NOVARTIS

Department Medical Affairs, Novartis Oncology Spain

Non-Interventional Study Protocol (PASS) with secondary use of data

Study protocol CDRB436BES04

Title	Retrospective analysis of safety in elderly metastatic or unresectable BRAF V600 melanoma patients treated with Tafinlar (dabrafenib) plus Mekinist (trametinib) and correlation with clinical features and non-elderly patients
Protocol version identifier	00 (original protocol)
Date of last version of protocol	11 January 2019
EU PAS register number	Study not registered yet
Active substance	L01XE23 (dabrafenib mesylate) L01XE25 (trametinib)
Medicinal product	Tafinlar/Mekinist
Product reference	Tafinlar 50 mg hard capsules EU/1/13/865/001 EU/1/13/865/002 Tafinlar 75 mg hard capsules EU/1/13/865/003 EU/1/13/865/004 Mekinist 0.5 mg film-coated tablets EU/1/14/931/001

	EU/1/14/931/002 Mekinist 2 mg film-coated tablets EU/1/14/931/005 EU/1/14/931/006
Procedure number	Not applicable
Name of Marketing authorization holder(s)	Novartis
Joint PASS	No
Research question and objectives	The primary objective of the study is to describe safety and real-world management of dabrafenib and trametinib in the elderly (≥ 75 years old) Spanish population. The secondary objectives are as follows: - to describe the clinical characteristics of elderly melanoma patients treated with dabrafenib and trametinib in Spain - to describe efficacy in patients ≥ 75 y.o. - to describe safety and initial dose of patients < 75 y.o. - to describe clinical variables that influence on the initial-dose decision and safety - to explore differences in efficacy depending on the age and dose density
Country (-ies) of study	Spain
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List of abbreviations

AE	Adverse Event
CRF	Case Report/Record Form
CRO	Contract Research Organization
EC	Ethic Committee
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GCP	Good Clinical Practice
GMA	Global Medical Affairs
HA	Health Authority
HCP	Health Care Provider
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
NVS	Novartis
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
SAP	Statistical Analysis Plan
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

1 Responsible parties

Table 1-1 Responsible parties

Main protocol author	[redacted] [redacted] Novartis Farmacéutica. S.A. [redacted] [redacted] Spain Email: [redacted]
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2 Abstract

Title

Retrospective analysis of safety in elderly metastatic or unresectable BRAF V600 melanoma patients treated with Tafinlar (dabrafenib) plus Mekinist (trametinib) and correlation with clinical features and non-elderly patients

Version and date

00, 11 January 2019

Name and affiliation of main author

[redacted]

[redacted]

Novartis Farmacéutica S.A., [redacted]

[redacted], Spain

Email: [redacted]

Rationale and background

Safety and efficacy of the recommended dose of dabrafenib and trametinib for unresectable or metastatic melanoma has been previously studied in two Phase III studies and one supportive Phase I/II study. In the randomized phase III COMBI-d and COMBI-v there were 11 patients (5%) and 21 patients (6%) respectively with age ≥75 years old (y.o.).

Melanoma in elderly patients has different features. These patients present with a lower proportion of BRAF mutation (25% for patients >70 years old), and, among those, there is a higher proportion of non-V600E mutations than in other ages. Therefore, this population has a higher risk of comorbidities and polypharmacy, which could influence on dabrafenib + trametinib safety and efficacy.

Spain is the third country worldwide in life expectancy (82,4 y.o.) and has one of the oldest populations: 18.4% are >65 years old and 8% are older than 80. For these reasons, treatment of senior melanoma patients is a common situation for Spanish Physicians. There is an unmet need of information regarding safety and efficacy, and treatment differs between different sites. Following some physician's feedback, treatment either with monotherapy or combination with reduced doses can be a strategy in Spain for trying to increase safety, although this observation has not been confirmed.

The purpose of this study is to define the real-world care of elderly metastatic or unresectable BRAF V600 melanoma patients treated with dabrafenib and trametinib in Spain, and provide more data regarding safety in this population. As secondary endpoints, this study provides the opportunity to explore potential differences in safety and efficacy of dabrafenib plus trametinib between elderly and non-elderly patients. The secondary endpoints will also analyze potential confounding factors, as well as exploratory differences on efficacy.

Research question and objectives

The primary objective is to describe the safety and real-world management of combined dabrafenib and trametinib in the elderly (≥ 75 y.o) Spanish population.

Secondary objectives are as follows:

- to describe the clinical characteristics of elderly melanoma patients treated with dabrafenib plus trametinib in Spain
- to describe efficacy in patients ≥ 75 y.o.
- to describe safety and initial dose of patients <75 y.o.
- to describe clinical variables that influence on the initial-dose decision and safety

- to explore differences in efficacy depending on the age and dose-density

Study design

This is a non-interventional, national and purely retrospective study based on secondary use of data from individual medical records to evaluate the safety and real-world management of dabrafenib or combination with trametinib in elderly and non-elderly patients with metastatic or unresectable BRAF V600 melanoma

The study includes a selection period of 7 months and a single visit aimed at obtaining the informed consent of patients (when the patient is alive), which will coincide with one of those regularly conducted by patients over their routine follow-up, without interfering with the investigator' clinical practice.

Setting and study population

The study population will be adult patients with metastatic or unresectable BRAF V600 melanoma, who have received at least one dose of dabrafenib combined with trametinib or dabrafenib monotherapy (in case that combination treatment was available and monotherapy was considered a medical decision).

It is planned to include 205 patients from 15 centers in Spain. For selection criteria, see section 7.2.

Variables

Safety variables: occurrence and severity (grade CTCAE v4.03) of adverse events, dose delays, dose adjustments, or treatment discontinuation for management of adverse events.

Efficacy variables: response rate, progression-free survival and overall survival.

Demographics and clinical characteristics: age, sex, comorbidities and concomitant drugs (at the time of initiation of dabrafenib as monotherapy or combined with trametinib), ECOG performance status (closest assessment to the initiation of dabrafenib as monotherapy or combined with trametinib), LDH levels (closest assessment to the initiation of dabrafenib as monotherapy or combined with trametinib), stage IIIc or IV based on AJCC 7th edition (closest stage to the initiation of dabrafenib as monotherapy or combined with trametinib), and presence of central nervous system (CNS) metastases.

Real-world management: line of treatment, start/end dates of treatment, duration of treatment, initial doses of dabrafenib and trametinib, dose intensity, dose delays, dose adjustments, and treatment discontinuation for reasons other than safety, including disease progression.

Data sources

For all variables of interest, data sources will be the patients' medical records.

Study size

The focus is essentially on those patients aged 75 years or older. According to previous studies, which did not considered age as a restriction, estimated that approximately 20% of the included patients would turn out to be ≥75 years. Based on these, in order to obtain 41 patients ≥75 years, it would be necessary to include a total of 205 patients in the study. Sample size rationale is presented below:

Among the points included in the main objective, grade ≥3 adverse effect rates will be prioritized for the calculation of the sample size. Previous data highlighted that 25% (Martin Algarra et al., 2017) of unselected patients will have grade ≥3 side effects, and 29% will need a dose reduction (Martin Algarra et al., 2017). Based on these values, we estimate a rate of 27% as the average of the two figures.

Considering a rate of 27%, a precision of ±14%, in a two-sided analysis, and an alpha risk of 0.05, it will be necessary to include 41 valid cases. Estimating a percentage of losses (e.g. incomplete or incongruent data, etc.) not higher than 5%, a total sample size of 205 patients should be recruited.

Data analysis

- Patient demographic and clinical characteristics will be summarized using descriptive statistics. For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical ones, patient counts and percentages will be provided. Categories for missing data will be presented if necessary. The variable performance status may be captured as Karnofsky Performance Score or as ECOG. The statuses recorded as Karnofsky will be recoded to ECOG scores.
- Real-world management of treatment, will be also descriptive and summarized using descriptive statistics. For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical ones, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.
- Overall Survival, defined as the time from the initiation of combined dabrafenib and trametinib or dabrafenib as monotherapy to the date of death due to any cause, will be calculated using Kaplan-Meier (KM) estimates. The KM graph will show the median OS time and the 95%CI will indicate the number of events and patients censored. Patients that had not died will be censored at last known date alive.
- Progression-free survival (PFS), defined as the time from the initiation of combined dabrafenib and trametinib or dabrafenib as monotherapy to the date of first document tumor progression (by RECIST v1.1) or death to any cause, whichever occurs first, will be calculated using KM method. The KM graph will show the median PFS and the 95%CI the number of events and patients censored. Patients who did not progress or die will be censored on the date of their last evaluable tumor assessment.
- The response rate (by RECIST v 1.1) will be shown by their frequency and percentage distribution along with their 95%CI.
- The safety of dabrafenib or combination with trametinib will be assessed by analyzing the occurrence and intensity (grade CTCAE) and the following additional safety variables:
    - dose delays and or/dose adjustments and
    - discontinuations of treatment for safety reasons.

For continuous variables, descriptive statistics (n, mean, and standard deviation, median, minimum and maximum) will be provided. For categorical variables, patient counts and percentages will be provided with categories for missing data presented if necessary.

- The clinical variables influencing on the initial-dose decision and safety will be explored by multiple linear regression and logistic regression models.
- The differences in OS and PFS depending on the age and dose density will be identified by the Logrank test; differences in response as regards the age and dose density will be explored by the Chi-squared test.

Management and reporting of adverse events/adverse reactions

- As this is a study based on secondary use of data, safety monitoring and safety reporting, is provided on an aggregate level only.
- Reports of adverse events/adverse reactions should be summarized in the study report, i.e. the overall association between an exposure and an outcome.
- Relevant findings from the study report will be included in the periodic aggregated regulatory reports submitted to Health Authorities

Milestones

Planned dates of study milestones:

Start of data collection; i.e. start date of data extraction: 1 March 2019

End of data collection; i.e. date from which the analytical dataset is completely available: 15 October 2019

Registration in the EU PAS register: 10 February 2019

Final report of study results: 01 September 2020

3 Amendments and updates

None

4 Milestones

Table 4-1 Planned dates of study milestones

Milestone	Planned date
Start of data collection	01 March 2019
End of data collection	15 October 2019
Registration in the EU PAS register	10 February 2019
Final report of study results	01 September 2020

5 Rationale and background

Melanoma seems to have a different pattern of presentation, pathology and outcomes dependent on the age of the patient that certainly influence treatment selection and survival outcomes. Elderly patients often have poor prognostic features compared with younger patients, including ulceration, elevated mitotic rate and head and neck location that contribute to the observed differences in mortality rates (Tsai et al., 2010), and older age is an independent adverse prognostic factor even after considering all other factors (Tsai et al., 2010).

Unfortunately, objective evidence regarding efficacy and safety of current melanoma therapies in elderly population is scarce, adding to the fact that treatment strategies and management of melanoma in the elderly can be different among sites. Therefore, there is little reference for healthcare professionals in individual patient management and shared decision-making.

Melanoma treatment in the elderly entails a complex decision making, with the consequence of a general undertreatment compared with their younger counterparts. Elderly patients generally have a higher risk of medical comorbidities and polypharmacy that makes them not candidates for intensive therapies and unable to tolerate the adverse side effects of these therapies (Tsai et al., 2010). Treatment either with monotherapy or combination with reduced doses could be a strategy in Spain to increase safety in this population. In fact, the use of reduced doses other than the specified in the Summary of Products Characteristics, or the use of monotherapy in older population is a recognized practice among some clinicians, although it is not known if this occurs in specific subpopulations and centers, or it is a generalized practice. This study, by collecting the baseline situation of elderly patients at the time of therapy with dabrafenib and with trametinib, along with the regimen (combination or monotherapy) and doses administered will reveal the current landscape in the management of IIIc unresectable or IV melanoma in such subpopulation. These data will also highlight if the management of metastatic or unresectable disease is independent of the age range or is associated with other patient-specific characteristics.

As the population continues to age, physicians will be faced with the care for an increasing number of senior melanoma patients. Spain is the third country worldwide in life expectancy with a mean of 83.1 years old, and has one of the oldest populations; according to 2016 INE

(Spanish Statistical Office) estimates, 18.4% of Spanish population is above the age of 65, and 8% above the age of 80.

BRAF-targeted therapies

Approximately 50% of malignant melanomas harbor an activating mutation of BRAF, an intracellular signaling kinase in the MAPK pathway (Davies et al., 2002, Dhillon et al., 2007); most BRAF-activating mutations occurring in melanomas are at residue V600, usually V600E. The frequency of BRAF mutant melanoma shows an inverse correlation with the age and elderly patients present with a lower proportion of BRAF mutation (25% for patients older than 70); also, among the elderly there is a higher proportion of non-V600 mutations than in other ages (Menzies et al., 2012). The development of molecular targeted kinase inhibitors for the treatment of metastatic melanoma dramatically improved outcomes for BRAF mutant metastatic melanoma, by improving objective response and survival outcomes for those patients treated (Coit et al., 2018).

BRAF/MEK inhibitor combination therapy

Targeted inhibition of the RAF–MEK–ERK (MAPK) pathway with BRAF inhibitors dabrafenib or vemurafenib, as compared with chemotherapy, improves the progression free and overall survival of patients who have metastatic melanoma with BRAF V600 mutations. However, resistance develops in a majority of patients, resulting in a median progression free survival of 6 to 7 months (Long et al., 2014)

Alternates mechanisms for targeting the MAPK pathway by inhibiting the downstream partner, MEK, were proven to be an effective therapeutic strategy in BRAF V600-mutant melanoma (Flaherty et al., 2012). These inhibitors of MEK1 and MEK2 (trametinib and cobimetinib), when combined with a BRAF inhibitor, show better efficacy than BRAF inhibitor monotherapy in previously untreated unresectable or metastatic disease (Larkin et al., 2014, Long et al., 2015, Robert et al., 2015). Longer follow up of clinical trials demonstrated that long-term survival is achievable with BRAF+MEK inhibitors in a relevant proportion of patients with BRAF V600-mutant metastatic melanoma and that long-term treatment is tolerable, with no new safety signals (Long et al., 2017)

BRAF and MEK inhibitor toxicities

As with other targeted therapies, acute and chronic exposure to these drugs is associated with predictable patterns of side effects. The update of Combi-d study data with longer follow-up (Long et al., 2017) did not show new safety signals with respect previous analysis (Long et al., 2015). The adverse events of grade 3/4 occurred in <1% or in 1% of patients treated with dabrafenib monotherapy were fatigue, chills, nausea/vomiting, and cutaneous AEs, including rash and hyperkeratosis. The incidence of grade 3/4 pyrexia was 2%.

The risk of toxicity does not increase by adding the MEK inhibitor trametinib with most AEs being similar (Johnson et al., 2014, Long et al., 2017, Long et al., 2015, Robert et al., 2015) and cutaneous AEs being minor (Sanlorenzo et al., 2014, Long et al., 2017, Long et al., 2015) compared with dabrafenib monotherapy, except pyrexia which was more commonly reported associated with combined therapy(Long et al., 2017, Long et al., 2015, Robert et al., 2015).

The longest follow-up to date with dabrafenib and trametinib combination in BRAF V600-mutant MM indicated that long-term dabrafenib plus trametinib treatment is tolerated with no new AEs associated with long-term use (Long et al., 2018).

This study carried out in conditions of routine clinical practice in a cohort of patients representative of the patient population seen in centers in Spain, aims at reviewing our site 'experience with patients 75 years or older diagnosed of metastatic or unresectable BRAF V600 melanoma, and providing an overview of their management with dabrafenib and with trametinib. Findings from this study will highlight if there is a need to personalize melanoma management based on patient's characteristics, and also will provide more information about the efficacy and safety profile in Spanish elderly population.

6 Research question and objectives

The primary objective of the study is to describe the safety and real-world management of dabrafenib plus trametinib in the elderly patients (≥ 75 y.o.) Spanish population

The secondary objectives of the study are as follows:

- to describe the clinical characteristics of elderly melanoma patients treated with dabrafenib and trametinib in Spain
- to describe efficacy in patients ≥ 75 y.o.
- to describe safety and initial dose of patients <75 y.o.
- to describe clinical variables that influence on the initial-dose decision and safety
- to explore differences in efficacy depending on the age and dose-density

7 Research methods

7.1 Study design

This is a non-interventional and pure retrospective study, based on secondary use of data from review of medical records. This is a study where the studied medicinal products are prescribed in the usual manner in accordance with the terms of the marketing authorization; the assignment of the patient to a particular therapeutic strategy is not decided in advance by the study but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures will be applied to the patients. The purely retrospective design does not require interviewing the patient at the visit date and the evaluation of further variables that are not in the existing dataset, so, all the information required as per protocol will be collected by a retrospective review of patients' records where all the events of interest have already happened.

The study includes a selection period of 7 months and a single visit aimed at obtaining the informed consent (IC) of patients (provided that the patient is alive), see Section 8. That visit will coincide with one of those regularly conducted by patients over their routine follow-up, without interfering with the investigator' clinical practice. Once the written consent of patients

to participate in the study and to use their clinical data has been obtained and eligibility for study entry confirmed, individual medical records at the site of investigator will be reviewed and the information of interest retrospectively collected.

Approximately 205 patients with metastatic or unresectable BRAF V600 melanoma in Spain who have received at least one dose of dabrafenib combined with trametinib or dabrafenib as monotherapy are planned to be included. These patients will have to meet the selection criteria specified in Section 7.2

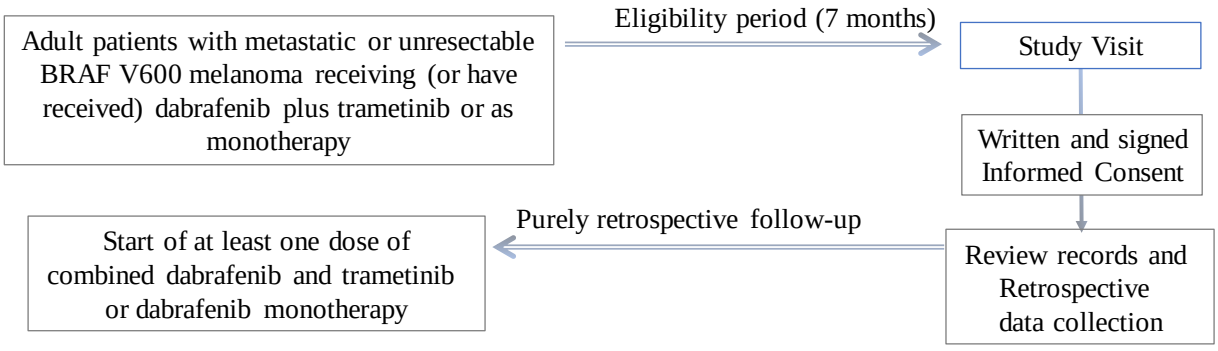
For the purposes of our analysis, patients will be divided into two groups according to the age: <75 y.o. and ≥ 75 y.o. The main analysis is focused on those patients aged 75 years and older who constitute a relevant population in Spanish consultations. The population of patients aged less than 75 years will provide the opportunity of exploring potential differences in terms of safety and efficacy of studied medicinal products between elderly and non-elderly patients.

The primary and secondary endpoints, along with the main measures and other data of interest are detailed in Section 7.3

This study was designed within the context of routine clinical practice with real-world data, and the heterogeneity of patients who are treated in reality. Experts recognize the importance of real data obtained in routine clinical practice conditions as a complement to the data obtained in a controlled setting, to improve the external validity of the latter and encompass a broader and more representative population.

The non-interventional studies, like the present one, where the observer does not interfere with practice but capture realty as it is are necessary to offer data on benefits and harms of the professional's interventions in different patient populations. In addition, the retrospective design will enable of answering new questions with existing data about managing BRAF V600-mutant melanoma.

Figure 7- 1 Study design



7.2 Setting and study population

The study will be performed in approximately 15 experienced centers in combined therapy with dabrafenib and trametinib, defined as centers that have treated at least 12 patients; i.e., the site selection process will ensure that the sites participating are representative as regards to the combination therapy for their patients with metastatic or unresectable BRAF V600 melanoma.

Sites participating should have a proportion of elderly patients (≥75 y.o.) treated with dabrafenib plus trametinib of 15-40%. A higher proportion will not be allowed to avoid centers that mostly prescribe this combination therapy to elderly patients and not as standard of care in melanoma patients. To ensure an elderly population (≥ 75 y.o.) large enough to get the sample size initially powered for the main analysis of the study, this study will restrict the recruitment of non-elderly population to approximately 160 patients.

To avoid screening biases, Investigators will have to consecutively include every patient in their respective institution that meet the eligibility criteria to participate in the study based on medical records review. Patient inclusion will end when the planned number of patients is reached. The start date will be the date of the first data collection, i.e., the date from data on the first patient is recorded in the database, and the end of study will be the date from which the analytical set is completely available. The study period will last from Q1 2019 to Q4 2019, with a recruitment period of 7 months.

Study Population:

Criteria for inclusion: Patients will be included in the study if all of the following criteria are met:

1. Age≥ 18 years old
2. Stage IIIC unresectable or stage IV melanoma with BRAF V600 mutation
3. Treatment with at least one dose of dabrafenib plus trametinib, or with dabrafenib monotherapy due to clinician decision (safety, contraindications, etc.) at one of the participating study sites. Patients treated in a compassionate use program are eligible following local regulation.
4. Written informed consent following local regulation (if the patient is alive). If the effort to obtain the informed consent is beyond that is reasonable and feasible, then Ethics Independent Committees (EICs) approval must be obtained (as established in local the regulation Orden SAS 3470/2009).
5. Available medical records

Criteria for exclusion**:** Patients are excluded from participating in this study if one or more of the following criteria are met:

1. Patients treated with dabrafenib monotherapy before trametinib was available (June 2013).

7.3 Variables

Safety measures and endpoints are as follows, and should be provided in the analysis for patients <75 y.o. and ≥ 75 y.o. (primary endpoint) separately:

- occurrence and intensity (grade CTC-AE v4.03) of adverse events
- dose delays, dose adjustments, or treatment discontinuation for the management of adverse events.

Secondary efficacy measures and endpoints are as follows, and should be provided in the analysis for patients <75 y.o. and ≥ 75 y.o.:

- Response rate by RECIST (v1.1)
- Progression-free survival (PFS), defined as the time from the initiation of combination therapy with combined dabrafenib and trametinib or dabrafenib monotherapy to date of first document tumor progression (by RECIST v1.1) or death due to any cause, whichever occurs first.
- Overall survival (OS), defined as the time from the initiation of combination therapy with combined dabrafenib and trametinib or dabrafenib as monotherapy to the date of death due to any cause.

In addition, the following data will be captured and should be used to describe:

Patient demographics and clinical characteristics: age, sex, stage of disease based on AJCC 7th edition, metastatic disease including the presence of brain metastasis, comorbidities, concomitant medications, ECOG performance status and LDH. Comorbidities, concomitant medication, performance status and LDH should had been captured before treatment initiation (with dabrafenib monotherapy or combined with trametinib) or in the first 30 days after treatment initiation; otherwise, it will considered as missing data. The other variables included should be captured at the closest assessment to the initiation of the treatment.

Real-world management: line of treatment, start/end dates of treatment, duration of treatment, initial doses of dabrafenib and trametinib, dose intensity, dose delays, dose adjustments and treatment discontinuation for reasons other than safety, including disease progression.

7.4 Data sources

As this is a non-interventional study, with secondary use of data, data sources might include medical records or any other documentation performed as part of normal clinical practice, where all the events of interest have already happened.

For all variable of interest in this study, data sources will be the patients' medical records.

7.5 Study size/power calculation

The focus is essentially on those patients aged 75 years or older. According to previous studies, which did not considered age as a restriction, estimated that approximately 20% of the included patients would turn out to be ≥75 years. Based on these, in order to obtain 41 patients ≥75 years, it would be necessary to include a total of 205 patients in the study. Sample size rationale is presented below:

Among the points included in the main objective, grade ≥3 adverse effect rates will be prioritized for the calculation of the sample size. Previous data highlighted that 25% (Martin Algarra et al., 2017) of unselected patients will have grade ≥3 side effects, and 29% will need a dose reduction (Martin Algarra et al., 2017). Based on these values, we estimate a rate of 27% as the average of the two figures.

Considering a rate of 27%, a precision of ±14%, in a two-sided analysis, and an alpha risk of 0.05, it will be necessary to include 41 valid cases. Estimating a percentage of losses (e.g.

incomplete or incongruent data, etc.) not higher than 5%, a total sample size of 205 patients should be recruited.

7.6 Data management

The data collection system for this study uses electronic data capture (EDC). The designated investigator staff will enter the data required by the protocol into the electronic Case Report Forms (eCRF). The data received using the e-Clinical methodology will be submitted to the appropriate work procedures to comply with 21 CFR Part 11 requirements, which ensures that data received via electronic transmission are as valid as the originals received on paper. This regulation establishes the rules for the use of electronic data and defines the requirements of all the systems for collection, storage, maintenance and security of the data. Automatic validation programs check for data discrepancies in the eCRFs and by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff.

Designated investigator site staff will not be given access to the EDC system until they have been trained. The Principal Investigator is responsible for assuring that the data entered into the eCRF is complete, accurate, and that entry is performed in a timely manner.

7.7 Data analysis

All analyses will be performed by the designated CRO [redacted]

This study is descriptive in nature and no formal hypotheses will be tested. The first step in the evaluation of the data will be to use standard exploratory and descriptive analyses to gain and understanding of the qualitative and quantitative nature of the data collected and of the characteristics of the sample studied.

Once the study has been completed and the analytical dataset is completely available, the database will be closed and statistical analysis will be performed. The proposed methods for statistical analysis presented below are a summary of the methods to be used on the data collected to answer the study objectives. However, the main statistical features will be described in more detail in the study analysis plan. This plan may be completed during the progress of the study and it may be necessary to incorporate corrections if unusual features are detected in the data during the analyses.

All patients meeting the selection criteria will be included in the analysis, and a list will be given of the patients removed from the analysis, as well as the reason for their removal. All data collected and endpoints will be summarized using descriptive statistics in addition to statistical modeling. Absolute and relative frequency distributions of qualitative variables will be presented, as well as the measures of central tendency and dispersion (mean, standard deviation, median, minimum and maximum values) of quantitative ones. Ninety-five percent (95%) confidence intervals (CI) will be presented for the main quantitative variables of results associated with the primary objective and the main secondary variables. Free-text answers will be converted posteriori into appropriate coding schemes and will be analyzed using frequency scales.

Missing data will not be imputed and will be left as lost. No subgroup analyses will be defined a priori.

Analysis will be performed using the SPSS software. When an inferential analysis is required, parametric tests will be used for continuous variables and nonparametric tests in the case of ordinal or categorical or nonparametric variables. All hypothesis tests will be two-sided and with a significance level of 0.05. For variables not fitting a normal (or parametric) distribution, the Mann-Whitney test (for unpaired data) and the Wilcoxon test (paired data) will be used. Contingency tables and the comparison of proportions and/or frequency distributions will be analyzed using the chi-square test (or Fischer's exact test when appropriate) will be used.

The main measures and endpoints for the study objectives are described below:

Safety Analysis:

The safety of dabrafenib monotherapy or combined with trametinib, will be assessed by analyzing the occurrence and intensity of the adverse events (grade CTCAE) and the following additional safety variables:

- dose delays and dose adjustments for safety reasons and
- discontinuations of treatment for safety reasons.

For continuous variables, descriptive statistics (n, mean, and standard deviation, median, minimum and maximum) will be provided. For categorical variables, patient counts and percentages will be provided with categories for missing data presented if necessary.

Efficacy Analysis:

- Overall Survival, defined as the time from the initiation of combined dabrafenib and trametinib or dabrafenib as monotherapy to the date of death due to any cause, will be calculated using Kaplan-Meier (KM) estimates. The KM graph will show the median OS time and the 95%CI will indicate the number of events and patients censored. Patients that had not died will be censored at last known date alive.
- Progression-Free Survival, defined as the time from the initiation of combined dabrafenib and trametinib or dabrafenib as monotherapy to the date of first document tumor progression (by RECIST v1.1) or death to any cause, whichever occurs first, will be calculated using KM method. The KM graph will show the median PFS and the 95%CI the number of events and patients censored. Patients who did not progress or die will be censored on the date of their last evaluable tumor assessment.
- The Response Rate (by RECIST v1.1) will be shown by their frequency and percentage distribution along with the 95%CI.

Other secondary objectives:

- Patient demographic and clinical characteristics will be summarized using descriptive statistics. For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be provided. For categorical ones, patient counts and percentages will be provided. Categories for missing data will be presented if necessary. The variable performance status may be captured as Karnofsky Performance Score or as ECOG. The statuses recorded as Karnofsky will be recoded to ECOG scores.

- Real-world management of treatment, will be also descriptive and summarized using descriptive statistics. For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be provided. For categorical ones, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

- To determine the clinical variables influencing on the initial-dose decision and safety multiple linear regression and logistic regression models will be used, respectively.

- The differences in OS and PFS depending on the age and dose density will be identified by the Logrank test; differences in response as regards the age and dose density will be explored by the Chi-squared test.

7.8 Quality control

The sponsor (or its representatives) will review the data entered by investigational staff for completeness and accuracy. Electronic data clarification requests (queries) stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

At the conclusion of the study the occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis

The data generated may be also reviewed by competent health authorities and the Ethics Committees (EC) of each site, as appropriate. Therefore, the investigator and the site will ensure the EC and the competent authorities the access to the study documents.

7.9 Limitations of the research methods

This is a real-world research having the inherent limitations of observational studies, whose data are generated from experience with routine medical care and systematically recorded in medical records.

The target population of the study is the population of patients with metastatic or unresectable BRAF V600 melanoma treated with dabrafenib or combination with trametinib, in the real-life setting in Spain. Sample representativeness may be compromised by selection and information biases and also by site feasibilities in the use of dabrafenib and trametinib in elderly patients that does not follow the standard of care in all melanoma patients.

Information bias refers to non-existing information or inaccurate assessment of the outcome which may impact on the study results and estimates; to minimize this risk of bias, unavailable data/assessments will be stated in the CRF as not available and be left as missing in the statistical analysis. It is expected, however, that most data of interest in this study will be registered in medical records as they are part of the routine clinic follow-up of the patients.

Selection bias may produce factitious associations if the study population does not reflect the population of interest. For this, patients to be included comprise a heterogeneous population barely selected, with the only inclusion criteria of having received at least one dose of

dabrafenib or combination with trametinib. This inclusion criteria, however, could take physicians to include a high proportion of patients aged 75 years or older because is the standard of care in their centers but not in all melanoma patients. For this, the site selection process will ensure that the participant sites have a proportion of elderly patients treated with dabrafenib and trametinib of 15-40%. Candidates centers will have to have treated more than 12 patients with combined dabrafenib and trametinib.

8 Protection of human subjects

The study sponsor and investigators should ensure the confidentiality of the patients' data and the compliance with Personal Data Protection Act 15/1999, of 13 December, and the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council, of 27 April 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. For this purpose, the personal information of the patients participating will always be processed using a code (i.e., pseudonymized) so that only the Investigator will know their real identify, but also so that no personal data is included in the study data sets that are transmitted to promotor (or third parties), and in no study document or material will patient be identified.

The information recorded will be encrypted for its transfer to the study database. In addition, daily, weekly and monthly backup copies are made of all internal, external and cloud servers. All servers have anti-virus protection, firewalls, controlled accesses, continuous surveillance, alarms, and other pertinent security measures, to ensure your information is protected against attacks and accidental losses.

Regarding the eCRF, each investigator will be given a sealed document with a user name and a password of between 4 to 6 digits. These codes will be considered confidential and nontransferable and are subject to the same confidentiality requirements as the rest of the documents, including the protocol. The investigators are responsible for keeping their passwords secret and not disclosing them to third parties. The study sponsor and its representatives will have access codes permitting only read-only access to eCRF, but at no time will they be able to modify the information entered by the investigators.

The study database and CRF will be coded and protected from nonpermitted uses by persons unrelated to the research and, therefore, will be considered strictly confidential and will not be disclosed to third parties. However, the data generated by the study must be available for inspection upon request by representatives of the national and local health authorities, monitors of the marketing authorization holder, representatives and collaborators of the sponsor, and the EC of each study site, as appropriate.

Ethical conduct of the study

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016) (Public Policy Committee, 2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al., 2007), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (EMA, 2016).

Subject information and consent:

Each patient who is invited to participate in the study (except if dead, or lost to follow-up in which case the efforts to get the consent would exceed what is reasonable and possible) will be given an information sheet in which the study objectives, methods, planned duration, number of participating patients, the expected benefits, and potential risks will be explained in detail. This document will be written with a vocabulary that allows its content to be completely readable and understandable for the patient. Patients will also be explained that they are free to refuse to participate in the study and to withdraw from the study at any time without it affecting their future treatment and medical care.

The willingness of the patient to participate in the study will be documented in writing in a consent form. The patient (or legal representative, when the patient is incapable of making decisions or his/her physical or mental state does not allow him/her to take charge of his/her situation), or an impartial witness (if the patient or his/her legal representatives cannot read) will sign the informed consent form indicating the date of signature. Each investigator will keep the original consent documents and give a copy to the patients. In the case of deceased patients, the IRB/IEC may waive the need for consent. Patients may revoke at any time their consent to continue participating in the study and to use their data in the analysis.

Independent Ethics Committee (IEC)/ Institutional Review Board (IRB)

The final protocol, any amendments, informed consent and other relevant supporting information will be reviewed and approved by an Institutional Review Board(s) (IRB and/or Independent Ethics Committees (IEC) for each site participating in the study.

9 Management and reporting of adverse events/adverse reactions

As this is a study based on secondary use of data, safety monitoring and safety reporting, where there is a safety relevant result, is provided on an aggregate level only; no reporting on an individual case level is required. In studies based on secondary use of data with a safety relevant result, reports of adverse events/adverse reactions should be summarized in the study report, i.e. the overall association between an exposure and an outcome. Relevant findings from the study report will be included in the periodic aggregated regulatory reports submitted to Health Authorities.

10 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

For applicable non-interventional PASS (in the EU or mandated by an EU Health Authority outside the EU), the final manuscript will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within two weeks after first acceptance for publication.

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12 Annexes

12.1 Annex 1 – List of stand-alone documents

None

12.2 Annex 2 – ENCePP checklist for study protocols

Pending, it will be updated after the study register in EU PAS register.