4
Prednisolone	4
Methylprednisolone	5
Dexamethasone	30

All summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

Additional summaries will be provided to report medications starting between 31 days after last dose of study treatment and 150 days after last dose of PDR001/placebo.

All reported concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 150 days after the last dose of PDR001/placebo or 30 days after last dose of study treatment whichever comes last, will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

2.5 Analysis of the primary objective

The primary objective of part 3 is to determine whether treatment with PDR001 in combination with dabrafenib and trametinib prolongs progression-free survival (PFS) compared to treatment with placebo in combination with dabrafenib and trametinib in unresectable or metastatic BRAF V600 mutant melanoma patients.

2.5.1 Primary endpoint

The primary endpoint for part 3 is PFS, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. For the primary efficacy analysis, PFS will be based on local investigator review of tumor assessments and using RECIST 1.1 criteria (see Appendix 1 of the study protocol). The primary analysis will be based on FAS and will include all data observed up to the cut-off date.

If a patient has not progressed or died at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date. PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1. documented disease progression or death) will be counted as events for the primary analysis provided tumor assessments continue after initiation of new cancer therapy. See Section 2.5.3 for additional details regarding censoring rules and determination of date of last adequate tumor assessment.

Discontinuation due to disease progression (collected on the 'End of Treatment' and 'End of Post Treatment Follow-up' disposition pages) without supporting objective evidence satisfying progression criteria per RECIST 1.1 will not be considered disease progression for PFS derivation. Clinical deterioration will not be considered as a qualifying event for progression for the primary analysis.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be the comparison of the distribution of PFS (based on investigator assessment of RECIST 1.1 criteria) between the two treatment groups. The following statistical hypothesis will be tested to address the primary efficacy objective:

$$H_{01}: \theta_1 \geq 1 \quad \text{vs.} \quad H_{A1}: \theta_1 < 1$$

where θ_1 is the PFS hazard ratio (PDR001 in combination with dabrafenib and trametinib vs placebo in combination with dabrafenib and trametinib). The analysis to test this hypothesis will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance. Stratification will be based on the randomization stratification factors: LDH level (< 1 x ULN vs ≥ 1 to < 2 x ULN vs ≥ 2 x ULN) and ECOG PS (0 vs 1 vs 2).
The primary efficacy variable PFS will be analyzed based on the data observed in the FAS up to the cut-off date, according to the treatment group and strata assigned at randomization. The distribution of PFS will be estimated using the Kaplan-Meier method. The results will be plotted graphically by treatment group. The median and 25th and 75th percentiles of PFS along with 95% confidence intervals will be presented by treatment group. A stratified Cox regression will be used to estimate the hazard ratio (HR) of PFS, along with 95% confidence interval using the same strata information as the primary efficacy comparison.

2.5.3 Handling of missing values/censoring/discontinuations

This is an event-driven trial and the final analysis for PFS will be performed after approximately 352 PFS events have been documented (or at approximately 24 months after last patient randomized whichever occurs first) based on local investigator review of tumor assessments (TAs).

In the primary analysis (based on investigator assessment of RECIST 1.1 criteria), PFS will be censored at the date of the last adequate TA if no PFS event is observed prior to the analysis cut-off date.

Disease progressions documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1. documented disease progression) will be counted as PFS events for the primary analysis provided an adequate TA is available after initiation of new cancer therapy. Deaths documented after the initiation of new anti-neoplastic therapy will also be counted as PFS events for the primary analysis.

The date of last adequate TA is the date of the last TA with overall lesion response of CR, PR or SD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment will be used. If no post-baseline assessments are available (before an event or a censoring reason occurred) then the date of randomization/start date of treatment will be used.

In particular, PFS will be censored at the last adequate TA if one of the following occurs: absence of event; the event occurred after two or more missing TAs. The term "missing adequate tumor assessment" is defined as a TA not performed or TA with overall lesion response of "UNK". The rule to determine number of missing TAs is based on the time interval between the date of last adequate TA and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more.

Note that according to the protocol the first TA should occur at 12 weeks and then the frequency should be 8-weekly up to 18 months following first dose before moving to a 12-weekly schedule. For patients who discontinue from treatment without PD TAs should be taken Every 12 weeks starting from the last TA until documented disease progression per RECIST 1.1.

In order to account for the change in TA scheduling in the Efficacy follow-up period following treatment discontinuation the standard Novartis RECIST macro will have to be adapted. Full details on the algorithm for determining censoring due to ">=2 missing assessments prior to event" will be provided in the PDS document.

Refer to Table 2-12 for censoring and event date options and outcomes for PFS.

Table 2-12 Outcome and event/censor dates for PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of randomization	Censored
Progression or death at or before next scheduled Assessment	Date of progression (or death)	Event
Progression or death after exactly one missing assessment	Date of progression (or death)	Event
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored

Situation	Date	Outcome
Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	Ignore clinical progression and follow situations above	As per above situations
New anticancer therapy given prior to protocol defined progression (including patients who crossover from the control to the treatment arm)	Ignore the new anticancer therapy and follow situations above	As per above situations
Death before first PD assessment	Date of death	Event

2.5.4 Supportive analyses

Check of proportional hazard assumption (based on investigator assessment of RECIST 1.1 criteria) will be performed as described in Section 5.4.1. If proportional hazard assumption is violated as a result of a delayed treatment effect, additional statistical methods described below will be employed to examine the PFS endpoint.

Restricted mean survival time (RMST) for PFS at a prespecified time t* is defined as the interval from randomization until first documented progression or death due to any cause or t* whichever comes first. For determination of t* we will use the minimum of the time of last event time between two arms rounded downwards to the previous quarterly (i.e. 3-monthly) value. For example if the maximum event time in treatment arm is at 16.5 months and in placebo arm is at 17 months then the truncation time t* will be 15 months.

In the presence of non-proportional hazards due to a delayed treatment effect RMST can be considered a preferable alternative to HR for the estimation of treatment effect since . No proportional hazards assumption is assumed for this method. The RMST and 95%CIs also be computed for each treatment arm separately. Difference in RMST for PFS between the experimental and the control arms (and 95% CI) will be estimated using Kaplan Meier approach.

Kaplan Meier plots showing the area under the curve for each treatment group will also be displayed.

Milestone overall progression-free survival rates (and 95% CIs) at 12 and (if available) 24 months will presented by treatment group based on the Kaplan Meier analysis. The comparison of PFS rates at each timepoint between two treatment arms will be based on the difference of complementary-log-log (cloglog) transformed survival functions at the timepoint. The hazard ratios and 95% CI at month 12 and month 24 will be based on the same cloglog transformation.

The null hypothesis of equal probabilities at month 12 and 24 will be tested at one-sided α=0.025 to produce descriptive p values using the cloglog test statistic [Klein et al, 2007].

$$\chi^2(1) = \frac{(\log(-\log(\hat{S}_1)) - \log(-\log(\hat{S}_2)))^2}{\frac{\hat{\sigma}_1^2}{(\log(\hat{S}_1))^2 \hat{S}_1^2} + \frac{\hat{\sigma}_1^2}{(\log(\hat{S}_2))^2 \hat{S}_2^2}},$$

Under H0, this statistic follows a chi-square distribution with one degree of freedom.

The following summaries will be produced: the estimated PFS rate at 12 and 24 months for each study arm together with 95% CI, the absolute difference of progression-free survival probabilities at each of the timepoints together with the estimated hazard ratio, 95% CI and the p-value.

A stratified piecewise Cox regression analysis will be performed based on PFS to estimate a hazard ratio within pre-specified time periods (0-5 months and >5 months, based on assumed 5 month delayed effect for PFS. A similar analysis will also be performed with periods based on the assumption of a 3 month delayed effect. Other analyses may be performed with periods based on alternative delayed effect durations indicated by the data). The estimated hazard ratio in the time period after delayed effect period (i.e. > 5months or after 3months depending on actual data) will be used as a complementary measure of PFS treatment effect estimate. The analysis will be performed by incorporating a time-dependent covariate into the model and estimating the treatment effect for each of the two time periods. The hazard ratio, 95% CIs and Wald based p-value will be provided for each time period.

If proportional hazard assumption is violated as a result of a delayed treatment effect, a weighted log-rank test with $G^{\rho,\gamma}$ Fleming-Harrington (FH) class of weights will be performed as a sensitivity analysis in order to assess the robustness of the primary analysis for PFS. Parameters ρ and γ define the weight function with values (0, 0) corresponding to unweighted log-rank test. The values (0, 1) will be used which corresponds to a greater weighting for later events. The weights are specified and justified based on clinical (e.g. expected time when treatment effect starts) and statistical (i.e. power) arguments. Moreover, sensitivity analyses with different selection of weights (e.g. equal weights) to assess the robustness of conclusions may be needed.

Impact of delayed treatment effect on PFS (based on investigator assessment of RECIST 1.1 criteria) will be evaluated using landmark analysis [Anderson et al 1983, 2008]. To do that, all randomized patients who are alive, still being followed for progression and who have not had a disease progression at the landmark times of 3 and 5 months will be included. Analyses may also be performed based on other clinically relevant landmark times as indicated by the data.No formal statistical comparison will be performed. Hazard ratio with 95% CI along with Kaplan-Meier estimate of survival at pre-specified time points of 6, 12, 24, 36, 48, and 60 months (if the timepoint estimate can be obtained at time of analysis data cut) will be displayed. To evaluate a potential selection bias, the baseline characteristics and the patients' disposition will be tabulated for patients included in the landmark analysis for the landmark time thought to be of most interest. As a sensitivity analysis to assess the impact of stratification, the two treatment groups will be compared using the unstratified log-rank test (based on investigator assessment of RECIST 1.1 criteria). The HR together with the associated 95% confidence interval obtained using the unstratified Cox regression model will also be presented.

The primary analysis will be repeated using the PPS if the number of patients in the FAS and PPS differ by more than 5 percent.

A multivariate, covariate adjusted Cox regression model stratified by randomization stratification factors will be fitted to evaluate the effect of other baseline demographic and disease characteristics on the estimated hazard ratio (based on investigator assessment of RECIST 1.1 criteria). The fitted model adjusting the treatment difference for key baseline and prognostic factors will include as covariates the following:

- gender,
- age group (<65, ≥ 65 years),
- Number of metastatic organs at baseline (< 3, ≥ 3)
- stage at study entry ([IIIC], [IVM1a, IVM1b or IVM1c]),
- central BRAF mutation (V600E, V600K),
- prior adjuvant checkpoint inhibitor therapy (yes, no),
- PD-L1 status (positive, negative) where a positive status is defined as having ≥ 1% tumor cell staining
- Sum of diameters at baseline (<66 mm, >= 66 mm)

The following sensitivity analyses will be performed for the primary efficacy endpoint of PFS The following will be provided: Kaplan-Meier estimates, estimate of the median PFS along with 95% confidence interval, and hazard ratio obtained using stratified Cox proportional hazards model.

- using the primary analysis source (i.e. investigator of RECIST 1.1 criteria) on the FAS and including events whenever they occur, even after two or more missing tumor assessments. In the summary tables, this approach is referred to as ‘actual event PFS sensitivity analysis’.
- using the primary analysis source (i.e. investigator of RECIST 1.1 criteria) on the FAS and backdating events that occurred after missing one or more tumor assessments i.e. if progression/death is observed after one or more missing tumor assessments, it is considered as an event at the date of the next scheduled assessment following the last adequate tumor assessment.. In the summary tables, this approach is referred to as ‘backdating PFS sensitivity analysis’.

- using the primary analysis source (i.e. investigator of RECIST 1.1 criteria) on the FAS and censoring PFS at the date of the last adequate tumor assessment before the start of new anticancer therapy if no PFS event is observed prior to the start of new antineoplastic therapy (not counting biopsies as a new antineoplastic surgery). In the summary tables, this approach is referred to as 'new anticancer therapy PFS sensitivity analysis'.
- using the primary analysis source (i.e. investigator of RECIST 1.1 criteria) on the FAS and considering treatment discontinuation due to 'disease progression' without documented progression as an event. In the summary tables, this approach is referred to as 'clinical PD sensitivity analysis'.
- using the primary analysis source (i.e. investigator of RECIST 1.1 criteria) on the FAS and backdating events that occurred after withdrawal of treatment for reasons other than progressive disease. These events would be reassigned according to a fixed protocol scheduled assessment schedule which ignores any change in schedule following treatment withdrawal.

According to the protocol the first assessment should occur at 12 weeks and then the frequency should be 8-weekly up to 18 months following first dose before moving to a 12-weekly schedule. Patients who withdraw from therapy without progression will have their next assessment scheduled 12 weeks after the last assessment and this could introduce possible bias into the analysis. e.g. if there are a greater percentage of withdrawals due to AE in one of the treatment groups.

To assess the impact of such possible bias a sensitivity analysis will backdate events observed off-treatment in patients who withdraw without progression. i.e. if a progression or death occurs after the date at which the assessment would have been taken had the patient not withdrawn from therapy then the event will be backdated to this date. If the progression or death occurred before this date then no action will be taken.

Examples

Patient X has a SD assessment on Day 84, but withdraws from therapy due to AE on Day 102. The next assessment occurs (as per protocol) on Day 168 and response is PD. For the sensitivity analysis the event will be backdated to Day 140 (i.e. according to schedule had the patient continued treatment).

Patient Y has a SD assessment at Day 84, but withdraws from therapy due to AE on Day 102. The patient then dies on Day 115. Since this occurred prior to Day 140 no action needs to be taken and the PFS event time is Day 115.

Patient Z has a SD assessment at Day 84, but withdraws from therapy due to AE on Day 102. The patient then has a SD assessment on Day 168 (as per protocol) and then dies on Day 204. For the sensitivity analysis the event will be backdated to Day 196 (i.e. according to schedule had the patient continued treatment).

Note that censoring due to >=2 missing assessments will still be implemented prior to any re-assignment of event time for this sensitivity analysis.

Further sensitivity analyses will include:

- Repeating the primary efficacy analysis using derived BIRC assessment using RECIST 1.1 criteria. No p-value will be presented.

- Repeating the primary efficacy analysis using combined local radiology/BIRC assessments using RECIST 1.1, i.e. taking earlier of events from the two sources. No p-value will be presented.
- Analysis of iPFS using BIRC assessment using tumor response criteria based on guidelines for immunotherapy (see Section 2.13 for further details). No p-value will be presented.

Further supportive analyses will include:

- If there is a high rate of discrepancy (> 20%) between the strata classifications constructed using the eCRF data and those obtained from the IRT, a sensitivity analysis will be performed in which a stratified Cox regression model will be used to estimate the treatment hazard ratio and the associated 95% confidence intervals based on the eCRF-derived strata. No other inferential statistics will be provided.
- Timing of all tumor assessments according to RECIST 1.1 will be depicted graphically, separately for central radiology and investigator/local radiology and displayed by treatment group.
- Although investigator reported radiology assessments are used for primary analysis, there is a potential for informative censoring, leading to these events being censored by the central radiology review. If there is a high rate of discordance between central and local assessments (>40%), some exploratory analyses such as the Marginal Structural Cox Proportional Hazards Model [Robins and Tsiatis 1991] using the Inverse Probability of Censoring Weighted (ICPW) method [Robins and Finkelstein 2000] may be considered to explore the effect of informative censoring on the treatment effect.
- A sensitivity analysis will be performed in which a stratified Cox regression model will be used to estimate the treatment hazard ratio and the associated 95% confidence intervals based on the central BRAF test results (i.e. mutation positive (yes/no). No other inferential statistics will be provided.

Subgroup analyses for the primary endpoint

If the primary efficacy analysis is statistically significant, the primary endpoint of PFS will be summarized for the subgroups specified in Section 2.2.1 and using the same conventions as for the primary analysis.

For each of the subgroups, the following analyses will be performed:

- Kaplan-Meier estimates of median PFS time with 95% CI
- Hazard ratio with 95% CI using stratified Cox proportional hazards model

Efficacy analyses in subgroups are intended to explore the consistency (homogeneity) of treatment effect. A forest plot (including sample size/number of events and HR with 95% CI) will be produced to graphically depict the treatment effect estimates in key subgroups of interest. Separate forest plots will be produced to depict estimates for biomarker subgroups (including key exploratory subgroups of cold tumors with lack of immunogenicity as defined by either low TMB /low PD-L1 or low TMB / low T-cell inflamed signature), [redacted]

[redacted] (see Section 2.2.1). No inferential statistics (p-values) will be produced for the subgroups. Estimates will be obtained by fitting models using data for each subgroup separately. Randomization stratification factors (LDH group, ECOG PS) will be included in all subgroup analysis models, except for models assessing LDH or ECOG subgroups, respectively.

Kaplan-Meier curves will be produced for the following subroups:

- Stratification factors of LDH group (< 1 x ULN, ≥ 1 to < 2 x ULN, ≥2 x ULN) and ECOG PS (0, 1, 2) (based on randomization data from IRT)
- PD-L1 status (positive, negative), where a positive status is defined as having ≥ 1% tumor cell staining and negative is defined as having <1% tumor cell staining
- PD-L1 status (positive, negative), where a positive status is defined as having ≥ 5% tumor cell staining and negative is defined as having <5% tumor cell staining
- PD-L1 status (positive, negative), where a positive status is defined as having ≥ 10% tumor cell staining and negative is defined as having <10% tumor cell staining
- Cold tumors with lack of immunogenicity as defined by low TMB (< 10 Mut/MB) and low PD-L1 (<1% tumor cell staining) vs. all others
- Cold tumors with lack of immunogenicity as defined by low TMB (< 10 Mut/MB) and low T-cell inflamed signature levels (<6.29) vs. all others
- High vs. low TMB (tumor mutation burden) (< 10 Mut/MB, ≥ 10 Mut/MB)
- T-cell inflamed signature subgroups (low, high; <6.29, ≥ 6.29)
- Sum of diameters at baseline (<66 mm, >= 66 mm)
- Brain metastates at baseline (yes/no)
- Elevated LDH at baseline (<ULN , ≥1 x ULN)
- Number of metastatic organs at baseline (< 3, ≥ 3)

Censoring pattern of PFS

The number of patients with a PFS event and number of patients censored for the PFS analysis will be summarized. In addition, a summary of reasons for PFS censoring will be provided by treatment group based on the following reasons:

1. Ongoing without event
2. Lost to follow-up
3. Withdrew consent
4. Adequate assessment no longer available
5. Event after ≥ 2 missing tumor assessments

The PFS censoring reasons are defined in the following way.

If the time interval between the last adequate TA date and the earliest of the following dates is smaller or equal to interval of 2 missing TA:

1. Analysis cut-off date,
2. Date of consent withdrawal,
3. Visit date of study treatment discontinuation or end of post-treatment follow-up discontinuation due to lost to follow-up.

Then the PFS censoring reason will be:

1. 'Ongoing',
2. 'Withdrew consent',
3. 'Lost to follow-up'

If the time interval is larger than the interval of 2 missing TA with no event observed, then the PFS censoring reason will always default to 'Adequate assessment no longer available.' If the time interval between the last adequate TA date and the PFS event date is larger than the interval of 2 missing TA then the patient will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments.'

These summaries on censoring reasons will be produced for PFS by investigator and BIRC using RECIST 1.1 and response criteria for immunotherapy. The censoring patterns will be compared between treatment groups within each of the two comparisons and also between investigator and BIRC using RECIST 1.1.

Concordance analysis of PFS using RECIST 1.1

Cross-tabulation of 'PFS by central radiology' vs. 'PFS by investigator' by PFS event type (i.e. 'death', 'PD', 'censor' for each of the two sources resulting in a 3-by-3 table) and by treatment will be constructed to investigate discordance between the two sources on a patient-by-patient basis. Discordance rate between central radiology and investigator will be calculated and presented as % as follows: 100 x ($n_{13} + n_{23+} n_{31} + n_{32}$) / N by treatment group.

Table 2-13 Comparison of PFS using RECIST 1.1 between investigator and BIRC

Investigator PFS	BIRC PFS result		
	Death	PD	Censor
Death	n_{11}	n_{12}	n_{13}
PD	n_{21}	n_{22}	n_{23}
Censor	n_{31}	n_{32}	n_{33}

A cross-tabulation will be produced displaying the PFS timing for the local investigators' assessment compared to the BIRC assessment. For progression assessments, the frequency and percent of subjects with complete agreement, progression later, progression earlier, and cases where progression was called by one method and censored by the other will be displayed. Similarly, if censoring was recorded, the frequency and percent of subjects with complete agreement, censoring called later, censoring called earlier, and cases where censoring was called by one method and progression was called by the other method will be displayed.

Table 2-14 Comparison of PFS event times using RECIST 1.1 between BIRC and local assessments

Investigator	BIRC	Treatment group (N = XXX)			
		Same time n (%)	BIRC after investigator n (%)	BIRC before investigator n (%)	Total
PD	PD	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	Death	xx (xx.x)	0	0	xx (xx.x)
Censor	Censor	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD	Censor	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD	Death	0	xx (xx.x)	0	xx (xx.x)
Death	PD	0	0	xx (xx.x)	xx (xx.x)
Censor	PD	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Censor	Death	0	xx (xx.x)	0	xx (xx.x)
Total		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

2.6 Analysis of the key secondary objective

The key secondary objective of the study is to determine whether PDR001 in combination with dabrafenib and trametinib prolongs OS compared with placebo in combination with dabrafenib and trametinib.

2.6.1 Key secondary endpoint

The key secondary endpoint for part 3 is overall survival (OS), defined as the time from the date of randomization to the date of death due to any cause. A cut-off date will be established for each analysis of OS. All deaths occurring on or before the cut-off date in the FAS will be used in the OS analysis.

If a patient is not known to have died at the time of analysis cut-off, OS will be censored at the date of last contact.

2.6.2 Statistical hypothesis, model, and method of analysis

The key secondary efficacy analysis will be the comparison of the distribution of OS between the two treatment groups. The following statistical hypothesis will be tested to address the key secondary efficacy objective:

$$H_{02}: \theta_2 \geq 1 \quad \text{vs.} \quad H_{A2}: \theta_2 < 1$$

where θ_2 is the OS hazard ratio (PDR001 in combination with dabrafenib and trametinib vs placebo in combination with dabrafenib and trametinib). The analysis to test this hypothesis will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance. Stratification will be based on the randomization stratification factors: LDH level (< 1 x ULN vs ≥ 1 to < 2 x ULN vs ≥ 2 x ULN) and ECOG PS (0 vs 1 vs 2).

The key secondary efficacy variable OS will be analyzed at the interim look and final analysis of a group sequential design, using a Lan-DeMets (O'Brien-Fleming) alpha spending function

[Lan and DeMets 1983] based on the data observed in the FAS up to the cut-off date, according to the treatment group and strata assigned at randomization. The survival distribution of OS will be estimated using the Kaplan-Meier method. The results will be plotted graphically by treatment group. The median and 25th and 75th percentiles of PFS along with 95% confidence intervals will be presented by treatment group. A stratified Cox regression will be used to estimate the hazard ratio (HR) of PFS, along with 95% confidence interval using the same strata information as the primary efficacy comparison.

OS data will be presented at each analysis but will be formally tested hierarchically as follows:

If PFS is statistically significant at the interim PFS analysis:

- Interim OS data will be tested at the time of the interim and final PFS analyses.
- A final analysis for OS is planned when approximately 245 deaths have occurred (or earlier if specifically requested by health authorities).

If PFS is not statistically significant at the interim PFS analysis :

- Interim OS data will not be tested at the time of the interim PFS analysis.

If PFS is statistically significant at the final PFS analysis:

- Interim OS data will be tested at the time of the primary PFS analysis. If OS is not statistically significant at this stage, a final OS analysis will be planned after approximately 245 deaths.

If PFS is not statistically significant at the final PFS analysis:

- Interim OS data will not be tested and there will also not be testing of OS data at the planned final OS analysis .

If a patient is not known to have died at the time of analysis cut-off, then OS will be censored at the date of last contact.

Supportive Analyses

Check of proportional hazard assumption will be performed as described in Section 5.4.1. If proportional hazard assumption is violated as a result of a delayed treatment effect, additional statistical methods as described below will be employed to examine OS.

Restricted Mean Survival Time (RMST) for OS at a prespecified time t* is defined as the interval from randomization until first documented progression or death due to any cause or t* whichever comes first. For determination of t* we will use the minimum of the time of last event time between two arms rounded downwards to the previous quarterly (i.e. 3-monthly) value. For example if the maximum event time in treatment arm is at 16.5 months and in placebo arm is at 17 months then the truncation time t* will be 15 months.

In the presence of non-proportional hazards due to a delayed treatment effect RMST can be considered a preferable alternative to HR for the estimation of treatment effect since . No proportional hazards assumption is assumed for this method.

The RMST and 95%CIs will be computed for each treatment arm separately. Difference in RMST for OS between the experimental and the control arms (and 95% CI) will be estimated using Kaplan Meier approach.

Kaplan Meier plots showing the area under the curve up to t* for each treatment group will also be displayed.

Milestone overall survival rates (and 95% CIs) at 12 and (if available) 24 months will presented by treatment group based on the Kaplan Meier analysis. The comparison of overall survival rates at each timepoint between two treatment arms will be based on the difference of complementary-log-log (cloglog) transformed survival functions at the timepoint. The hazard ratios and 95% CI at month 12 and month 24 will be based on the same cloglog transformation.

The null hypothesis of equal probabilities at month 12 and month 24 will be tested at one-sided α=0.025 to produce descriptive p values using the cloglog test statistic [Klein et al, 2007].

$$\chi^2(1) = \frac{(\log(-\log(\hat{S}_1)) - \log(-\log(\hat{S}_2)))^2}{\frac{\hat{\sigma}_1^2}{(\log(\hat{S}_1))^2 \hat{S}_1^2} + \frac{\hat{\sigma}_1^2}{(\log(\hat{S}_2))^2 \hat{S}_2^2}},$$

Under H0, this statistic follows a chi-square distribution with one degree of freedom.

The following summaries will be produced: the estimated OS rate at 12 and 24 months for each study arm together with 95% CI, the absolute difference of survival probabilities at each of the timepoints together with the estimated hazard ratio, 95% CI and the p-value.

A stratified piecewise Cox regression analysis will be performed based on OS to estimate a hazard ratio within pre-specified time periods (0-5 months and >5 months, based on assumed 5 month delayed effect for OS). Other analyses may be performed with periods based on alternative delayed effect durations indicated by the data). The analysis will be performed by incorporating a time-dependent covariate into the model and estimating the treatment effect for each of the two time periods. The hazard ratio, 95% CIs and Wald based p-value will be provided for each time period.

If proportional hazard assumption is violated as a result of a delayed treatment effect, a weighted log-rank test with $G^{\rho,\gamma}$ Fleming-Harrington (FH) class of weights will be performed as a sensitivity analysis in order to assess the robustness of the key secondary analysis for OS. Parameters ρ and γ define the weight function with values (0, 0) corresponding to unweighted log-rank test. The values (0,1) will be used. The weights are specified and justified based on clinical (e.g. expected time when treatment effect starts) and statistical (i.e. power) arguments. Moreover, sensitivity analyses with different selection of weights (e.g. equal weights) to assess the robustness of conclusions may be needed.

Impact of delayed treatment effect on OS will be evaluated using landmark analysis (Anderson et al, 1983, 2008). To do that, all randomized patients who are alive at the landmark time of 5

months will be included. Analyses may also be performed based on other clinically relevant landmark times as indicated by the data. No formal statistical comparison will be performed. Hazard ratio with 95% CI along with Kaplan-Meier estimate of survival at pre-specified time points of 12, 24, 36, 48, and 60 months (if the timepoint estimate can be obtained at time of analysis data cut) will be displayed. To evaluate a potential selection bias, the baseline characteristics and the patients' disposition will be tabulated for patients included in the landmark analysis for the landmark time thought to be of most interest.

As a sensitivity analysis to assess the impact of stratification, the two treatment groups will be compared using the unstratified log-rank test. The HR together with the associated 95% confidence interval obtained using the unstratified Cox regression model will also be presented.

The key secondary analysis will be repeated using the PPS if the number of patients in the FAS and PPS differ by more than 5 percent.

A multivariate, covariate adjusted Cox regression model stratified by randomization stratification factors will be fitted to evaluate the effect of other baseline demographic and disease characteristics on the estimated hazard ratio. The fitted model adjusting the treatment difference for key baseline and prognostic factors will include the same covariates that will be assessed for PFS (refer to Section 2.5.4).

If the key secondary efficacy analysis of OS is statistically significant, the following will be summarized by treatment group for each of the subgroups identified in Section 2.2.1:

- Kaplan-Meier estimates of median OS time with 95% CI
- Hazard ratio with 95% CI using stratified Cox proportional hazards model

Efficacy analyses in subgroups are intended to explore the consistency (homogeneity) of treatment effect but note that subgroup analyses of OS will primarily be performed at the time of the final PFS analysis when the survival data is sufficiently mature. A forest plot (including sample size/number of deaths, HR, 95% CI) will be produced to graphically depict the treatment effect estimates in key subgroups of interest. Separate forest plots will be produced to depict estimates for additional PD-L1 subgroups to support secondary efficacy objective, key exploratory subgroups of cold tumors with lack of immunogenicity, [redacted] (see Section 2.2.1). No inferential statistics (p-values) will be produced for the subgroups. Randomization stratification factors (LDH group, ECOG PS) will be included in all subgroup analysis models, except for those assessing subgroups of LDH or ECOG (for which they will instead by the subgroup factor), respectively.

Kaplan-Meier curves will only be produced for the following subroups:

- Stratification factors of LDH group (< 1 x ULN, ≥ 1 to < 2 x ULN, ≥2 x ULN) and ECOG PS (0, 1, 2) (based on randomization data from IRT)
- PD-L1 status (positive, negative), where a positive status is defined as having ≥ 1% tumor cell staining and negative is defined as having <1% tumor cell staining
- PD-L1 status (positive, negative), where a positive status is defined as having ≥ 5% tumor cell staining and negative is defined as having <5% tumor cell staining

- PD-L1 status (positive, negative), where a positive status is defined as having ≥ 10% tumor cell staining and negative is defined as having <10% tumor cell staining
- Cold tumors with lack of immunogenicity as defined by low TMB (< 10 Mut/MB) and low PD-L1 (<1% tumor cell staining) vs. all others

- Cold tumors with lack of immunogenicity as defined by low TMB (< 10 Mut/MB) and low T-cell inflamed signature levels (< 6.29) vs. all others
- Sum of diameters at baseline (<66 mm, >= 66 mm)
- High vs. low TMB (tumor mutation burden) (< 10 Mut/MB, ≥ 10 Mut/MB)
- T-cell inflamed signature subgroup (low vs. high) (< 6.29, ≥ 6.29)
- Brain metastatses at baseline (yes/no)
- Elevated LDH at baseline (<ULN , ≥1 x ULN)
- Number of metastatic organs at baseline (< 3, ≥ 3)

The pattern of censored data will be examined between the treatment groups: reasons for censoring ('Alive' or 'Lost to follow-up') and death cause will be summarized by treatment group. In addition, survival status, reason for censoring and death cause will be listed. Patients not known to have died will be censored for 'Lost to follow-up' if the time between their last contact date and the analysis cut-off date is longer than the protocol specified interval between the survival follow-up assessments plus 2 weeks, i.e., 14 weeks for this study.

A sensitivity analysis will be performed in which a stratified Cox regression model will be used to estimate the treatment hazard ratio and the associated 95% confidence intervals based on the central BRAF test results (i.e. mutation positive (yes/no). No other inferential statistics will be provided.

2.6.3 Handling of missing values/censoring/discontinuations

If a patient is not known to have died at the time of analysis cut-off, then OS will be censored at the date of last known date patient was alive, i.e., last contact date (see Table 2-4).

2.7 Analysis of secondary efficacy objective(s)

The other secondary efficacy objectives are to:

- Evaluate the two treatment groups with respect to overall response rate and disease control rate (using investigator assessment according to RECIST 1.1)
- Describe duration of response in each treatment arm (using investigator assessment according to RECIST 1.1)
- Evaluate the two treatment groups with respect to patient reported outcomes (PROs) of EORTC QLQ-C30, EQ-5D, and FACT-M melanoma subscale
- Evaluate the two treatment groups with response to PFS (using investigator assessment according to RECIST 1.1) and OS by PD-L1 expression

2.7.1 Secondary endpoints

All secondary efficacy endpoints according to RECIST 1.1 will be based on tumor assessments as per local investigator review. The blinded independent review committee (BIRC) assessments of RECIST 1.1 and tumor response criteria based on guidelines for immunotherapy will only be used as supportive analysis (refer to Section 2.13).

Overall response (ORR)

ORR is defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1 (see Appendix 1 of the study protocol). Complete and partial responses must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met. ORR will be calculated based on the FAS using local investigator review of tumor assessment data. Tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of BOR.

Disease control rate (DCR)

DCR is defined as the proportion of patients with a BOR of CR, PR, or stable disease (SD) lasting 24 weeks or longer according to RECIST 1.1 criteria. A patient will be considered to have SD for 24 weeks or longer if a SD (or NCRNPD) response is recorded at 24 weeks or later from randomization. DCR will be calculated using the FAS based on the investigators' tumor assessments.

Duration of response (DOR)

DOR only applies to patients whose BOR is CR or PR according to RECIST 1.1 based on local investigators review of tumor assessment data. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due toany cause. Patients continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment using similar censoring rules described for PFS analysis with the following exception. i.e.

- Patients who received new anti-cancer therapy will be censored at the date of their last adequate tumor assessment prior to the therapy.

PRO assessments: EORTC QLQ-30, EQ-5D, and FACT-M

See Section 2.11 for details on PRO assessments and analyses.

Subgroup analysis of PFS and OS by PD-L1 expression

Tables and forest plots of PFS and OS by PD-L1 subgroups will be produced using cut-offs of ≥ 1%, ≥ 5%, and ≥10% for PD-L1 positivity.

Table 2-15 PD-L1 expression status definitions

Analyte	Parameter	Negative	Positive
PD-L1	Percent positive tumor	<1 % tumor cell staining	≥ 1% tumor cell staining
PD-L1	Percent positive tumor	<5 % tumor cell staining	≥ 5% tumor cell staining
PD-L1	Percent positive tumor	<10 % tumor cell staining	≥ 10% tumor cell staining

See Section 2.2.1, Section 2.5.4 and Section 2.6.2 for details on these analyses.

2.7.2 Statistical hypothesis, model, and method of analysis

Overall response (ORR)

ORR will be compared between two treatment groups using a Cochran Mantel-Haenszel chi-square test at a one-sided 2.5% level of significance. The stratification will be based on the randomization stratification factors: LDH level (< 1 x ULN vs ≥ 1 to < 2 x ULN vs ≥ 2 x ULN) and ECOG PS (0 vs 1 vs 2).

ORR will be summarized using descriptive statistics (N, %) by treatment group, along with two-sided exact binomial 95% CIs [Clopper and Pearson 1934]. As a supportive analysis, ORR will also be summarized using descriptive statistics (N, %) based on the BIRC review of tumor data (using RECIST 1.1 and response criteria for immunotherapy).

Duration of response (DOR)

DOR will be listed and summarized by treatment group for all patients in the FAS with confirmed BOR of CR or PR, as well as for the subgroup of FAS patients with confirmed BOR of CR only and the subgroup of FAS patients with confirmed BOR of PR only. The distribution of duration of response will be estimated using the Kaplan-Meier method and the median duration of response will be presented along with 95% confidence interval only if a sufficient number of responses is observed. A responders-only analysis will also be performed in this case. No inferential analysis that compares duration of response between the two treatment groups will be performed.

Disease control rate (DCR)

DCR will be compared between two treatment groups using a Cochran Mantel-Haenszel chi-square test at a one-sided 2.5% level of significance. The stratification will be based on the randomization stratification factors: LDH level (< 1 x ULN vs ≥ 1 to < 2 x ULN vs ≥ 2 x ULN) and ECOG PS (0 vs 1 vs 2).

DCR will be summarized using descriptive statistics (N, %) by treatment group, along with two-sided exact binomial 95% CIs [Clopper and Pearson 1934]. As a supportive analysis, DCR will also be summarized using descriptive statistics (N, %) based on the BIRC review of tumor data (using RECIST 1,1 and response criteria for immunotherapy).

2.7.3 Handling of missing values/censoring/discontinuations

Overall response rate (ORR)

Patients with unknown or missing best overall response (BOR) will be counted as failures. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the best overall response must be "Unknown" unless progression is reported. For the computation of ORR, these patients will be included in the FAS and will be counted as 'failures'.

Note that patients with non-measurable disease only at baseline will still be assessed for response and included in the analysis, although in this case only patients with a confirmed CR response will be counted as a responder. In the central review a non-PD/non-CR assessment is available as a response category but this is not available for the local review assessment. For the local review assessment an SD response will be appropriate in place of a non-PD/non-CR assessment.

2.8 Safety analyses

All safety analyses will be based on the Safety Set.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during the on-treatment period. Additional summaries will be displayed to report all AEs, AEs related to study treatment, all SAEs and SAEs related to study treatment collected up to 150 days after last administration of PDR001/placebo. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AEs with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the investigational group (PDR001 in combination with dabrafenib and trametinib).

The following adverse event summaries will be produced by treatment group: overview of adverse events and deaths (number and % of patients with any AE, treatment-related AE, SAE, fatal AE, AE leading to discontinuation, AE leading to dose reduction/interruption, or AE requiring additional therapy), AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose adjustment and/or interruption, leading to dose reduction (for dabrafenib and/or trametinib only), requiring additional therapy, requiring immunosuppressive medication, and leading to fatal outcome. In addition, a summary of serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

For legal requirements of clinicaltrials.gov and EudraCT, two required tables for on-treatment adverse events which are not SAE's with an incidence greater than and equal to 5% and on-treatment SAE's and SAE's suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

2.8.1.1 Adverse events of special interest / grouping of AEs

All AE groupings for a clinical program are stored in the Compound Case Retrieval Strategy sheet (CRS) with clear versioning and reference to the MedDRA version used.

All AESI definitions or AE grouping need to be specified in the CRS. If a CRS update is necessary, the final version needs to be available in a reasonable time ahead of the DBL. The CRS version should be included in a footnote of the AESI tables.

Data analysis of AESIs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to PDR001, and the combination of 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. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

The following are the list of AESIs for each drug but note that the definitive list is documented separately and may be updated periodically.

AESI for PDR001 are (with “immunemediated” as prefix apart from infusion-reaction):

- Endocrinopathies
- Pneumonitis
- Colitis
- Hepatitis
- Nephritis
- Encephalitis
- Rash
- Infusion reaction
- Other immune disorders

AESI for dabrafenib are:

- Hypersensitivity
- Pyrexia
- Cutaneus squamous cell carcinoma (cuSCC) including keratoacanthoma
- Non-cutaneous treatment emergent malignancies
- New primary melanoma
- Pre-renal and intrinsic renal failure
- Uveitis
- Hyperglycemia
- Pancreatitis

AESI for trametinib are:

- Skin related toxicities

- Ocular events
- Cardiac related events
- Hepatic disorders
- Pneumonitis/interstitial lung disease
- Bleeding events
- Diarrhea
- Hypertension
- Edema
- Hypersensitivity
- Deep vein thrombosis/pulmonary embolism

AESI for combination of dabrafenib and trametinib are:

- Neutropenia

Summaries of these AESIs will be provided by treatment group (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death, requiring immunosuppressive medication etc.). If sufficient number of events occurred, analysis of time to first occurrence of AESIs will be applied (see Section 2.8.4.5). Summaries of grade 3 or higher AESIs by month of occurrence will also be provided by treatment group.

Additional summaries will be provided to report all AESIs and AESIs related to study treatment that were collected during the on-treatment period and up to 150 days after last administration of PDR001/placebo.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced by treatment group, system organ class and preferred term. Additional summary will be displayed to report all deaths up to 150 days after last administration of PDR001/placebo.

If study indication is primary reason for death (and not coded accordingly in the database) it must be included in the summary table. All deaths will be listed; post treatment deaths will be flagged. The death summaries cover patients from the Safety Set. A separate listing of deaths prior to starting treatment will be provided for all screened patients.

2.8.3 Laboratory data

Laboratory data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.1). All laboratory assessments will be listed and those collected later than 30 days after the last study treatment/exposure date will be flagged in the listings.

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high (low and high) classification to compare baseline to the worst on-treatment value.
- Trends of chemistry and hematology lab parameter values over time should be displayed via boxplots based on time windows and corresponding tables displaying the statistics used for the box plots by the selected time points.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTCAE grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTCAE grade 3 or 4 laboratory toxicities

Liver parameters

Liver parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
    - TBL > 2xULN
    - TBL > 3xULN
    - ALT or AST > 3xULN & TBL > 2xULN
    - ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN (potential Hy's law)

Potential Hy's Law events are defined as those patients with occurrence of AST or ALT > 3xULN and TBL > 2xULN, and ALP < 2xULN at initial presentation during the on-treatment period. Note that the criteria relating to combined elevations of AST (or ALT) and TBL are based on the peak values at any post-baseline time for a subject.

For patients with abnormal ALT or AST baseline values, a clinically significant liver safety signal corresponding to Hy's law is defined by : [ALT or AST > 3*baseline] OR [ALT or AST >8*ULN], whichever is lower, combined with [TBIL >2*baseline AND >2*ULN]

Further medical review has to be conducted to assess potential confounding factor such as, liver metastates, liver function at baseline etc.

A figure displaying time course of hepatic function tests (ALT, AST, TBL, ALP) in patients with Hy's law will be displayed in the Safety Set. Additonally, evaluation of drug-induced serious hepatotoxicity (eDISH) plots will be produced to display ALT and AST values by TBL values in units of ULN.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

At scheduled visits, single 12-lead ECG's will be performed, with the exception of Screening and Cycle 2 Day 1 where triplicates will be performed. ECG machines will automatically calculate heart rate and measures of PR, QRS, QT, and QTcF intervals. All ECG assessments will be read and interpreted locally.

Unscheduled safety ECG's may be performed at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECG's with clinically significant findings should be collected in triplicate.

ECHO/MUGAs will be performed to assess cardiac ejection fraction. The same procedure (either ECHO or MUGA) should be performed at baseline and follow-up visits. All ECHO/MUGA assessments will be read and interpreted locally.

Data handling

In case of unscheduled triplet ECG assessments, the average of the ECG parameters at that assessment should be used in the analyses.

Data analysis

The number and percentage of patients with notable ECG values will be presented by treatment group.

- QT and QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm

- Decrease from baseline >25% and to a value < 50 bpm

- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

For each of the ECG parameters (QT, QTc, QRS, HR and PR intervals), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point will be summarized.

Figures of change from baseline in ECG parameter values over time will be displayed via boxplots based on time windows.

Patients with notable ECG interval values will be listed and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG values.

A listing of all ECG assessments will be produced by treatment group and notable values will be flagged. A separate listing of only the subjects with notable ECG values may also be produced. In the listing, the assessments collected during the post-treatment period will be flagged.

For left ventricular ejection fraction (LVEF), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point will be summarized by treatment group.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-16 below.

Table 2-16 Clinically notable changes in vital signs

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. Descriptive statistics will be tabulated for baseline, at each post-baseline time point and changes from baseline at each post-baseline time point for each vital sign measure.

Figures of change from baseline in systolic and diastolic blood pressure values over time will be displayed via boxplots based on time windows.

A listing of all vital sign assessments will be produced by treatment group and notable values will be flagged. A separate listing of only the patients with notable vital sign values may also be produced. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.3 ECOG performance scale

The ECOG performance status will be used to assess physical health of patients, ranging from 0 (most active) to 5 (least active):

Table 2-17 ECOG performance scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Frequency counts and percentages of patients in each score category will be provided by treatment group and time point based on the windows defined in Table 2-1. Shift tables of

ECOG performance status at baseline to worst post-baseline ECOG status by score will be provided. Shift tables of ECOG performance status at baseline to best post-baseline ECOG status by score will also be provided. ECOG performance status at each time point will be listed.

Time to definitive deterioration in ECOG PS is defined as the time from the date of randomization to the date when ECOG PS has definitively deteriorated by at least one category compared with baseline. Deterioration is considered definitive if there is no subsequent improvement in ECOG PS back to the baseline category or above. Patients will be censored if no definitive deterioration in ECOG PS is observed before the first to occur out of the analysis cut-off date and the date when a new anti-neoplastic therapy is started. The censoring date will be the date of the last ECOG PS assessment prior to cut-off/start of new anti-neoplastic therapy.

Time to definitive deterioration in ECOG PS will be analyzed in the FAS according to the treatment group and strata assigned at randomization. Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for the time to definitive deterioration in ECOG PS will be calculated, along with its 95% confidence interval, using a stratified Cox model. A stratified log-rank test at the one-sided 2.5% level of significance will be used to compare the two treatment groups.

2.8.4.4 Ophthalmic examinations

A listing of all ophthalmic examinations will be produced by treatment group. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.5 Additional analyses

Time to first occurrence

Time to first occurrence of each AESI is defined as time from start of study treatment to the date of first occurrence of an AESI, i.e. time in days is calculated as (start date of first occurrence of event) – (start of study treatment) +1. Refer to Section 2.8.1.1 for the definition of AESI's. For cases where a patient has more than 1 PT occurring for the same AESI, only the PT(s) that occurred on the earliest date will be considered.In the absence of an event during the on-treatment period, the censoring date applied will be **the earliest** of the following dates:

- death date
- new anticancer antineoplastic therapy start date,
- end date of on-treatment period
- data cut-off date
- withdrawal of informed consent date.

Failure curves (ascending Kaplan-Meier curves) will be constructed for the Safety set by treatment group. Median together with 95% confidence interval as well as 25th percentile and 75th percentile will be presented.

In addition, the median time to occurrence for the subset of patients who experienced the event of interest will be calculated. Simple descriptive statistics, median, min and max as well as 25th percentile and 75th percentile, will be presented.

2.9 Pharmacokinetic endpoints

PK concentrations

Descriptive statistics (n, m (number of non-zero concentrations), mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for PDR001, dabrafenib, and trametinib concentrations will be presented at each scheduled time point by treatment for the PAS-PDR001 and PAS-D+T, respectively.

The mean (+/- SD) and geometric mean concentration-time profiles for PDR001, dabrafenib, and trametinib concentrations by treatment over time will be displayed graphically for the PAS-PDR001 and PAS-D+T, respectively, on the linear view.

All individual serum PDR001, and plasmar dabrafenib and trametinib concentration data will be listed by treatment group for the Full analysis set.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) (i.e. < 0.25 µg/mL for PDR001, < 1 ng/mL for dabrafenib, (GSK2118436), < 1 ng/mL for hydroxy-dabrafenib (GSK2285403), < 1 ng/mL for desmethyl-dabrafenib (GSK2167542), < 5 ng/mL for carboxy-dabrafenib (GSK2298683) and < 0.250 ng/mL for trametinib (GSK1120212)) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

2.10 PD and PK/PD analyses

2.10.1 Immunogenicity

2.10.1.1 Sample ADA status

Each IG sample is assessed in a three tiered anti-drug anti-body (ADA) testing approach. All IG samples are analyzed in the initial screening assay (first tier). Samples testing positive in the screening assay are then subjected to a confirmatory assay to demonstrate that ADA are specific for the therapeutic protein product (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier). Samples identified as positive in the confirmatory assay are considered ADA positive and are further characterized in the neutralization assay to indicate the presence of neutralizing antibodies (NAb). Samples can test negative in either the screening or confirmatory assay but for analysis purposes they are not differentiated. The following properties of each sample will be provided in the source data:

- Result of assay according to pre-specified confirmatory cut point: ADA positive (yes) or ADA negative (no)
- Titer (for positive samples): numerical representation of the magnitude of ADA response
- Presence of NAb (for positive samples, if NAb assay results are available): yes or no

- Drug tolerance level: highest drug concentration that does not interfere in the ADA detection method
- Fold titer change (i.e. x-fold): threshold for determining treatment boosted

Sample ADA status is determined based on the following definitions:

- *ADA-inconclusive sample*: Sample where assay is ADA negative and PDR001 PK concentration at the time of IG sample collection is greater than or equal to the drug tolerance level or missing.
- *Unevaluable sample*: Sample where assay is not available.
- *Determinant sample:* Sample that is neither ADA-inconclusive nor unevaluable.

The following definitions apply only to determinant samples:

  - *ADA-negative sample*: Determinant sample where assay is ADA negative and PDR001 PK concentration at the time of IG sample collection is less than the drug tolerance level.
  - *ADA-positive sample*: Determinant sample where assay is ADA positive.
  - *ADA-positive NAb sample*: Determinant sample where assay is ADA positive and presence of NAb = yes.

The following definitions apply only to post-baseline ADA-positive samples with a corresponding determinant baseline sample. To be classified as *treatment-boosted* or *treatment-unaffected*, both the post-baseline and baseline titer must be non-missing:

- *treatment-induced ADA-positive sample:* ADA-positive sample post-baseline with ADA-negative sample at baseline.
- *treatment-boosted ADA-positive sample:* ADA-positive sample post-baseline with titer that is at least *the fold titer change* greater than the ADA-positive baseline titer.
- *treatment-unaffected ADA-positive sample*: ADA-positive sample post-baseline with titer that is less than *the fold titer change* greater than the ADA-positive baseline titer.

NOTE: PK concentrations which are flagged for exclusion will still be used to determine ADA-inconclusive and ADA-negative samples.

The following summaries of ADA sample status (n and %) will be provided using *Immunogenicity prevalence set*:

- ADA-positive samples (i.e. ADA prevalence) and ADA-positive NAb samples, both overall and by time point (including baseline). For summaries by time point, the denominator is the number of subjects at that time point with a determinant sample.

Listings will be provided of sample ADA status (including titer for positive samples).

2.10.1.2 Subject ADA status

Any IG sample collected after 150 days of the last dose of PDR001/placebo will not be used for summaries or derivations and will only be included in the listing.

Subject ADA status is defined as follows:

- *Treatment-induced ADA-positive subject*: subject with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample.
- *Treatment-boosted ADA-positive subject*: subject with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample.
- *Treatment-unaffected ADA-positive subject*: subject with ADA-positive sample at baseline, no treatment-boosted ADA-positive samples, and at least one treatment-unaffected ADA-positive sample.
- *Treatment-reduced ADA-positive subject*: subject with ADA-positive sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- *ADA-negative subject*: subject with ADA-negative sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- *Inconclusive subject*: subject who does not qualify as treatment-induced ADA-positive, treatment-boosted ADA-positive, treatment-unaffected ADA-positive, treatment-reduced ADA-positive, or ADA-negative

The following overall summaries of ADA subject status (n and %) will be provided using the *Immunogenicity incidence set*:

- Treatment-boosted ADA-positive subjects; denominator is the number of subjects with an ADA-positive sample at baseline.
- Treatment-induced ADA-positive subjects; : denominator is the number of subjects with an ADA-negative sample at baseline.
    - ADA-negative subjects; denominator is the number of subjects in *Immunogenicity incidence set*.
    - ADA-positive subjects (i.e. ADA incidence): calculated as the number of treatment-boosted ADA-positive and treatment-induced ADA-positive subjects; denominator is the number of subjects in *Immunogenicity incidence set*.

Listings will be provided of subject ADA status

2.11 Patient-reported outcomes

2.11.1 General PRO analysis considerations

The FAS will be used for analyzing PRO data unless specified differently.

The outcome of most importance for PRO evaluation is the EORTC QLQ-C30 pain subscale. Of the other PRO outcomes measured the QLQ-C30 global health status and fatigue, insomnia and physical functioning sub-scales are also considered important. The remaining PRO data will be regarded as supportive and will be analyzed in a purely descriptive fashion.

Note that although the FACT-M subscales of pain and fatigue are very relevant for patients these components are already well represented by QLQ-C30 and therefore they will also only be analyzed descriptively.

The statistical analyses will examine the impact of study treatment only while the treatment is being taken and before the start of new anticancer therapy.

The protocol does specify that PRO assessments should be collected at 30 and 60 days post-progression so if there is sufficient data this may be used to help address and evaluate the potential issue of informative censoring in the analyses of time to definitive deterioration.

Since the impact of the investigational treatment on individual components can be in either direction all statistical tests will be two-sided at the 5% level of significance.

The statistical analyses will be used to address clinical questions related to the maintenance and/or improvemment of quality of life as follows:-

Maintenance of quality of Life

With respect to the important PRO outcomes listed above the main question of importance is whether there is any difference between the treatment groups in the maintenance of quality of life **while on treatment**.

Since the main intention is to try and maintain quality of life as long as possible, the time to definitive deterioration analysis will be the main statistical method to answer the question above. A deterioration event is “definitive” if it has no subsequent improvement above the specified threshold since it is recognized that there may be an initial deterioration in the specific outcome before subsequent normalization. (refer to section 2.11.3 for definition of definitive deterioration)

Additional supportive analyses of time to definitive deterioration will examine the impact of study treatment on patients with (and without) the specific symptom/function at baseline. For example, for global health state and physical functioning those subjects having baseline value <=90 are considered to have reported functioning burden as yes. Similarly, for symptom scales of pain, fatigue and insomnia those subjects having baseline value >=10 are considered to have reported symptom burden as yes.

Supportive analyses of time to (first non-definitive) deterioration will also be performed but note that this is used to assess a slightly different clinical question.

Improvement in quality of life

Along with examining whether study treatment maintains quality of life another question of secondary importance to be addressed is whether either treatment is better at improving the respective PRO outcome. This question will primarily be addressed by an analysis of responders who have the specific symptom at baseline.

The main analyses of the pain subscale will address whether study treatment maintains or improves the pain symptom irrespective of analgesic use being given. Additional analyses will address the impact on pain accounting for analgesic use.

Supportive exploratory analyses

To support the above analyses repeated measures modelling of longitudonal data will be used to estimate differences between treatment groups over time. In addition exploratory analyses looking at the impact of different assumptions regarding missing data may also be performed.

2.11.2 Data Collection

The PRO instruments are planned to be administered during screening, at Cycle 4 Day 1 and every 8 weeks, then from Cycle 22 Day 1, every 12 weeks until disease progression per RECIST 1.1 and/or end of treatment. PRO assessments will continue to be collected for 30 and 60 days post disease progression per RECIST 1.1.

The baseline is defined as the last PRO assessment on or prior to randomization.

Compliance to the schedule of administration of PRO assessments will be summarized by treatment group, for baseline and post-baseline on treatment assessments and scheduled post-treatment time points. The following categories, as collected on the eCRF, will be used to describe whether the questionnaire was completed at a specific time point:

1. yes
2. yes, fully completed
3. yes, partly completed
4. no, patient missed scheduled assessment visit
5. no, patient refused due to poor health
6. no, patient refused (unrelated to health)
7. no, study staff felt patient was too ill
8. no, questionnaire not available in appropriate language
9. no, institutional error
10. no, device not available
11. no, technical issues
12. no, other
13. no

A summary of the number and percentage of patients with questionnaire completion of 'yes' or 'no' (where categories 1-3 are counted as 'yes' and categories 4-13 are counted as 'no') will also be summarized by treatment group and time point.

Scoring of PRO data and methods for handling of missing items or missing assessments will be handled according to the scoring manual and user guide for each respective patient questionnaire [Fayers 2001, Askew 2009, van Reenen 2015]. No imputation procedures will be applied for missing items or missing assessments.

2.11.3 Details of statistical analysis methods

Time to definitive deterioration analysis

Analysis of the time to definitive deterioration in the PRO outcomes of most relevance described in 2.11.1 (QLQ-C30 global health status score and subscales for pain, fatigue, insomnia, and physical functioning) will be performed.

Definitive deterioration will be determined using minimal important difference (MID) threshold. MID of 10-points or more in the QLQ-C30 score from baseline (with no later change above this threshold) will be considered as an event of definitive deterioration [Osoba 1998]. For symptom sub-scales, a 10-point or more increase will be considered as deterioration for the QLQ C30 . For global health status and functioning sub-scales, a 10-point or more decrease will be considered as deterioration.

The time to definitive deterioration is calculated from the date of randomization to the date of definitive deterioration event. Only on-treatment PRO data will be included in the analysis. A single measure reporting a worsening of at least 10-points (QLQ-C30) is considered definitive only if it is the last one available for the patient. Patients with no events at cut-off date are censored at date of last assessment before cut-off. Patients who discontinued the study treatment prior to the analysis data cut off will be censored at the date of their last assessment before study treatment discontinuation. Patients receiving any further anti-neoplastic therapy before definitive worsening will be censored at the date of their last assessment before starting this therapy. If a definitive deterioration is observed after two or more missing assessments, the patient will be censored at the date of their last available questionnaire prior to the deterioration. Patients with no baseline data will be censored at Day 1.

If the baseline condition for a particular sub-scale is so severe that a 10 point deterioration is not possible then the patient will be censored at Day 1. . For example, If baseline score is >90 at baseline for symptoms scales, then a 10-pt deterioration will not be possible hence will be censored at day 1. Similarly, if baseline score is <10 for functioning scales and global health state, then a 10-pt deterioration will not be possible hence will be censored at day 1.

Death is considered as an event when it occurs within a period of time from last non-missing PRO assessment defined by 2 times the period between two assessments as planned in the study protocol. This avoids overestimating the time to definitive worsening in patients dying after an irregular assessment scheme. Patients who die after more than twice the planned period between two assessments since the last assessment are censored at the date of their last available questionnaire.

Time to definitive deterioration in QLQ-C30 scores will be compared between the two treatment groups using a stratified log-rank test (strata based on IRT data) at 2 sided 5% level of significance. The survival distributions will be presented descriptively using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier distributions will be determined, including the median time to 10-point (QLQ-C3-) deterioration and the proportion of patients without deterioration at 12, 24, 36, 48, and 60 months. Both point estimates and 95% CIs will be presented. A stratified Cox regression model will be used to estimate the hazard ratio (HR) of time to deterioration, along with 95% confidence interval. Sensitivity analysis of time to definitive deterioration with different cut-off definitions (e.g. 5, or 15 points) may also be considered if the number of events per arm is judged sufficient to draw relevant conclusions. Additional supportive analyses may be performed where PRO assessments after the initiation of new anti-neoplastic therapy are included provided there are sufficient of these assessments recorded.

Time to definitive deterioration will also be considered for the pre-specified QLQ-C30 subscales of most relevance for this patient population for two subgroups of patients; those who did and also those who did not report the symptom/function at baseline.

Note that for global health state and physical functioning those subjects having baseline value <=90 are considered to have reported functioning burden as yes. Similarly, for symptom scales of pain, fatigue and insomnia those subjects having baseline value >=10 are considered to have reported symptom burden as yes.

A sensitivity analysis may be performed whereby non-completion of the questionnaire, due to the reasons “patient too ill” or “refusal due to poor health” would also be counted as events provided there were no subsequent PRO assessments.

If there are sufficient post-progression PRO assessments further sensitivity analyses may be considered to check the impact of informative censoring due to treatment withdrawal due to PD without prior deterioration. If a PRO assessment indicating no deterioration was available at the time of the treatment withdrawal due to PD (or within 7 days prior) this analysis would assign a definitive deterioration event at the date of the next scheduled assessment (assuming the patient had continued on therapy); otherwise if there was no PRO assessment available then the analysis would assign the event at the progression date. For this analysis non-completion of the questionnaire, due to the reasons “patient too ill” or “refusal due to poor health” would also be counted as events at the last available PRO assessment provided there were no subsequent PRO assessments

An analysis of time to deterioration for the PRO outcomes of most relevance will be considered which will not take into account assessments after the point at which the threshold is first met.

The main analysis of time to definitive deterioration for the QTQ-C30 pain subscale will not take into account analgesic use.

An additional supportive analysis of the pain subscale to examine the impact of analgesic use will take into account the WHO scoring system (0 for no use, 1 for use of non-opiate analgesics (e.g. non-steroidal anti-inflammatory drugs, acetaminophen, antidepressants, and agents targeting neuropathic pain) 2 for use of weak opiates for moderate pain (e.g. codeine and tramadol) and 3 for strong opiates for severe pain (e.g. morphine and fentanyl). The sensitivity analysis will be adjusted for the WHO scoring sytem as follows:-

For the time to pain deterioration endpoint if pain increases by less than the threshold but the patient has had an increase in >=1 point in the WHO criteria score then this will be handled as an event for the purposes of a sensitivity analysis. In addition any initiation of opoid use is considered to be a pain event (change in WHO criteria score from 0 or 1 to 2 or 3) irrespective of the change in PRO pain score.

Responder Analysis

Responder analyses will be performed for the global health status score and for pain, fatigue, insomnia, and physical functioning of QLQ-C30 sub-scales , only for FAS patients who reported having the symptom/function at baseline. (i.e. subjects only having score <=90 at baseline for physical functioning and Global health state; >=10 at baseline for symptom scales will be considered into the analysis set for responder analyses.This cut-off will allow to see a 10-pt response in all relevant scales).

Response is defined as at least 10-point improvement in the QLQ-C30 relevant subscale score. Response data will be analyzed using Generalized Linear Mixed Model (GLMM) including terms for treatment, stratification factors, visit, treatment by visit interaction, and baseline score, with logit as link function. Individual patient random effects will be included in the model. The odds ratio between treatment arms at each scheduled time point will be estimated and presented together with a two-sided 95% confidence interval.

The main responder analysis for the QTQ-C30 pain subscale will not take into account analgesic use.

An additional supportive analysis of responders for the pain subscale will be adjusted for the WHO scoring sytem as follows:-

For the responder analysis if pain decreases by more than the threshold but the patient has had an increase in >=1 point in the WHO criteria score then the reduction in pain is assumed to be analgesic related and not study-treatment related i.e. evaluation is not a “response” for the purposes of a sensitivity analysis.

Improvements analyzed as status change
Patients will be categorized as having perceived improvement at least once (improvement of 10 points from baseline at any time during the study), regardless of potential worsening at other timepoints; or remaining stable at other timepoints. This endpoint will be analyzed as a binary endpoint, comparing the proportion of patients with improvements between treatment groups using logistic regression. The model will include terms for treatment, stratification factors and baseline value as main effects.

Descriptive analysis

Descriptive statistics will be used to summarize the scored scales and subscales of the EORTC QLQ-C30, EQ-5D-5L (VAS Score) and FACT- M Melanoma Subscale at each scheduled assessment time point as described in Table 2-3 for each treatment group. The PRO outcomes of most relevance for this patient population are the EORTC QLQ-C30 global health status score and sub-scales for pain, fatigue, insomnia, and physical functioning. Additionally, change from baseline in the scale and subscale values at the time of each assessment will be summarized. Subjects with an evaluable baseline score and at least one evaluable post

baseline score during the treatment period will be included in the change from baseline analyses.

Longitudinal Data analysis

In addition, a repeated measures model for longitudinal data will be used to estimate differences between treatment groups in EORTC QLQ-C30 global status and subscales identified as most relevance, . The modeling will be done on the actual score. Note that the modeling of the change in score or the actual score is equivalent since adjustment for baseline score is considered [CHMP Guideline on adjustment for baseline covariates 2015]. The repeated measures model will include terms for fixed effects of treatment, stratification factors, visit, baseline value as main effects, and an interaction term for treatment by visit. The differences in least square means between the treatment groups and corresponding 95% confidence interval will be presented by visit. This analysis will be restricted to patients with an evaluable baseline score and at least one evaluable post-baseline score. All data collected until end of treatment (including the end of treatment assessment) will be included in the analysis. Note that only data collected under treatment (i.e. while the patient is treated) will be included. The end of treatment assessment will be included if collected within 14 days of the last dose intake.

An additional repeated measures analysis will include time as a continuous variable expressed in weeks (from date of randomization), i.e. considering that PRO data follow a linear trend. As a first approach, an unstructured correlation matrix will be used to model the correlation within patients. The structure of the correlation matrix will be investigated and simplified using likelihood ratio tested if appropriate.

Repeated measured models will also be performed by the pre-specified QLQ-C30 of most relevance for this patient population for two subgroups of patients; those who did versus those who did not report the symptom/function at baseline.

The other exploratory analyses such as pattern mixture modeling may be performed and these will be documented in a separate exploratory SAP document. This type of analysis will assess the criteria of data being not missing at random in contrast to repeated measures model assuming the data to be missing at random.

2.12 Biomarkers

2.12.1 Introduction

As a project standard, Novartis Oncology Biostatistics will analyze only biomarkers collected in the clinical database. [redacted]

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue their analysis due to either practical or strategic reasons. Under such

circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

2.12.3 Biomarker data

The Full Analysis Set will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

Efficacy data will be analyzed in pre-defined PD-L1 subgroups as part of the secondary trial objectives (refer to section 2.7.1).

Table 2-18 summarizes the biomarker collection schedules and sample types. PD-L1 levels, TMB and T-cell inflamed signature are specifically mentioned

Table 2-18 Sample biomarker summary table

Biomarker	Part of study	Time point	Sample	Method
PD-L1 levels, Tumor Mutation Burden (TMB) T-cell inflamed signature	Part 3 (randomized)	Screening Screening Cycle 1 Day 15 Any time during Cycle 3 At disease progression	Archival or new tumor biopsy Optional new tumor biopsy Optional new tumor biopsy Optional new tumor biopsy Optional new tumor biopsy	IHC, DNA-seq, Nanostring

2.12.4 General data handling and preprocessing

The last (pre-dose) assessment performed closest to treatment dose will be used as the baseline value.

For assessments performed in tumor biopsies, fresh biopsy results will be used for baseline when both archived and fresh tumor samples are available for the same time point.

When more than one biomarker data value are available for a patient at any time point, the mean of the replicate values will be used for all statistical analyses.

2.12.5 Biomarker data analysis

PD-L1 levels, [redacted] are considered as core exploratory biomarkers in trials with immunotherapy and will be summarized. [redacted]

2.12.5.1 Categorization of IHC biomarker data

A Melanoma (MEL) score for PD-L1 expression [Daud 2016] will be derived and tabulated for all treated patients as described in Table 2-19. A MEL score ≥ 2 is considered PD-L1 positive.

Table 2-19 PD-L1 Melanoma (MEL) score definitions

Analyte	MEL score	Definition
PD-L1	0	No membrane staining
	1	Membrane staining in tumor and tumor-associated immune cells range of > 0% to < 1%
	2	Membrane staining in tumor and tumor-associated immune cells range of ≥ 1% to < 10%
	3	Membrane staining in tumor and tumor-associated immune cells range of ≥ 10% to < 33%
	4	Membrane staining in tumor and tumor-associated immune cells range of ≥ 33% to < 66%
	5	Membrane staining in tumor and tumor-associated immune cells range of ≥ 66%

2.12.5.2 Listing and summary statistics of IHC data

Baseline PD-L1, [redacted] data will be listed for each patient and ordered by treatment group.

For each quantitative measurement of the assays, the mean, standard deviation, %CV, median, minimum, maximum, inter-quartile range and number at baseline will be reported. Interquartile range is the number of data points between the 25th and 75th percentile. Data will be summarized by treatment group.

Biomarker status (i.e. +ve or –ve based on defined thresholds) will be summarized for the aforementioned markers.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.14 Interim analysis

Progression-Free Survival

An interim PFS analysis is planned after approximately 260 events which will allow for an early significance claim for a superior PFS result. If PFS is significant at this analysis an interim analysis of OS will also be performed at this time.

The timing and significance boundary of this interim PFS analysis has been chosen so that the efficacy threshold is met only when the PFS treatment effect is sufficiently large and clinically relevant (i.e. using a stringent significance level at interim anlayis with a small penalty for the final PFS analysis). The final PFS analysis, if performed at 352 events, will provide an 80% cumulative power to detect a statistically significant result if the delayed effect is indeed 5 months long as observed in KEYNOTE-022 and followed by an effect as currently assumed (i.e. HR=0.60).

A Gamma alpha spending function will be used to control the type 1 error probability with Gamma parameter = -9.7 (Hwang, Shih and DeCani, 1990). EAST version 6.4 will be used to determine the critical thresholds for the analysis based on the actual number of observed events at the time of the analysis. This particular Gamma alpha spending function was selected due to its conservative nature to ensure that statistical significance at the interim PFS analysis will only be declared for a clinically relevant PFS treatment effect.

The exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for PFS will depend on the number of PFS events that have been observed at the time of these analyses and for the final PFS analysis the α already spent at the time of the interim PFS analysis.

If the number of PFS events at the interim anlaysis is exactly 260 then a significant result will be obtained if p-value <0.00198 (or equivalently if HR<0.700). Similarly assuming 260 events have previously been observed at the interim, if there are exactly 352 events at the final PFS analysis then a significant result will be obtained if p-value <0.02483 (or equivalently if HR<0.811).

The interim PFS analysis will be performed by an external independent statistician. This will include an analysis of the primary PFS endpoint plus other critical efficacy endpoints and safety data. The results will be made available to the DMC who will then make a recommendation to Novartis.

The DMC recommendation at the interim PFS analysis will be based on whether the predefined efficacy threshold for primary endpoint PFS by investigator was met and will also take into account PFS results by central radiology review. The details on criteria used will be provided in the DMC charter.

Any recommendation to consider making the unblinded results available will be made after discussion with Novartis management. Full details of the decision-making process including who will have access to the unblinded results will be specified in the DMC Charter.

The projected timing of the interim and final PFS analysis based on current study data is summarized in Table 10-1. However, note that due to the limited follow-up the predictions for timing of analyses is highly uncertain. Indeed, doublet data from two pivotal randomized Phase III studies (MEK115306 [COMBI-d]) and MEK116513 [COMBI-v]) indicate that there could

be a rapid reduction in the event rate with longer follow-up which would lead to the targeted events occurring much later than predicted from the current study data alone.

Table 2-20 Estimated timelines for interim and final PFS analyses

Months after randomization of the first patient (prediction based on actual study data at Protocol Amendment 5)	# PFS Events (%Information fraction)	Cumulative PFS Power against a hazard ratio of 1 for first x months and a hazard ratio 0.60 after x months	
		x = 3 months Delayed Effect	x = 5 months Delayed Effect
19	260 (74%)	41.5%	15.5%
25	352 (100%)	93.8%	80.6%

Calculated using East 6.4

Key secondary endpoint: overall survival (OS)

Interim analyses for OS are planned at the time of the interim and primary PFS analysis

A hierarchical testing procedure will be adopted in part 3 and the statistical tests for OS will be performed only if the primary efficacy endpoint PFS is statistically significant.

A maximum of three analyses are planned for OS;

1. at the time of the interim analysis for PFS (provided PFS is significant),.
2. at the time of the final analysis for PFS (provided interim or final PFS is significant),
3. a final analysis for OS when approximately 245 deaths are expected (expected approximately 36 months from date of first patient to be randomized according to a prediction analysis using actual study data, although at this point this prediction based on limited study follow-up is still highly uncertain).

An α-spending function according to Lan-DeMets (O'Brien-Fleming) as implemented in East 6.4 along with the testing strategy outlined below will be used to maintain the overall type I error probability [Lan and DeMets 1983]. This guarantees the protection of the overall level α = 2.5% across the repeated testing of the OS hypotheses in the interim and the final analysis [Glimm et al 2010]. The trial allows for the an early significance claim for efficacy for a superior OS result, provided the primary endpoint PFS has already been shown to be statistically significant favoring the test treatment group. The exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the α for OS already spent at the time of earlier analyses.
At the time of final PFS analysis, both PFS and interim OS analysis will be performed by the sponsor's clinical team. Investigators and patients will remain blinded to study treatment and all patients will continue to be followed for OS until study closure.

3 Sample size calculation

3.1 Primary analysis

For part 3, the sample size calculation is based on the primary variable PFS. The hypotheses to be tested and details of the testing strategy are described in Section 2.5.2.

Based on data from two pivotal randomized Phase III studies (MEK115306 [COMBI-d]) and MEK116513 [COMBI-v]), the median PFS time in the control arm is expected to be 11 months. Ignoring delayed treatment effect, it would be expected that the experimental treatment response would result in a hazard ratio of 0.60 (which corresponds to an increase in median PFS to 18.33 months under the exponential model assumption). Given knowledge of a potential delayed treatment effect, it is hypothesized that there will be no difference between treatment arms until 5 months after the start of treatment for PFS. Therefore, it is assumed that the HR between the groups will be equal to 1 for the first 5 months. Thereafter, exponential survival distributions are assumed, with an HR of 0.60. This will result in an overall average HR=0.739 (Kalbfleisch 1981) at the time of final analysis (given the assumed 5 month delayed treatment effect, this equates to median PFS times of 15.0 and 11 months in the PDR001 in combination with dabrafenib and trametinib combination arm and the dabrafenib and trametinib plus placebo group, respectively).

In order to ensure 80% power for PFS using the above assumptions for HR=1 for the first 5 months and HR=0.60 thereafter, it is calculated that a total of 352 PFS events need to be observed. This calculation was made using the software package EAST 6.4 and assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance where subjects are randomized to the two treatments in a 1:1 ratio.

It should be noted that the cumulative 80% power refers to the overall HR of 0.739 that combines both the period of no effect and the subsequent delayed effect period and this represents ‘alternative hypothesis’ value.

The calculation also assumes a two-look group sequential design i.e. that there will be an interim analysis performed after 260 events (73.9% of total) with a Gamma alpha spending function used to control the type 1 error probability, with Gamma parameter = -9.7 (Hwang, Shih and DeCani, 1990)..

Based on predictions using actual blinded PFS data from the 532 patients randomized to part 3 of the study, the 352 events are expected to occur approximately 25 months after the randomization date of the first subject. The data cutoff for the interim PFS analysis is expected to occur approximately 19 months after the first patient was randomized. It should be noted that those future predictions are associated with reletively high level of uncertainty since they are based on the data with limited follow up.

The total of approximately 352 PFS events targeted for the final anlaysis represent a large percentage of the patients randomized in the study (66.2%) and therefore the rate of PFS events is likely to decrease with longer follow-up. In addition, formation of a plateau in the PFS Kaplan-Meier curve might occur in the combination arm with PDR001 based on patterns seen in studies with other checkpoint inhibitors and might lead to additional delay in the event accrual.

For those reasons it might actually take significantly longer to obtain the targeted number of PFS event and this is why the final anlaysis cutoff will be chosen based on both event numbers and calendar time.

3.2 Power for analysis of key secondary variables

For part 3, OS, as the key secondary variable, will be formally statistically tested, provided that the primary variable PFS is statistically significant. The hypotheses to be tested and details of the testing strategy are provided in 2.62.

Based on data from two pivotal randomized Phase III studies (MEK115306 [COMBI-d]) and MEK116513 [COMBI-v]), the median OS time in the control arm is expected to be 25 months. Ignoring delayed treatment effect, it would be expected that the experimental treatment response would result in a hazard ratio of 0.60 (which corresponds to an increase in median OS to 41.67 months under the exponential model assumption). Given knowledge of a potential delayed treatment effect, it is hypothesized that there will be no difference between treatment arms until 5 months after the start of treatment for OS. Therefore, it is assumed that the HR between the groups will be equal to 1 for the first 5 months. Thereafter, exponential survival distributions are assumed, with an HR of 0.60. This will result in an overall average HR=0.693 (Kalbfleisch 1981) at the time of final analysis (given the assumed 5 month delayed treatment effect, this equates to median OS times of 38.3 and 25 months in the PDR001 in combination with dabrafenib and trametinib combination arm and the dabrafenib and trametinib plus placebo group, respectively).

In order to ensure 80% power for OS using the above assumptions for HR=1 for the first 3 months and HR=0.60 thereafter, it is calculated that a total of 245 deaths need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, subjects randomized to the two treatments in a 1:1 ratio, and a 3-look group sequential design with a Lan-DeMets (O'Brien-Fleming) alpha spending function. These calculations were made using the software package East 6.4.

It should be noted that the cumulative 80% power refers to the overall HR of 0.693 that combines both the period of no effect and the subsequent delayed effect period and this represents 'alternative hypothesis' value.

At the final OS analysis 245 deaths will need to be observed. The final OS analysis is expected to be performed after approximately 36 months from the date of first subject randomized based on a prediction analysis using actual study data. However, note that this prediction is also associated with high uncertainty as described above.

4 Change to protocol specified analyses

The changes summarized in Table 4-1 were made between the protocol statistical section (Amendment 5) and the SAP.

Table 4-1 Summary of changes to protocol specified analyses

Protocol section	SAP section	Change and reason
Section 10.5.2	Section 2.7.3	DOR definition clarified i.e. to emphasize that deaths not to any cause will be regarded as an event and new anti-cancer therapy will lead to censoring at last adequate assessment

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 1 should not be applicable for final CSR. All patients should have EOT page complete before the Database lock for Final CSR

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date: **Use Dec31yyyy**

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date: **Use EOT date**

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date: **Use last day of the Month (mm)**

Case 5: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm = the month of EOT date: **Use EOT date**

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment: **Use the treatment start date**

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds, and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	No imputation will be done for completely missing dates

Missing Element	Rule
day, month	• If available year = year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY o Else set start date = study treatment start date. • If available year > year of study treatment start date then 01JanYYYY • If available year < year of study treatment start date then 01JulYYYY
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month and year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	**Rule** (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawl of consent date))
day, month, and year	Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

The above imputations are only used for analyses of time to and duration of AEs and concomitant medications.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is

progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date, then the evaluation is considered post-cut-off date and will be excluded from analysis.

5.2 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 should be specified in the footnote of relevant tables.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

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).

5.3 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. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used (refer to Table 5-3).

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high 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. Grade 5 will not be used. 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.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

Table 5-3 CTC grades for laboratory values in Novartis Oncology (based on CTCAE v4.03 – June 2010)

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Hematology								
WBC ↓	10^9/L	WBC	**3.9 – 10.7 x 10^9/L**	≥ LLN	< LLN - 3.0 x 10^9 /L	< 3 0 – 2 0 x 10^9 /L	< 2.0 – 1.0 x 10^9 /L	< 1.0 x 10^9 /L
WBC [2] (Leukocytosis)	10^9/L	WBC			-	-	> 100 x 10^9 /L	-
Hemoglobin [2] (Anemia)	g/L	HGB	**120 - 160 g/L** or 7.4 - 9.9 mmol/L (F) **140 - 170 g/L** or 8.7 – 10 6 mmol/L (M)	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L	< 100 - 80 g/L < 6 2 - 4.9 mmol/L	< 80 g/L < 4.9 mmol/L	-
Hemoglobin ↑	g/L	HGB	*(16.113 x mmol/L = g/L)*		Increase >0-20 g/L above ULN	Increase >20-40 g/L above ULN	Increase >40 g/L above ULN	-
Platelets ↓	10^9/L	PLAT	**150 - 350 x 10^9/L**	≥ LLN	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9 L	< 50.0 - 25 0 x 10^9/L	< 25.0 x 10^9 /L
Neutrophils [3]↓	10^9/L	NEUT		≥2x10^9 /L	< 2 0 - 1.5 x 10^9 /L	< 1 5 - 1.0 x 10^9 /L	< 1.0 - 0.5 x 10^9 /L	< 0.5 x 10^9 /L
Lymphocytes [3]↓	10^9/L	LYM		≥1.5x10^9 /L	< 1 5 - 0.8 x 10^9 /L	< 0 8 - 0.5 x 10^9 /L	< 0.5 - 0.2 x 10^9 /L	< 0.2 x 10^9 /L
Lymphocytes ↑	10^9/L	LYM			-	> 4 - 20 x 10^9 /L	> 20 x 10^9 /L	-
Biochemistry								
AST ↑	U/L	AST	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3 0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3 0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin ↑	umol/L	B LI	**5.1 – 20.5 umol/L** or 0 3 – 1.2 mg/dL *(17.1 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1 5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	**36 - 92 U/L** or 0.5 - 1 5 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2 5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine [4]↑	umol/L	CREAT	**61.9 - 115 umol/L** or 0.7 – 1 3 mg/dL *(88.4 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1 5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase [4]↑	U/L	CK	**30 - 170 U/L** or 0.5 – 2 83 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2 5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Albumin [2] (Hypoalbuminemia)	g/L	ALB	**35 - 55 g/L** or 3 5 to 5 5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-
Total Cholesterol ↑	mmol/L	CHOL	**3.88 – 5.15 mmol**/L or 150 - 199 mg/dL *(38.67 x mg/dL = mmol/L)*	≤ ULN	> ULN - 7.75 mmol/L > ULN - 300 mg/dL	> 7.75 -10.34 mmol/L > 300 – 400 mg/dL	>10 34-12.92 mmol/L > 400 – 500 mg/dL	>12 92 mmol/L > 500 mg/dL
Lipase ↑	U/L	LIPASE	**<95 U/L** or <1.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1 5 x ULN	> 1 5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	**0 - 130 U/L** or 0 – 2.17 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1 5 x ULN	> 1 5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Uric acid [2] (Hyperuricemia)	umol/L	URATE	**150 - 470 umol/L** or 2.5 – 8 mg/dL *(59.48 x mg/dL = umol/L)*	≤ ULN	> ULN – 10 mg/dL > ULN – 595 umol/L	-	-	> 10 mg/dL > 595 umol/L
ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range								

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Phosphorus[2] (Hypophosphatemia)	mmol/L	PHOS	**0.97 – 1.45 mmol/L** or 3 0 - 4.5 mg/dL *(0.32 x mg/dL = mmol/L)*	≥ LLN	< LLN - 2.5 mg/dL < LLN - 0.8 mmol/L	< 2 5 - 2.0 mg/dL < 0 8 - 0.6 mmol/L	< 2 0 - 1 0 mg/dL < 0 6 - 0 3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L
Calcium (corrected) [2] (Hypercalcemia)	mmol/L	CACALC	**2.2 - 2.6 mmol/L** or 9 - 10.5 mg/dL *(0.2495 x mg/dL = mmol/L)*	≤ ULN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L	> 11.5 - 12 5 mg/dL > 2 9 - 3.1 mmol/L	> 12.5 - 13 5 mg/dL > 3.1 - 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Calcium (corrected) [2] (Hypocalcemia)	mmol/L	CACALC		≥ LLN	< LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	< 8 0 - 7.0 mg/dL < 2 0 - 1.75 mmol/L	< 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Magnesium [2] (Hypermagnesemia)	mmol/L	MG	**0.62 – 0.99 mmol/L** or 1 5 – 2.4 mg/dL *(0.4114 x mg/dL = mmol/L)*	≤ ULN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3 3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L
Magnesium [2] (Hypomagnesemia)	mmol/L	MG		≥ LLN	< LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	< 1 2 - 0.9 mg/dL < 0 5 - 0.4 mmol/L	< 0.9 - 0.7 mg/dL < 0.4 - 0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L
Glucose (non-fasting) [2] (Hyperglycemia)	mmol/L	GLUCSN	**<7.8 mmol/L** or <140 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	-	> ULN - 250 mg/dL > ULN - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27 8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose (fasting) [2] (Hyperglycemia)	mmol/L	GLUCSF	**3.9 – 5.8 mmol/L** or 70 - 105 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	> ULN - 160 mg/dL > ULN - 8.9 mmol/L	> 160 - 250 mg/dL > 8 9 - 13 9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27 8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose [2] (Hypoglycemia)	mmol/L	GLUCSN/GLUCSF		≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3 0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium [2] (Hyperkalemia)	mmol/L	K	**3.5 - 5.0 mmol/L** *(0.2558 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 5.5 mmol/L	> 5 5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium [2] (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium [2] (Hypernatremia)	mmol/L	SODIUM	**136 - 145 mmol/L** *(0.435 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium [2] (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	-	< 130 - 120 mmol/L	< 120 mmol/L
Triglyceride [2] ↑	mmol/L	TRIG	**< 2.82 mmol/L** or < 250 mg/dL *(0.01129 x mg/dL = umol/L)*	< 150 < 1.71	≥ 150 - 300 mg/dL ≥ 1.71 – 3.42 mmol/L	> 300 - 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 - 1000 mg/dL > 5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L
Coagulation								
INR [2]↑	1	NR	**0.8 – 1.2**	≤ ULN	> ULN - 1.5 x ULN	> 1 5 - 2.5 x ULN	> 2.5 x ULN	-
Activated partial thromboplastin time[2]↑	sec	APTT	**25 - 35 sec**	≤ ULN	> ULN - 1.5 x ULN	> 1 5 - 2.5 x ULN	> 2.5 x ULN	-
Fibrinogen [4]↓	g/L	FIBRINO	**1.5 – 3.5 g/L** or 150 – 350 mg/dL *(0.01 x mg/dL = g/L)*	≥ LLN	< LLN - 0.75 x LLN	< 0.75 - 0 5 x LLN	< 0.5 - 0.25 x LLN	< 0.25 x LLN

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

(1) = **LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria**, e.g. if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≤ ULN.

(2) = **Life-threatening consequences and/or hospitalization are <u>not</u> considered** for determination of LAB CTC grades 3 and 4. Concomitant usage of anticoagulation therapy (for INR and Fibrinogen) is not considered either.

(3) = Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, **≥ 1.5 x 10^9 /L (lymphocytes) and ≥ 2 x 10^9 /L (neutrophils) are considered as LAB CTC grade 0**

(4) = For Creatinine and Fibrinogen, the **comparison with baseline is <u>not</u> considered** for derivation of LAB CTC grades

5.4 Statistical models

5.4.1 Primary analysis

Analysis of time to events Data

Hypothesis and test statistic

The null hypothesis stating that PFS survival distributions of the two treatment groups are equivalent will be tested against the one-sided alternative.

The following statistical hypotheses will be tested:

$$H_{01}: \theta_1 \geq 1 \quad \text{vs.} \quad H_{A1}: \theta_1 < 1$$

where θ_1 is the PFS hazard ratio (PDR001 in combination with dabrafenib and trametinib vs placebo in combination with dabrafenib and trametinib).

Stratified log-rank test adjusting for the strata used in the randomization will be implemented as follows: In each of the K strata separately, the LIFETEST procedure with STRATA statement including only the treatment group variable and with the TIME statement will be used to obtain the rank statistic S_k and variance var(S_k) where k=1, 2, …, K. The final test statistics will then be reconstructed as follows:

$Z=[S_1+\ldots+S_K]/\sqrt{\ [var(S_1)+\ldots+var(S_k)]}$.

The one-sided p-value will be obtained using a Z statistic.

Kaplan-Meier estimates

An estimate of the survival function in each treatment group 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 group 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].

Hazard ratio

Hazard ratio will be estimated by fitting the Cox proportional hazards model using SAS procedure PHREG (with TIES=EXACT option in the MODEL statement).

A stratified unadjusted Cox model will be, i.e. the MODEL statement will include the treatment group variable as the only covariate and the STRATA statement will include stratification variable(s).

Hazard ratio with two-sided 95% confidence interval will be based on Wald test.

Note: Ideally, the hazard ratio and the confidence interval should be derived by a method

consistent with the p-value calculation, i.e. in this case with log-rank test. This requirement would lead to the score test based intervals. However, since these intervals are not available in the SAS procedure PHREG, Wald test based intervals will be used.

Treatment of ties

Note: Ideally, the ties handling method used in LIFETEST and PHREG procedures should be consistent. However, since the main purpose of employing the PHREG procedure is to produce a hazard ratio with confidence interval and this cannot be obtained in a way consistent with log-rank based p-value produced by LIFETEST, it is recommended that the PHREG procedure should use a ties handling method which is considered optimal in given setting regardless of the consistency between LIFETEST and PHREG procedures.

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties. The PHREG procedure in SAS with option TIES=EXACT will be used to fit the Cox proportional hazards model.

Checking proportionality of hazard assumption

Plots (SURVIVAL LOGSURV LOGLOGS) generated by LIFETEST procedure in SAS will be used to provide visual checks of the proportional hazard assumption.

- SURVIVAL plots estimated survivor functions. The shape of the curves should be basically the same if hazards are proportional.
- LOGSURV plots the cumulative hazard functions The larger cumulative hazard should be a multiple of smaller if hazards are proportional
- LOGLOGS plots log (cumulative hazard). The LOGLOG plot will show parallel curves if hazards are proportional.

As an exploratory measure, to test the proportional hazard assumption, the treatment group * time interaction will be added in the MODEL statement in PHREG procedure in SAS. Evidence that interaction is not zero is evidence against proportional hazards.

5.4.2 Key secondary analysis

Same instructions as Section 5.4.1.

5.5 Rule of exclusion criteria of analysis sets

Not applicable.

5.6 Rule of derivation for immune related criteria

Immune related confirmed irPD is derived as followed:

Confirmed progression 1 (type 1, cPD1) is declared if a patient has 2 consecutive tumor assessments at least 4 weeks (28 days) apart both showing disease progression. Assessments with an irUNK response or irPD assessments < 28 days after initial irPD, are discarded.

The first irPD is flagged as cPD1 while all subsequent irPDs are flagged as xPD1.

Sequence of assessments	Instructions

1 irPD 2 irUNK 3 irPD (Assessment 1 + 30 days)	• Assessment 3 is ≥28 days after Assessment 1 • Assessment 3 represents confirmation of irPD at assessment 1 • Assessment 1 irPD is flagged cPD1 • Assessment 3 irPD is flagged xPD1
1 irSD 2 irPD 3 irPD (Assessment 2 + 20 days) 4 irPD (Assessment 2 + 30 days)	• Assessment 3 is < 28 days after Assessment 2 • Assessment 4 is ≥ 28 days after Assessment 2 • Assessment 4 represents confirmation of irPD at assessment 2 • Assessment 2 irPD is flagged cPD1 • Assessment 3 and 4 irPDs are flagged xPD1

The date of progression is the date of the assessment flagged as cPD1.

Confirmed progression 2 (type 2, cPD2) is declared if a patient discontinues treatment following a single irPD with no subsequent assessments. Assessments with an irUNK response or irPD assessments < 4 weeks (28 days) after initial irPD, are discarded. Discontinuation of treatment is obtained from EOT case report form.

The assessment is flagged as cPD2 and subsequent irPDs (<28 days after first PD) are flagged as xPD2.

The table below shows two hypothetical data scenarios and programming instructions.

Sequence of assessments	Instructions
1 irSD 2 irPD - EOT	• Patient withdraws after initial progression (Assessment 2) without confirmation • Assessment 2 irPD is flagged as cPD2
1 irPD 2 irPD (Assessment 1 + 20 days) - EOT	• Assessment 2 irPD is <28 days after Assessment 1, so does not represent confirmation • However, patient has completed treatment • Assessment 1 irPD is flagged cPD2 • Assessment 2 irPD is flagged xPD2

The date of progression is the date of the assessment flagged as cPD2.

Unconfirmed progression: Patients with a single irPD, and no assessment of irSD or better (assessment with an irUNK response or irPD assessments < 4 weeks after initial irPD will be considered as a confirmed irPD.

6 Reference

1. Anderson et al (1983). Analysis of survival by tumor response. J Clin Oncol; 1(11): 710-719.
2. Anderson et al (2008). Analysis of survival by tumor response and other comparisons of time-to-event by outcome variables. J Clin Oncol; 26(24): 3913-3915.
3. Askew BA, Xing Y, Palmer JL, et al (2009). Evaluating minimal important differences for the FACT-Melanoma quality of life questionnaire. Value in Health; 12(8): 1144-1150.

4. Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 - 41.
5. CHMP guideline on adjustments for baseline covariates in clinical trials (2015) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184923.pdf
6. Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 26, 404-413.
7. Collet D (1994). Modelling survival data in medical research. London, Chapman & Hall.
8. Daud A, Wolchok J, Robert C, et al (2016). Programmed death ligand 1 expression and response to the anti-programmed death 1 antibody pembrolizumab in melanoma. J Clin Oncol, 34:4102-4109.
9. Fayers PM, Aaronson NK, et al (2001). The EORTC QLQ-C30 scoring manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels.
10. Glimm E, Maurer W and Bretz F (2010). Hierarchical testing of multiple endpoints in group-sequential trials. Statistics in Medicine, 29, 219-228.
11. Hwang IK, Shih WJ, and DeCani JS (1990). Group sequential designs using a family of type I error probability spending functions. Statistics in Medicine, 9, 1439-1445.
12. Kalbfleisch, J. D., and Prentice, R. L. (1981). Estimation of the Average Hazard Ratio. Biometrika, 68, 105-112
13. Klein J.P., Logan B., Harhoff M and Andersen P K, Analyzing survival curves at a fixed point in time, Statist. Med., 2007, 26, 4505-4519.
14. Lan KKG, DeMets DL (1983). Discrete sequential boundaries for clinical trials. Biometrika, 70, 649-53.
15. Little (1995). Modeling the drop-out mechanism in repeated-measures studies. Journal of American Statistical Association; 90(431): 1112-1121.
16. Osoba D, Rodrigues G, Myles J, Zee B, Pater J (1998). Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol; 16(1): 139-144.
17. Robins JM and Finkelstein DM (2000). Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics, 56(3),779-88.
18. Robins JM and Tsiatis AA (1991). Correcting for non-compliance in randomized trials using rank preserving structural failure time models (RPSFTM). Commun. Statist.-Theory Meth., 20(8), 2609-31.
19. Schimmer BP and Parker KL (1996). Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In Goodman & Gilman's The Pharmacological Basis of Therapeutics (9th Edition), Published by McGraw-Hill, New York: 1459-1485.

[redacted]

21. Uno H et. al. (2014). Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. J. Clinical. Oncol., 32(22): 2380-2385

22. van Reenen M and Janssen B (2015). The EQ-5D scoring manual. Published by: EuroQoL Research Foundation, Rotterdam.