NOVARTIS

Clinical Development

DRB436 (GSK2118436) + TMT212 (GSK1120212)

CDRB436F2301 / NCT01682083

COMBI-AD: A phase III randomized double blind study of dabrafenib (GSK2118436) in COMBInation with trametinib (GSK1120212) versus two placebos in the ADjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection

Statistical Analysis Plan (SAP) for Final Analysis

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
14 August 2023	Prior final analyses DBL	To incorporate key OS and safety outputs. To incorporate update on other endpoints.	[redacted] To incorporate updated safety analysis with on-treatment and post treatment safety data. [redacted]	Only the relevant required analysis for final analysis has been incorporated.

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AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ANP	Anti-neoplastic Therapies
ATC	Anatomical Therapeutic Chemical
BOR	Best Overall Response
CP	Clinical Pharmacology
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMFS	Distant Metastasis-Free Survival
DMS	Document Management System
DRL	Drug Reference Listing
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FFR	Freedom From Relapse
MedDRA	Medical Dictionary for Drug Regulatory Affairs
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamics
PK	Pharmacokinetics

PT	Preferred Term
RAP	Reporting & Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Relapse Free Survival
SAE	Severe Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TFLs	Tables, Figures, Listings
ITT	Intent-To-Treat
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the final clinical study report (CSR) of study CDRB436F2301, a phase III randomized double blind study of dabrafenib (GSK2118436) in COMBInation with trametinib (GSK1120212) versus two placebos in the ADjuvant treatment of high-risk BRAF V600 mutation positive melanoma after surgical resection.

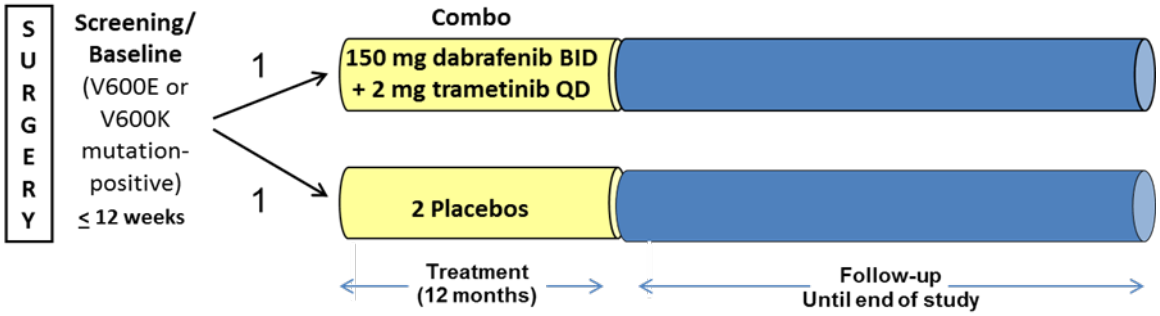
The content of this SAP is based on protocol CDRB436F2301 (Amendment 10). All decisions regarding final follow-up analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

Refer to the SAP (CDRB436F2301_SAP_M3) stored in Web-based document Management system (otherwise referred to as CREDI throughout) dated 30-June-2017.

Refer to Figure 1-1 for a study design.

Figure 1-1 BRF115532 Study Design Schema



1.2 Study objectives and endpoints

For all detailed objectives and endpoints of the study refer to the SAP (CDRB436F2301_SAP_M3) stored in CREDI dated 30-June-2017.

The majority of the study objectives were already analyzed at the time of primary analysis. The final CSR will only include analyses covering the objectives/end-points listed below as a part of study closeout. Only Overall Survival (OS) will be tested for statistical significance as per protocol and rest of the objectives will be summarized using appropriate descriptive statistics. Objectives, other than OS to be summarized are described in following sections.

Table 1-1 Objectives and related endpoints

Objective	Endpoint
• To evaluate and compare Overall Survival (OS) of dabrafenib and trametinib combination therapy compared to placebo.	• OS is defined as the time from randomization until death due to any cause

• To evaluate the safety of dabrafenib and trametinib in combination in the overall study population.	• Safety: Incidence and severity of AEs, SAEs including AESIs and ECOG PS.

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 and R version 4.1.0. (or later version if available at time of database lock) will be used to perform all data analyses and to generate tables, figures, and listings.

Data included in the analysis

For the final follow-up, all statistical analyses will be performed using all data collected in the database up to the data cut-off date, which will be the last patient last visit date of the study.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis.

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

Refer to the SAP (CDRB436F2301_SAP_M3) stored in CREDI dated 30-June-2017.

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: Also, please refer to the CDRB436F2301_SAP_M3 for detailed specifications.

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 drug administration record	Non-missing dose. Doses of 0 are allowed.
Start/End dates from further antineoplastic Therapy	Non-missing medication/procedure term.

Source data	Conditions
End of treatment date from end of treatment page	No condition.
Tumor (RECIST) assessment date	Evaluation is marked as 'done'.
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
[redacted]	[redacted]

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. For more details on imputation of partial dates refer to the SAP (CDRB436F2301_SAP_M3) stored in CREDI dated 30-June-2017.

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

2.2 Analysis sets

For the definition of Intent-To-Treat (ITT) population and Safety population refer to the SAP (CDRB436F2301_SAP_M3) stored in CREDI dated 30-June-2017.

2.2.1 Subgroup of interest

Efficacy

OS follow-up will be summarized by the following subgroups ***to examine the homogeneity of treatment effect*** in long term:

- BRAF V600K mutation positive
- BRAF V600E mutation positive
- Disease Stage: IIIa / IIIb / IIIc AJCC 7 (see Appendix 4.2)
- Disease Stage: IIIa / IIIb / IIIc AJCC 8 (see Appendix 4.2)
- Gender: Male/Female
- Age at screening: < 65 years / ≥ 65 years
- Race: White / Asian / Other

- Region: North America: USA and Canada / Europe and Israel / Asia/Pac excluding Australia and New Zealand / South America / Australia and New Zealand
- Nodal metastatic mass (micrometastasis / marcometastasis)
- Nodal metastatic mass and primary tumor ulceration (micrometastasis and ulceration / micrometastasis and no ulceration / macrometastasis and ulceration / macrometastasis and no ulceration)

Safety set

Key safety analyses *(*AEs, related AEs, SAEs, related SAEs, AESIs, AEs leading to treatment discontinuation, and deaths*)* will be repeated on safety set without any subgroups.

2.3 Participant disposition, demographics and other baseline characteristics

As the recruitment of study was completed before the primary analysis and no demographics/other baseline data are expected to change these will not be summarized again during the final analysis. Patient disposition, medical condition (current) will be summarized based on the current available data.

2.3.1 Patient disposition

A summary of subject status and reason for study withdrawal will be provided. This display will show the number and percentage of subjects who withdrew from the study, including primary reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF. A listing of reasons for study withdrawal will also be provided.

For additional details please refer to the SAP (CDRB436F2301_SAP_M3) stored in CREDI dated 30-June-2017.

2.3.2 Protocol deviations

The number (%) of patients in the ITT 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 (study treatment, rescue medication, concomitant therapies, compliance).

Refer to the SAP (CDRB436F2301_SAP_M3) stored in CREDI dated 30-June-2017.

2.3.3 Prior, concomitant and post therapies

Refer to the SAP (CDRB436F2301_SAP_M3) stored in CREDI dated 30-June-2017.

Prior anti-cancer therapy

The prior anti-cancer therapy data will not be summarized for the final analyses.

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 ITT population. 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 will be summarized by treatment group. The analysis will also be repeated for patients who discontinued therapy following progression. The number and percentage of patients will be provided as per the anti-cancer therapy. The time from Disease Recurrence to Start of Subsequent Anti-Cancer Therapy Excluding Radiotherapy and Surgery will be summarized using appropriate summary statistic. For additional details on subsequent anti-cancer therapies related outputs please refer to the SAP (CDRB436F2301_SAP_M3) stored in CREDI dated 30-June-2017.

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.

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.

All reported concomitant therapies will be listed. The safety set will be used for all concomitant medication tables and listings.

2.4 Analysis of the primary objective

This section describes the analysis of the objectives mentioned in the Table 1.1. The objectives RFS, DMFS and FFR are covered in primary CSR and will not be repeated. Please refer to the primary CSR (drb436f2301p01--legacy-clinical-study-report) stored in CREDI dated 12-OCT-2017 and Statistical Analysis for 5 Year RFS Update (Add reference here). Please refer to the SAP (CDRB436F2301_SAP_M3) stored in CREDI dated 30-June-2017 for any additional details.

2.4.1 Overall Survival

One of the secondary objectives of the study was to determine if combination of dabrafenib and trametinib prolongs OS compared with placebo. This is a main objective of the study for final analysis. The OS is defined as the time (in months) from the date of randomization to the date of death due to any cause.

2.4.2 Statistical hypothesis, model and method of analysis

Based on the hierarchical criteria of testing OS end-point mentioned in the SAP (CDRB436F2301_SAP_M3) stored in CREDI dated 30-June-2017 the OS data will be tested at the final OS analysis.

OS will be summarized using Kaplan-Meier estimates and compared between treatment arms using a stratified log-rank test (using randomization stratification factors). (See Section 3 for further details on the threshold for statistical significance). The Pike estimator [Berry, 1991] of the treatment HR based on the stratified log-rank test along with 95% CI will be provided. In addition, for each treatment group, the Kaplan-Meier estimates for the median overall survival time and the first and third quartiles will be presented, along with approximate 95% CIs. A graph of survival curves and a listing of survival times will also be provided. For details please refer to Section 4.1.

A forest plot of OS (including sample size/number of deaths, HR, 95% CI) will be produced to graphically depict the treatment effect estimates in key subgroups of interest as mentioned under Section 2.2.1. Kaplan-Meier curves will be produced based on use of different ANPs listed in Section 2.9.1. The later part will highlight the impact of post treatment new anti-cancer therapy on OS (if any).

Kaplan-Meier curves will be produced for the subgroups of interests; Disease stage and BRAF mutation mentioned under Section 2.2.1.

Additionally Cox regression analysis will be performed for OS with treatment as covariate and stratified Cox regression will be used to estimate HR for OS and 95% C.I. For stratified Cox regression treatment and other prognostic variables will be used as covariates. For both the Cox regression and stratified Cox regression mentioned here; any p-values (if provided) do not have any real meaning and are only exploratory and descriptive in nature.

2.4.3 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 Section 2.1.1).

2.5 Safety analyses

All safety analyses will be based on the Safety Set.

2.5.1 Adverse events (AEs)

Adverse events will be recorded from the time the first dose of study treatment is administered until 30 days after discontinuation of study treatment. Serious adverse events (SAEs) will be collected over the same time period as AEs except new malignancies and SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in

existing therapy), study treatment, concomitant medication which must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. On-treatment AEs are part of Primary Analysis CSR and will not be updated during the final analysis.

In the final CSR, tables will be produced to display summaries of all AEs, AEs related to study treatment, all SAEs and SAEs related to study treatment. Additionally, 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 the on-treatment period defined above 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 (MedDRA version 26). 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. AEs will be graded according CTCAE v4.0.

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 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 AEs, SAEs, fatal AEs, fatal SAEs most frequent AEs, Common non-serious AEs, AEs by maximum grade), AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment), seriousness (SAEs and non-SAEs) and leading to hospitalization, fatal outcome etc. 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). AE's 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 will be listed.

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.

2.5.2 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 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 specific AESI with at least one event of the AESI will be summarized using number and percentage of patients.

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 dabrafenib and trametinib 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
- Skin related toxicities
- Ocular events
- Cardiac related events
- Hepatic disorders
- Pneumonitis/interstitial lung disease
- Bleeding events
- Diarrhea
- Hypertension
- Edema
- Deep vein thrombosis/pulmonary embolism
- Neutropenia

Summaries of AESIs will be provided by treatment group (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, death, requiring medication etc.). Summaries of grade 3 or higher AESIs will be provided by treatment group.

Summaries of the number and percentage of subjects with these events will be provided for each type of events separately. The summary of event characteristics will also be provided,

including number of subjects with any event, number of events, number of subjects with any event that is serious, number of subjects with any event that is related to study treatment, the outcome of the event, maximum grade and the action taken for the event. The worst case approach will be applied at subject level for the event outcome, maximum grade and the action taken, i.e. a subject will only be counted once as the worst case from all the events that subject had.

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

2.5.3 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.

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.

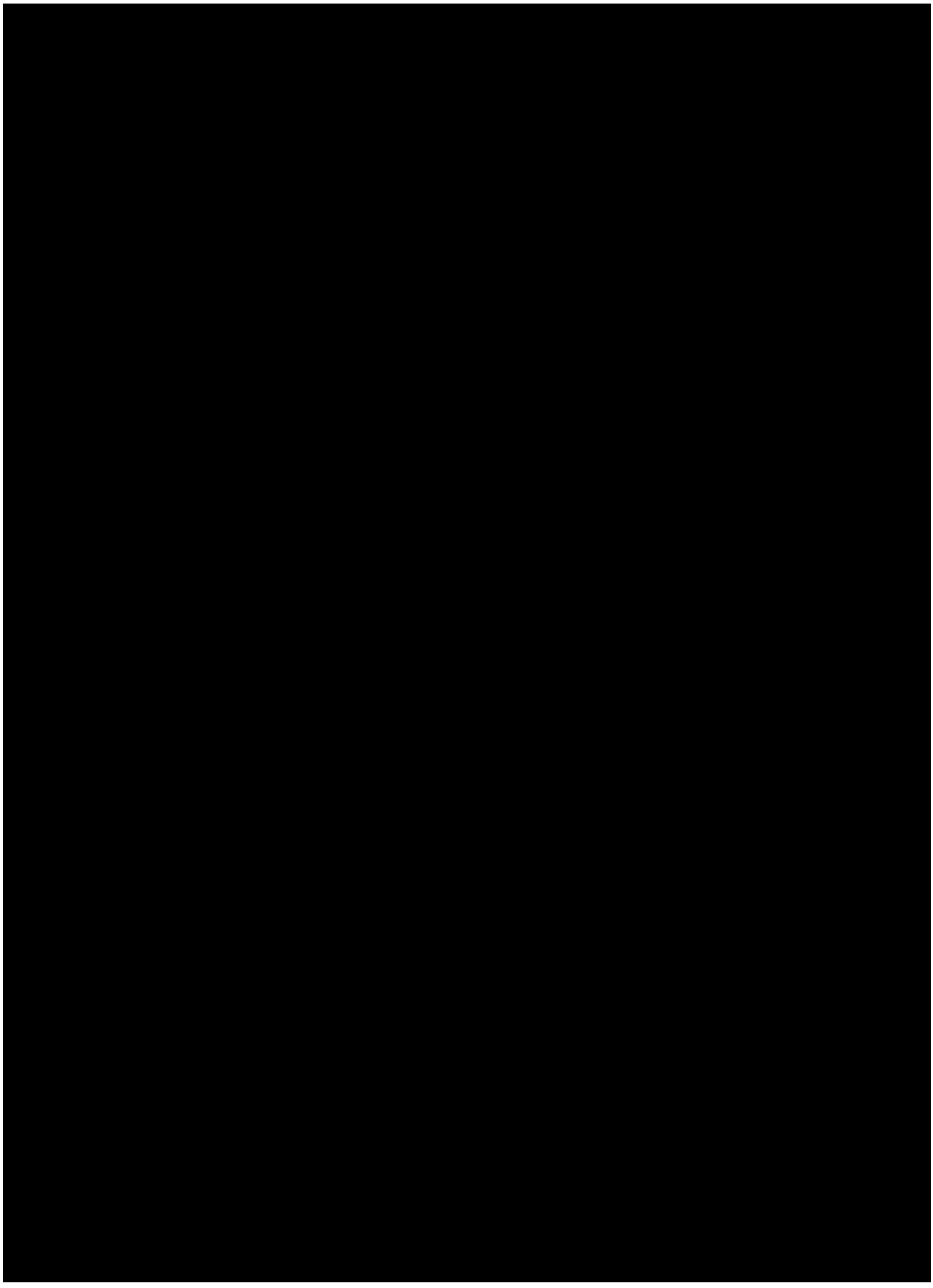
2.5.4 Laboratory data

Laboratory data were previously analyzed at the time of primary analysis and this analysis will not be repeated during the final analysis. For analysis related to laboratory data; please refer to primary CSR (drb436f2301p01--legacy-clinical-study-report) stored in CREDI dated 12-OCT-2017.

2.5.5 Other safety data

ECOG score (including post-treatment data) will be summarized using appropriate summary statistics. For the data analysis related to ECOG please refer to the SAP (CDRB436F2301_SAP_M3) stored in CREDI dated 30-June-2017. Vital signs data were previously analyzed at the time of primary analysis and this analysis will not be repeated during the final analysis. For the analysis related to other safety data; please refer to primary CSR (drb436f2301p01--legacy-clinical-study-report) stored in CREDI dated 12-OCT-2017.

[redacted]



[redacted]

2.10 Interim analysis

N/A

3 Sample size calculation

Refer to the SAP (CDRB436F2301_SAP_M3) stored in CREDI dated 30-June-2017.

4 Appendix

Refer to the SAP (CDRB436F2301_SAP_M3) stored in CREDI dated 30-June-2017.

4.1 Statistical models

Refer to the SAP (CDRB436F2301_SAP_M3) stored in CREDI dated 30-June-2017.

The OS interim analysis was performed when 153 OS events occurred (i.e. approximately 58.8% of 260 events) and as per Protocol Amendment 10, the final OS analysis will be performed when approximately 260 deaths are observed or at the end of July 2023, whichever comes first. Table 4-1 shows the power to detect various treatment effects. Conducting final analysis at 260 OS events affects the statistical power by 2%-6% (depending on different HR assumptions) compared to 299 OS events (the targeted OS events for final analysis as per Protocol Amendment 8). O'Brien-Fleming type stopping boundary will be used for all OS tests planned in the Amendment 10 to maintain the cumulative type-I error rate at 5% (two-sided). With O'Brien-Fleming boundaries (as in EAST 6), the interim threshold for claiming statistical significance was a two-sided P-value ≤ 0.00000953 (at interim analysis with 153 OS events) and the final threshold for claiming statistical significance is a two-sided P-value ≤ 0.04999977 (at final OS analysis assuming exactly 260 OS events). Note that, the exact number might be a bit higher/lower than 260 if new events are reported during final data cleaning. Considering the possibility of OS events other than 260 by the end of July 2023, the P-value and Z-value thresholds are listed in the Table 4-2 below.

The power considerations for OS are changed as compared to the initial protocol design, i.e. with 260 deaths, the study would have approximately 80% power to detect a hazard ratio of 0.70. The power scenarios for presented in Table 4-1 below.

Following the Protocol Amendment 10, Table 4-1 below shows the various power scenarios for testing OS at different OS events and different median OS assumed under both arms.

Table 4-1 Statistical Power Scenarios Following the Amendment 10

Median OS		% Improvement	Hazard Ratio	% Power at 255 OS events	% Power at 260 OS events	% Power at 299 OS events
Placebo	Combination Therapy					
47 months	72 months	53%	0.65	93%	93%	96%
48 months	74 months	54%	0.65	93%	94%	96%
49 months	75 months	53%	0.65	92%	93%	96%
47 months	67 months	43%	0.70	81%	81%	86%
48 months	68 months	42%	0.70	79%	80%	84%
49 months	70 months	43%	0.70	81%	82%	86%
47 months	63 months	34%	0.75	65%	65%	70%
48 months	64 months	33%	0.75	63%	64%	69%
49 months	65 months	33%	0.75	62%	62%	68%
47 months	59 months	26%	0.79	44%	45%	49%
48 months	61 months	27%	0.79	48%	49%	53%
49 months	62 months	27%	0.79	47%	47%	52%

Table 4-2 P-value and Z-value thresholds for different OS events

OS Events at final analysis	Lower Z threshold	P-value threshold*
252	-1.95996537	0.04999984
253	-1.95996544	0.04999983
254	-1.95996551	0.04999982
255	-1.95996558	0.04999981
256	-1.95996565	0.04999981
257	-1.95996573	0.04999980
258	-1.95996580	0.04999979
259	-1.95996588	0.04999978
260	-1.95996596	0.04999977
261	-1.95996604	0.04999976
262	-1.95996613	0.04999975
263	-1.95996621	0.04999974
264	-1.95996630	0.04999973
265	-1.95996639	0.04999972
*All values are two-sided		

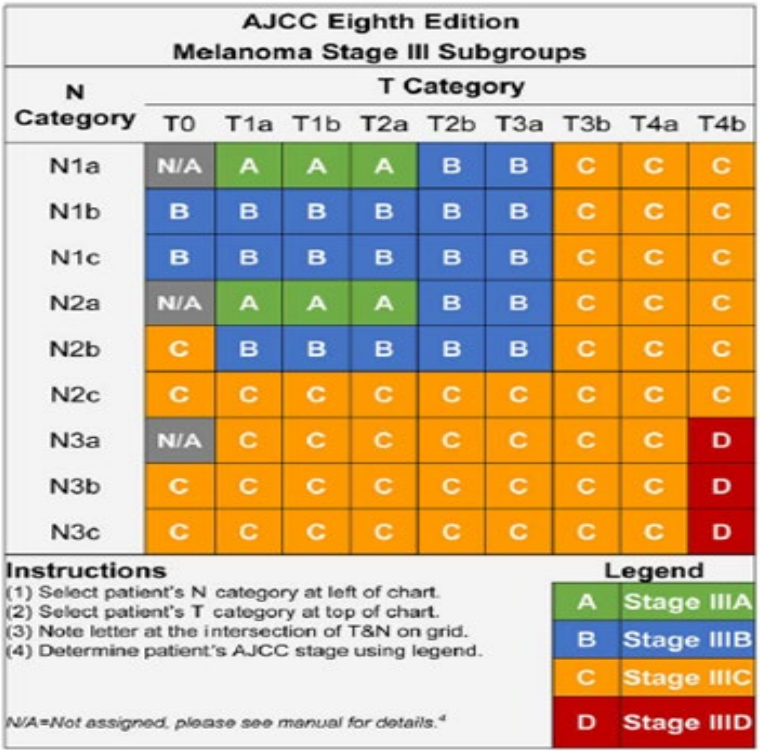
4.2 Additional variables

This section describes the difference between AJCC7 and AJCC8 criteria used for stagging. Patients disease stages will be rederived based on AJCC8 following the steps in below:

1. For those subjects who had N stage ‘N3’ under AJCC7 their disease stages under AJCC8 will be reviewed and provided by clinical team;
2. For those subjects whose N stages were not ‘N3’ under AJCC7:
   a) N stages under AJCC8: ‘N2C’ under AJCC7 will be mapped to ‘N1C’ under AJCC8; ‘N1A’, ‘N1B’, ‘N2A’ and ‘N2B’ under AJCC7 will stay the same under AJCC8;
   b) T stages and M stages will stage the same under AJCC8;

c) Rederive their disease stages based on AJCC8 rules below:

Figure 4-1 American Joint Committee on Cancer (AJCC) 8th Edition: Stage III Subgroups Based on T and N Categories



5 Reference

1. Bernstein L., Anderson J., Pike M. C. Estimation of the Proportional Hazard in Two-Treatment-Group Clinical Trials. *Biometrics.* 1981;37:513-519.
2. Berry G., Kitchin R.M., Mock P. A Comparison of Two Simple Hazard Ratio Estimators Base on the Logrank Test. *Statistics in Medicine.* 1991:749-755.
3. Cox D. R. Regression Models and Life Tables (with Discussion). *Journal of the Royal Statistical Society Series B.* 1972:187-220.
4. Eggermont A., Suciu S., Santinami M., Testori A., et al. Adjuvant Therapy with Pegylated Interferon alfa-2b versus Observation Alone in Resected Stage III Melanoma: Final Results of EORTC 18991, a Randomised Phase III Trial. *The Lancet.* 2008;372:117-126.
5. Lan K. K., DeMets, D. L. Discrete Sequential Boundaries for Clinical Trials. *Biometrika.* 1983:659-663.