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Tafinlar/Mekinist

Non-Interventional Study Final Report

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

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1 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

Version 1, 17/07/2020

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Keywords

Melanoma, Dabrafenib, Trametinib, Elderly, Aged, Unresectable

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

The study population have been 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).

Patients have been eligible for study participation as defined by following inclusion and exclusion criteria:

Inclusion criteria

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.

Exclusion criteria

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

Subjects and study size, including dropouts

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 this, 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.

Variables and data sources

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.

For all variables of interest, data sources have been the patients' medical records.

Statistical methods

- Patient demographic and clinical characteristics are summarized using descriptive statistics. For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) are provided. For categorical ones, patient counts and percentages are provided. Categories for missing data are presented if necessary. The variable performance status may be captured as Karnofsky Performance Score or as ECOG. The statuses recorded as Karnofsky have been recoded to ECOG scores.
- Real-world management of treatment, are also descriptive and summarized using descriptive statistics. For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) are provided. For categorical ones, patient counts and percentages are provided. Categories for missing data are 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, has been calculated using Kaplan-Meier (KM) estimates. The KM graph shows the median OS time and the 95%CI indicates the number of events and patients censored. Patients that had not died have been 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 documented tumor progression (by RECIST v1.1) or death to any cause, whichever occurs first, has been calculated using KM method. The KM graph shows the median PFS and the 95%CI the number of events and patients censored. Patients who did not progress or die have been censored on the date of their last evaluable tumor assessment.
- The response rate (by RECIST v 1.1) is shown by their frequency and percentage distribution along with their 95%CI.
- The safety of dabrafenib or combination with trametinib has been 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) are provided. For categorical variables, patient counts and percentages are provided with categories for missing data presented if necessary.

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

Results

- Clinical characteristics of elderly melanoma patients treated with Dabrafenib plus Trametinib in Spain are the presence of 3 or more comorbidities (mainly hypertension), 3 or more concomitant medications and having an ECOG status of 0-1. Regarding melanoma status, the majority of the patients had V600E or V600K BRAF-mutants melanoma; IIIc/M1a or M1b disease stage; without CNS metastases; and less than 3 disease sites.
- Real-world management of combined Dabrafenib and Trametinib in the elderly (≥75 years) Spanish population was mainly used in first and second lines-treatment, as well as for patients under 75 years of age.
- Dabrafenib (monotherapy or in combination) and Trametinib initial doses, dose intensity (DI) and relative dose intensity (RDI) were slightly lower in elderly patients

than in patients <75 years. Treatment duration was very similar in the group of patients ≥75 years, compared with younger patients.

- The main reason of elderly patients who discontinued or delayed treatment was progression of disease and appearance of adverse events, respectively.
- Most of the patients reported at least one adverse event regardless age, although the majority were grade ≤3 and there were no adverse events grade 5. The most common adverse events in overall population of the study were pyrexia, asthenia and arthralgia, but in the elderly group of patients most frequent adverse events were asthenia, decreased appetite and diarrhoea.
- Approximately 75% of patients had at least one treatment related adverse event, mainly related with Dabrafenib (in monotherapy or plus Trametinib). But, in the majority of the cases no action was taken with respect to delay, discontinuation or interruption of the treatment. The most common treatment related adverse events were also pyrexia, arthralgia and asthenia.
- Median Overall Survival (OS) of elderly patients (≥75 years) was estimated in 29.1 months (95% CI, 4.6-53.7 months); Progression-free Survival (PFS) in 10.2 months (CI 95% 0-21.4 months); and Duration of Response (DoR) in 10.9 months (CI 95% 2.1-19.7 months). Complete response (CR) was achieved in 31% of elderly patients; partial response (PR) in 31%; and stable disease (SD) in 13.8%, whereas progressive disease (PD) was observed in 3.4% of the patients in the group of ≥75 years.
- Gender (male vs. female) was independently associated with an increased rate of AE grade≥3, while age and stage were independently associated with increased rate of SAEs. In this sense, elderly and M1b or M1c with CNS metastases stage patients have more odds of presenting SAEs. But, M1c without CNS metastases or IIIc+M1a stage patients have less probabilities of presenting SAEs.
- Differences in efficacy among age groups and treatment dose-intensity did not show statistically significance in any of the analyses. In the same way, treatment dose intensity and age were not identified as significant statistically prognostic factors in terms overall survival, progression-free survival or duration of response.

Discussion

The results presented in this study provide a description of the clinical characteristics; melanoma status; Dabrafenib treatment management (in monotherapy or plus Trametinib); and general and treatment-related adverse effects, in real-world clinical practice in Spain.

Data presented here allow a real life practice description. In that sense, the results concerning elderly patients seem to be very similar compared with the management and characteristics of

patients <75 years with the same type of melanoma candidate to the treatment with Dabrafenib monotherapy or plus Trametinib.

It is important to note that no severe adverse events (grades 4 and 5) were observed in the population analyzed and most reported adverse events did not require any specific action or were resolved with usual clinical practice.

Conclusion

Analysis of the real-life management of Dabrafenib treatment (in monotherapy or more Trametinib) in mutated BRAF melanoma indicates that the clinical characteristics of elderly patients are similar to the general population that is a candidate for this treatment. Elderly patients benefit from the treatment with Dabrafenib plus Trametinib in terms of efficacy, without great treatment management modifications with an adequate and manageable safety profile.

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2 List of abbreviations

AE	Adverse Event
AJCC	American Joint Committee of Cancer
BRAF	B-Raf proto-oncogene
CI	Confidence Intervale
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report/Record Form
CTCAE	Common Terminology Criteria of Adverse Events
DI	Dose Intensity
DoR	Duration of Response
EC	Ethic Committee
ECOG	Eastern Cooperative Oncology Group
ERK	Extracellular signal-Regulated Kinase
HR	Hazard Ratio
IC	Informed Consent
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IU	International Units
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
MAPK	Mitogen-Activated Protein Kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	MAPK/ERK Kinase
NIS	Non-Interventional Study
NVS	Novartis
OR	Odds Ratio
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PR	Partial Response
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RWE	Real World Evidence
SAE	Serious Adverse Event
SD	Stable Disease
SD	Standard Deviation

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Contract research organization (CRO) activities:

[redacted]	Study protocol, informed consent (IC) and Patient Information Sheet
	Electronic Case Report Form (eCRF)
	Data management and Statistical Analysis
	Final Study Report

5 Milestones

Table 5-1 Study milestones

Table 5-1: 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 July 2020

6 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 highlight if there is a need to personalize melanoma management based on patient’s characteristics, and also provide more information about the efficacy and safety profile in Spanish elderly population.

7 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

8 Amendments and updates to the protocol

None

9 Research methods

9.1 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 were applied to the patients. The purely retrospective design did 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 was collected by a retrospective review of patients' records where all the events of interest had already happened.

The study included 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). That visit coincided 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 was obtained and eligibility for study entry confirmed, individual medical records at the site of investigator were reviewed and the information of interest retrospectively collected.

For the purposes of our analysis, patients were 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 common population in Spanish consultations that can reach 40% of all patients seen in clinics. The population of patients aged less than 75 years provides the opportunity of

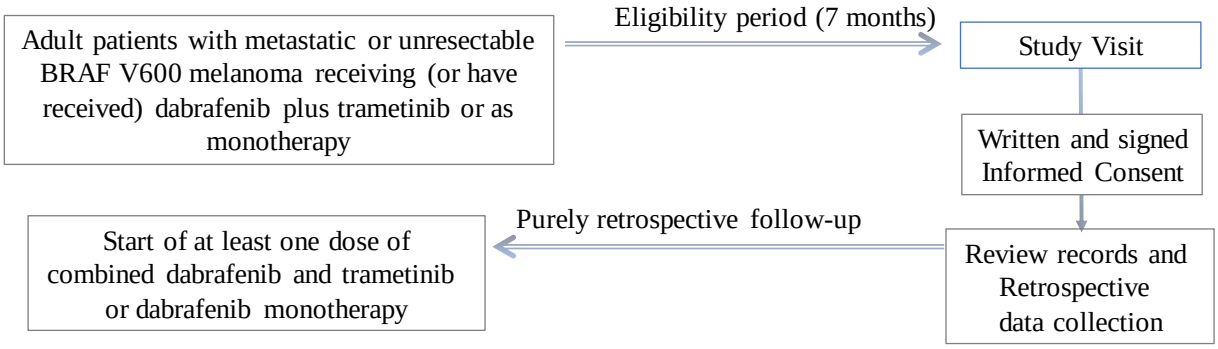
exploring potential differences in terms of safety and efficacy of studied medicinal products between elderly and non-elderly patients.

The primary and secondary endpoints, along with the main measures and other data of interest are detailed in Section 9.4.

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 enables of answering new questions with existing data about managing BRAF V600-mutant melanoma.

Figure 9-1: Study design



9.2 Setting

The study was performed in 10 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 ensured 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 had a proportion of elderly patients (≥75 y.o.) treated with dabrafenib plus trametinib of 15-40%. A higher proportion was not allowed to avoid centers

that mostly prescribe this combination therapy to elderly patients and not as standard of care in melanoma patients.

To avoid screening biases, investigators had 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 ended when the planned number of patients was reached. The study period was from Q1 2019 to Q4 2019, with a recruitment period of 7 months.

9.3 Subjects

Criteria for inclusion: Patients were included in the study if all of the following criteria were 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 were excluded from participating in this study if one or more of the following criteria were met:

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

9.4 Variables

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

- occurrence and intensity (grade CTCAE 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 were provided in the analysis globally and 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 documented 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 were captured and were used to describe:

Patient demographics and clinical characteristics: age, sex, comorbidities and concomitant medications (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 (closest assessment to the initiation of dabrafenib as monotherapy or combined with trametinib), stage of disease based on AJCC 7th edition (closest stage to the initiation of dabrafenib as monotherapy or combined with trametinib, and metastatic disease including the presence of brain metastasis.

9.5 Data sources and measurement

As this is a non-interventional study, with secondary use of data, data sources included 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 were the patients' medical records.

9.6 Bias

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 were stated in the CRF as not available and were left as missing in the statistical analysis. However, most data of interest in this study were 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 comprised 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 ensured that the participant sites have a proportion of elderly patients treated with dabrafenib and trametinib of 15-40%. Candidates centers had to have treated more than 12 patients with combined dabrafenib and trametinib.

9.7 Study size

The focus was essentially on those patients aged 75 years or older. According to previous studies, which did not considered age as a restriction, it was 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 was estimated 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 estimated 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 was 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 was estimated.

9.8 Data transformation

This study is descriptive in nature and no formal hypotheses have been tested. The first step in the evaluation of the data was 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 had been completed and the analytical dataset was completely available, the database was closed and statistical analysis performed. The proposed methods for statistical analysis are presented below as a summary of the methods used on the data collected to answer the study objectives.

9.9 Statistical methods

9.9.1 Main summary measures

All patients meeting the selection criteria were included in the analysis, and a list is given of the patients removed from the analysis, as well as the reason for their removal. All data collected and endpoints are summarized using descriptive statistics in addition to statistical modeling. Absolute and relative frequency distributions of qualitative variables are 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) are presented for the main quantitative variables of results associated with the primary objective and the main secondary variables. Free-text answers were converted posteriori into appropriate coding schemes and analyzed using frequency scales.

Missing data were not imputed and were left as lost. No subgroup analyses was defined a priori.

9.9.2 Main statistical methods

Analysis were performed using the SPSS software. When an inferential analysis was required, parametric tests was used for continuous variables and nonparametric tests in the case of ordinal or categorical or nonparametric variables. All hypothesis tests were 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) were used. Contingency tables and the comparison of proportions and/or frequency distributions were analyzed using the chi-square test (or Fischer's exact test when appropriate).

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

Safety Analysis:

The safety of dabrafenib monotherapy or combined with trametinib, was 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) are provided. For categorical variables, patient counts and percentages are 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, was calculated using Kaplan-Meier (KM) estimates. The KM graph shows the median OS time and the 95%CI indicates the number of events and patients censored. Patients that had not died were 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 documented tumor progression (by RECIST v1.1) or death to any cause, whichever occurs first, was calculated using KM method. The KM graph shows the median PFS and the 95%CI the number of events and patients censored. Patients who did not progress or die were censored on the date of their last evaluable tumor assessment.
- The Response Rate (by RECIST v1.1) is shown by their frequency and percentage distribution along with the 95%CI.

Other secondary objectives:

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

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

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

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

9.9.3 Missing values

Missing data were not imputed and were left as lost. No subgroup analyses was defined a priori.

9.9.4 Sensitivity analyses

None

9.9.5 Amendments to the statistical analysis plan

None

9.10 Quality control

The sponsor (or its representatives) reviewed the data entered by investigational staff for completeness and accuracy. Electronic data clarification requests (queries) stating the nature of the problem and requesting clarification were created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff was 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 was determined. After these actions were completed and the database was declared to be complete and accurate, it was locked and made available for data analysis

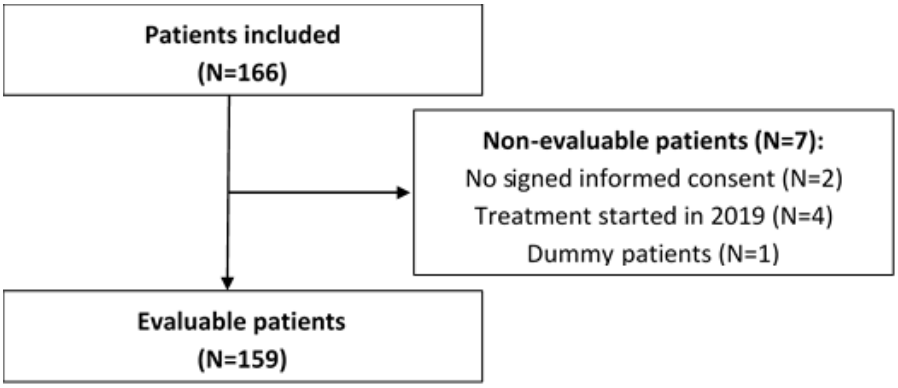
The data generated may be also reviewed by competent health authorities and the Ethics Committees (EC) of each site, as appropriate. Therefore, the investigator and the site ensure the EC and the competent authorities the access to the study documents.

10 Results

10.1 Participants

The total number of evaluable patients has been **159**.

Figure 10-1: Flow-chart study participants



10.2 Descriptive data

The main demographic and descriptive data collected in the study have been included under the heading "Main Results" as part of the main objective.

10.3 Outcome data

The variables have been described, for each age group (<75 vs. ≥75 years) and for the total number of patients: Overall, 159 patients have been evaluated, of which 130 patients (81.8%) were < 75 years and 29 patients (18.2%) were ≥75 years.

10.4 Main results

Primary objectives

Clinical characteristics of elderly melanoma patients treated with Dabrafenib plus Trametinib in Spain.

Data for all patients and separated by age <75 and ≥75 years, are shown in **Table 10-1**. The patients ≥75 years included in the study had a mean age (SD) of 81.3 (4.2) years, with a higher proportion of men (51.7%). Patient mean number of comorbidities was higher in the group of ≥75 years (3.4, SD 1.7) compare with <75 years (1.7, SD 1.8). Most of patients ≥75 years had 3 or more comorbidities (75.9%, 22/29), with hypertension being the most prevalent comorbidity in all the patients, but particularly in the case of patients ≥75 years (69%). The enrolled subjects had a mean of 2.9 concomitant medications (range 0–14) and more than half

of the patients ≥75 years took 3 or more concomitant medications (55.2%, 16/29). Seventeen (68%) subjects ≥75 years had an ECOG performance score of 1, and 5 (20%) had an ECOG score of 0.

Table 10-1: Demographic data and clinical characteristics

		Age (years)		
	All (N=159)	**<75 (N=130)**	**≥75 (N=29)**	***p*-value**
Age, years				
Mean (SD)	60 (15.6)	55.3 (13)	81.3 (4.2)	<0.001
Gender, N (%)				
Female	78 (49.1)	64 (49.2)	14 (48.3)	>0.999
Male	81 (50.9)	66 (50.8)	15 (51.7)	
Number of comorbidities, N (%)				
Mean (SD)	2.1 (1.9)	1.7 (1.8)	3.4 (1.7)	<0.001
0	48 (30.2)	46 (35.4)	2 (6.9)	
1	23 (14.5)	22 (16.9)	1 (3.4)	<0.001
2	28 (17.6)	24 (18.5)	4 (13.8)	
≥3	60 (37.7)	38 (29.2)	22 (75.9)	
Most frequent comorbidities[a], N(%)				
Hypertension	56 (35.2)	36 (27.7)	20 (69.9)	<0.007
Dyslipedemia	32 (20.1)	24 (18.5)	8 (27.6)	>0.999
Mellitus diabetes	18 (11.3)	14 (10.8)	4 (13.8)	>0.999
Number of concomitant medication, N (%)				
Mean (SD)	2.9 (3.1)	2.7 (3)	3.8 (3.4)	0.099
0	48 (30.2)	41 (31.5)	7 (24.1)	
1	22 (13.8)	19 (4.6)	3 (10.3)	0.677
2	19 (11.9)	16 (12.3)	3 (10.3)	
≥3	70 (44)	54 (41.5)	16 (55.2)	
Most frequent concomitant treatments[b], N (%)				
Omeprazole	32 (20.1)	24 (18.5)	8 (27.6)	0.434
Enalapril	16 (10.1)	12 (9.2)	4 (13.8)	0.518
Paracetamol	15 (9.4)	14 (10.8)	1 (3.4)	0.296
Dexamethasone	14 (8.8)	14 (10.8)	0 (0)	0.068
Metformine	14 (8.8)	10 (7.7)	4 (13.8)	0.472
Simvastatine	14 (8.8)	12 (9.2)	2 (6.9)	0.732
ECOG status[c], N (%)				
0	60 (43.5)	55 (48.7)	5 (20)	
1	61 (44.2)	44 (38.9)	17 (68)	
2	11 (8)	8 (7.1)	3 (12)	0.027
3	5 (3.6)	5 (4.4)	0 (0)	
4	1 (0.7)	1 (0.9)	0 (0)	

SD= Standard Deviation; ECOG= Eastern Cooperative Oncology Group

[a]Data were unknown in 49 cases (30.2%).

[b]Data were unknown in 49 cases (30.2%).

[c]Data were unknown in 21 cases (13.2%).

Characteristics of melanoma are shown in **Table 10-2**. The LDH level was elevated in 48.3% (N=14/29) of patients ≥75 years. The tumours of all patients had been tested for BRAF mutation status: 15 (51.7%) of patients ≥75 years had V600E and 8 (27.6%) had V600K *BRAF*-mutants melanoma. Among the enrolled patients ≥75 years, 9 (31%) had stage IIIc/M1a disease, 4 (13.8%) had stage M1b disease, and 16 had stage M1c, of whom 12 (41.4%) without CNS metastases and 4 (13.8%) with CNS metastases. Nineteen (65.5%) patients ≥75 years had less than 3 disease sites, compared with 43.8% (57/130) of patients <75 years.

Table 10-2: Melanoma related data

		Age (years)		
	All (N=159)	**<75 (N=130)**	**≥75 (N=29)**	***p*-value**
LDH (IU/l)[a], N (%)				
>Upper Limit of Normal	76 (48.1)	62 (48.1)	14 (48.3)	>0.999
≤Upper Limit of Normal	82 (51.9)	67 (51.9)	15 (51.7)	
***BRAF* mutation status, N (%)**				
V600[b]	49 (30.8)	43 (33.1)	6 (20.7)	0.001
V600E	96 (60.4)	81 (62.3)	15 (51.7)	
V600K	12 (7.5)	4 (3.1)	8 (27.6)	
V600E+V600K	1 (0.6)	1 (0.8)	0 (0)	
V600M	1 (0.6)	1 (0.8)	0 (0)	
Stage[c], N (%)				
IIIc / M1a	32 (20.1)	23 (17.7)	9 (31.0)	0.362
M1b	25 (15.7)	21 (16.2)	4 (13.8)	
M1c (without CNS metastases)	67 (42.1)	55 (42.3)	12 (41.4)	
M1c (with CNS metastases)	35 (22)	31 (23.8)	4 (13.8)	
Number of disease sites[d], N (%)				
<3	76 (47.8)	57 (43.8)	19 (65.5)	0.041
≥3	83 (52.2)	73 (56.2)	10 (34.5)	

LDH= Lactate dehydrogenese ; IU/l= International Units per Litre; CNS= Central Nervous System

[a]Data was unknown in 1 case (0.6%)

[b]Mutation subtype not specified

[c]Stage based on AJCC 7th edition at the time of initiation of Dabrafenib+Trametinib or Dabrafenib monotherapy

[d]Number of body sites of disease based on unique RECIST target and non-target lesions identified by the investigator, not the number of metastases.

Real-world management and safety of combined Dabrafenib and Trametinib in the elderly (≥75 y.o.) Spanish population.

Dabrafenib (monotherapy or in combination with Trametinib) treatment lines are shown in **Table 10-3**. Most of the patients, independently of their age, had been treated with Dabrafenib in monotherapy or in combination with Trametinib in first and second lines. Among the enrolled patients ≥75 years, 86.2% (25/29) had been treated in first line and 13.8% (4/29) in second line.

Table 10-3: Treatment related data

		Age (years)		
	All (N=160)[a]	**<75 (N=131)[a]**	**≥75 (N=29)**	***p*-value**
Lines by patients, N (%)				
First-line therapy	128 (80.5)	103[a] (78.6)	25 (86.2)	0.923
Second-line therapy	27 (17)	23 (17.6)	4 (13.8)	
Third-line therapy	3 (1.9)	3 (2.3)	0 (0)	
Fourth-line or subsequent therapy	2 (1.3)	2[a] (1.5)	0(0)	
Regimens of treatment, N (%)				
Debrafenib monotherapy	10 (6.3)	5 (3.8)	5 (17.2)	0.018[b]
First line	*6 (60)*	*2 (40)*	*4 (80)*	0.524
Second line	*3 (30)*	*2 (40)*	*1 (20)*	
Third line	*1 (10)*	*1 (20)*	*0 (0)*	
Dabrafenib + Trametinib	150 (93.8)	126 (96.2)	24 (82.8)	0.018[b]
First line	*122 (81.3)*	*101[a] (80.2)*	*21 (87.5)*	0.884
Second line	*24 (16)*	*21 (16.7)*	*3 (12.5)*	
Third line	*2 (1.3)*	*2 (1.6)*	*0 (0)*	
Fourth line	*2 (1.3)*	*2[a] (1.6)*	*0 (0)*	

[a]In a case with "First-line therapy" and "Fourth-line"

[b]Fisher's Exact Test comparing dabrafenib as monotherapy vs. dabrafenib combined with trametinib.

Dabrafenib (monotherapy or in combination) treatment doses are shown in **Table 10-4**. Mean initial dose (SD) for patients ≥75 years was 270 (67.1) mg/day in Dabrafenib monotherapy

group and 283.3 (45.8) mg/day in Dabrafenib in combination plus Trametinib group, slightly lower than in patients <75 years, with initial doses of 300 (0) mg/day and 286 (43.3) mg/day, respectively. The mean initial dose (SD) of Trametinib was 1.64 (0.77) mg/day in patients ≥75 years, compared with 1.92 (0.39) mg/day in patients <75 years. Mean dose intensity (SD) was 247.9 (61.4) mg/day in patients ≥75 years, whereas in the case of patients <75 years reached a mean of 269.9 (53.9) mg/day. Trametinib mean dose intensity was also lower in patients ≥75 years than in patients <75 years, with 1.41 (0.82) mg/day and 1.83 (0.54) mg/day, respectively. Regarding relative dose intensity (RDI), defined as the percentage of dose intensity with respect to the planned dose intensity for each patient and day, patients ≥75 years received a barely lower percentage than patients <75 years, with a median percentage difference of less than 3%.

Table 10-4: Treatment dosage

	Age (years)			
	All	**<75**	**≥75**	
	N=159[a]	**N=130**	**N=29**	***p*-value**
Initial dose (mg/day), Median (Min, Max)				
Dabrafenib monotherapy	300 (150, 300)	300 (300, 300)	300 (150, 300)	0.690
Dabrafenib (in combination)	300 (150, 300)	300 (150, 300)	300 (150, 300)	0.699
Trametinib (in combination)	2 (0[b], 2)	2 (0, 2)	2 (0, 2)	0.001
Dose intensity (DI)(mg/day)				
Dabrafenib monotherapy	**N=10**	**N=5**	**N=5**	
Mean (SD)	265.9 (55.8)	269.9 (53.9)	247.9 (61.4)	
Median	300	300	294.6	0.024
(Min, Max)	(134.5, 302.4)	(134.5, 302.4)	(150, 300)	
Trametinib (in combination)	**N=149**	**N=125**	**N=24**	
Mean (SD)	1.75 (0.62)	1.83 (0.54)	1.41 (0.82)	0.020
Median (Min, Max)	2 (0, 4.91)	2 (0, 4.91)	1.94 (0, 2.17)	
Relative DI (%)[c]				
Dabrafenib monotherapy	**N=10**	**N=5**	**N=5**	
Mean (SD)	88.6 (18.6)	90 (18)	82.6 (20.5)	
Median	100	100	98.2	0.024
(Min, Max)	(44.8, 100.8)	(44.8, 100.8)	(50, 100)	
Trametinib (in combination)	**N=149**	**N=125**	**N=24**	
Mean (SD)	87.6 (31)	91.3 (27.2)	70.7 (41)	
Median	100	100	97.1	0.020
(Min, Max)	(0, 245.4)	(0, 245.4)	(0, 108.6)	

SD= Standard Deviation; DI= Dose Intensity

[a]In two cases with "Continue at the last follow-up of the patient" the date of death is unknown. The last available date has been considered for these patients.

[b]Patients in monotherapy.
[c]Relative DI (%)= 100* DI (mg/day) / PDI (mg/day). [PDI=Planned Dose Intensity (300 mg/day for Dabrafenib)]. An RDI of 100% indicates that the drug was administered at the right dose within the planned timeframe.

Dabrafenib and Trametinib treatment modifications (discontinuation, delay or dose modification) number and patients and the records with the main reasons for them, are shown in the **Table 10-5**. Twenty two (75.9%) and 17 (70.8%) patients ≥75 years discontinued Dabrafenib and Trametinib treatment, respectively. The main reason in both cases was progression disease (68.2%, Dabrafenib and 52.9%, Trametinib). Thirteen (44.8%) patients ≥75 years delayed Dabrafenib treatment, mostly because of some adverse event (81%). This was also the main reason for Trametinib treatment delay in patients ≥75 years (72.2%), which occurred in 50% of patients (12/29). Finally, dose modification was reported for 41.4% and 25% patients ≥75 years (Dabrafenib and Trametinib, respectively), mainly because of appearance of some adverse event (87.5%, Dabrafenib and 83.3%, Trametinib).

Table 10-5: Treatment modifications

	All (N=159)	Age (years) <75 (N=130)	Age (years) ≥75 (N=29)	*p*-value
Drabafenib, N (%)				
Discontinuation[a]	104 (65.4)	82 (63.1)	22 (75.9)	0.205
Cases records:				
Disease progression	*83 (79)*	*68 (81.9)*	*15 (68.2)*	
Adverse Event	*14 (13.3)*	*10 (12)*	*4 (18.2)*	0.247[a]
Other	*8 (7.6)*	*5 (6)*	*3 (13.6)*	
Delay[a]	56 (35.2)	43 (33.1)	13 (44.8)	0.283
Cases records:				
Adverse Event	*65 (80.2)*	*48 (80)*	*17 (81)*	>0.999[a]
Other	*16 (19.8)*	*12 (20)*	*4 (19)*	
Dose modification[a]	41 (25.8)	29 (22.3)	12 (41.4)	0.039
Cases records:				
Adverse Event	*49 (87.5)*	*35 (87.5)*	*14 (87.5)*	>0.999[a]
Other	*7 (12.5)*	*5 (12.5)*	*2 (12.5)*	
Trametinib, N (%)				
Discontinuation[a]	98 (65.8)	81 (64.8)	17 (70.8)	0.644
Cases records:				
Disease progression	*71 (71.7)*	*62 (75.6)*	*9 (52.9)*	
Adverse Event	*19 (19.2)*	*15 (18.3)*	*4 (23.5)*	*0.064[a]*
Other	*9 (9.1)*	*5 (6.1)*	*4 (23.5)*	
Delay[a]	45 (30.2)	33 (26.4)	12 (50)	0.029
Cases records:				
Adverse Event	*47 (77)*	*34 (79.1)*	*13 (72.2)*	*0.739[a]*
Other	*14 (23)*	*9 (20.9)*	*5 (27.8)*	
Dose modification[a]	19 (12.8)	13 (10.4)	6 (25)	0.086
Cases records:				
Adverse Event	*21 (95.5)*	*16 (100)*	*5 (83.3)*	*0.273[a]*
Other	*1 (4.5)*	*0 (0)*	*1 (16.7)*	

[a]N patients with one discontinuation and at least one dose delay or modification.

[b]Fisher's Exact Test comparing main discontinuation, delay or dose modification reasons

Mean treatment duration was slightly longer in the group of patients ≥75 years in all cases, as shown in **Table 10-6**. Mean (SD) was 453.7 (467.6) and 384.1 (352.1) days for Dabrafenib (monotherapy and in combination, respectively), 32 and 12 days longer than in the group of

patients <75 years. In the case of Trametinib, mean duration treatment was very similar, regardless of patient's age.

Table 10-6: Treatment duration

	Age (years)			
	All	**<75**	**≥75**	
	N=159[a]	**N=130**	**N=29**	***p*-value**
Duration of treatment (days)				
Dabrafenib monotherapy	**N=10**	**N=5**	**N=5**	
Mean	427.4	421.5	453.7	0.961
(SD)	(445.1)	(441.6)	(467.6)	
Dabrafenib (in combination)[b]	**N=149**	**N=125**	**N=24**	
Mean	374.4	372.6	384.1	0.928
(SD)	(354.8)	(356.6)	(352.1)	
Trametinib (in combination)	**N=149**	**N=125**	**N=24**	
Mean	357.1	356.9	358.2	0.877
(SD)	(351.4)	(353)	(350.6)	

SD= Standard Deviation

[a]In two cases with "Continue at the last follow-up of the patient" the date of death is unknown. The last available date has been considered for these patients

[b]Duration of treatment (dabrafenib with trametinib) has been calculated from the beginning of dabrafenib from end trametinib.

Secondary objectives

Efficacy in patients ≥75 years

Overall response data are shown in **Table 10-7**. A higher percentage of patients ≥75 years achieved *complete response* (CR) compared to patients <75 years (31% vs. 22.3%). In contrast, a greater percentage of patients under that age reached *partial response* (PR)(31% vs. 41.5%). Data on *stable disease* (SD) were very similar (13.8% vs. 13.1%), although, progressive disease had less impact on patients ≥75 years than on those under that age (3.4% vs. 6.9%).

Table 10-7: Overall response data

	Age (years)			
	All	**<75**	**≥75**	
	N=159	**N=130**	**N=29**	***p*-value**
Best tumour response[a], N (%)				
CR				
N	38[b]	29	9	0.640[c]
% (95% CI)	23.9 (17.5-31.3)	22.3 (15.5-30.4)	31 (15.3-50.8)	
PR				
N	63[b]	54	9	0.640[c]
% (95% CI)	39.6 (32-47.7)	41.5 (33-50.5)	31 (15.3-50.8)	
SD				
N	21[b]	17	4	0.640[c]
% (95% CI)	13.2 (8.4-19.5)	13.1 (7.8-20.1)	13.8 (3.9-31.7)	
PD				
N	10[b]	9	1	0.640[c]
% (95% CI)	6.3 (3.1-11.3)	6.9 (3.2-12.7)	3.4 (0.1-17.8)	

CR= Complete Response; PR= Partial Response; SD= Stable Disease; PD= Progressive Disease; CI= Confidence Interval.

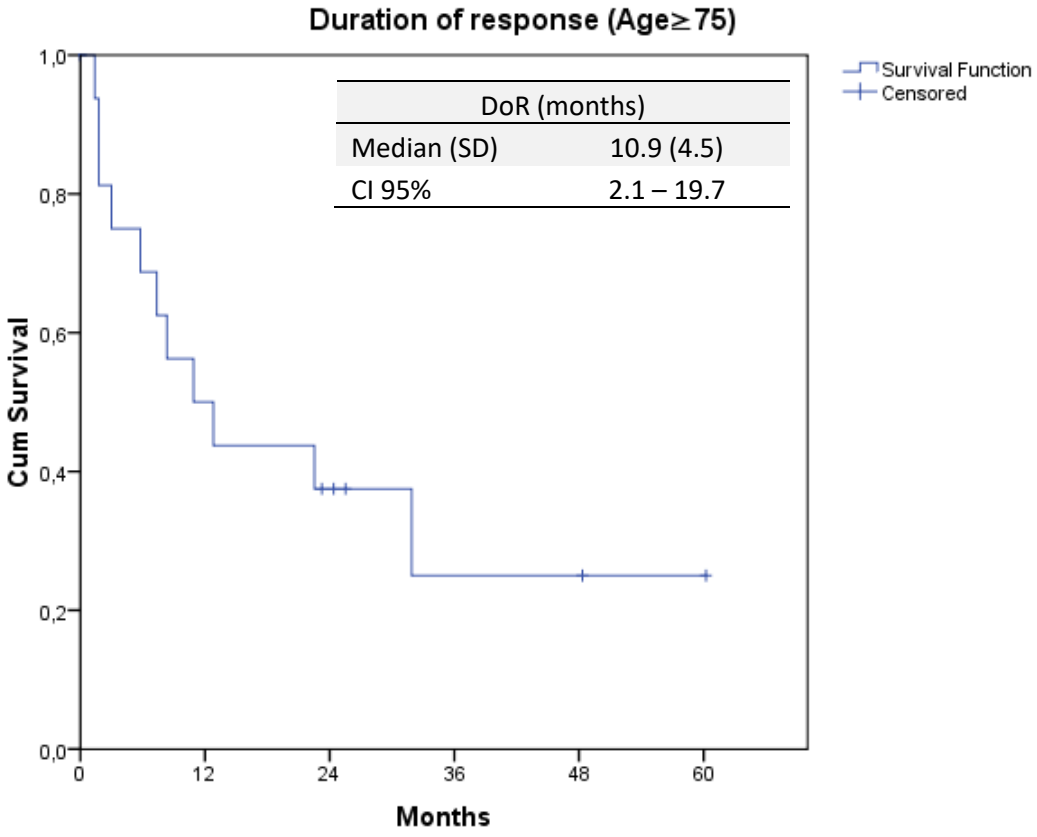
[a]Best tumor response to treatment has been calculated the best response by patient, independently of the treatment line.

[b]Data not evaluable in 2 cases (1.25%).

[c]Fisher's Exact Test comparing best tumour response independently of the treatment line.

Duration of response (DoR) was defined as the time, in months, from first documented evidence of CR or PR until disease progression or death due to any cause among subjects who achieve an overall response. Median DoR and 95%CI, as well as patients censored, are shown in **Figure 10-2**. Patients who did not progress or die have been censored on the date of their last evaluable tumor assessment (see progression date previous section). Median DoR was estimated in 10.9 months (CI 95% 2.1-19.7 months).

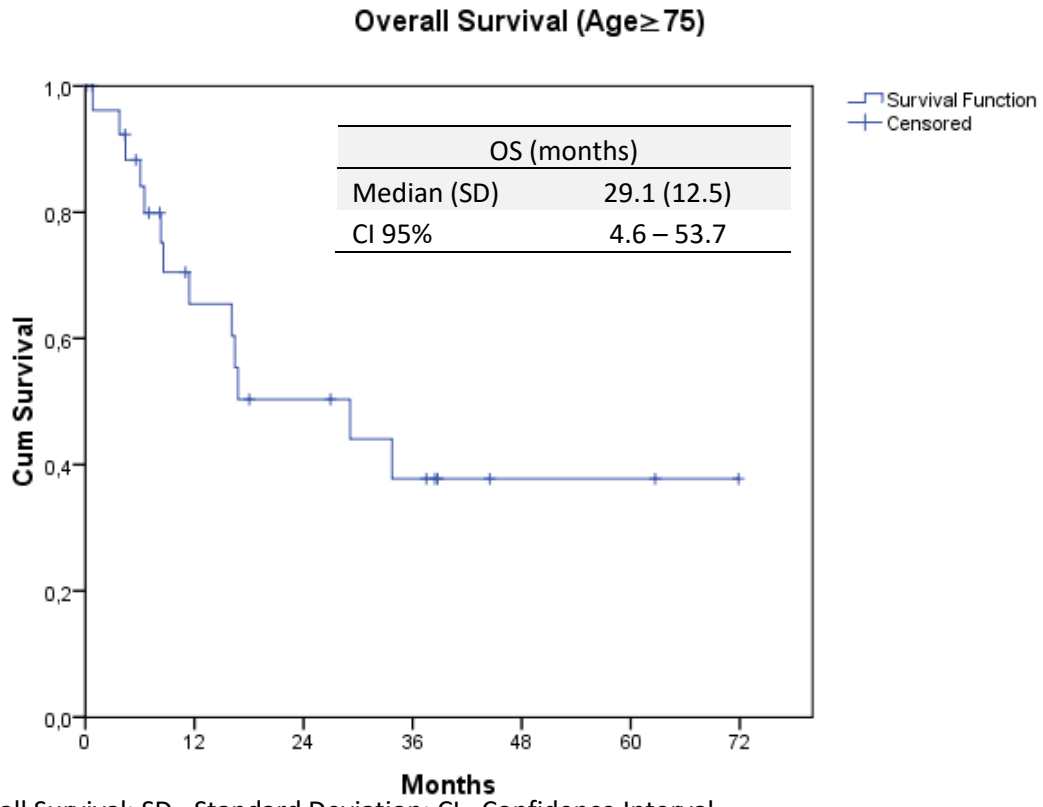
Figure 10-2: Duration of Response (DoR) (AGE ≥75 years)



DoR= Duration of Response; SD= Standard Deviation; CI= Confidence Interval

At the time of this analysis, 13 deaths had occurred and 15 (53.6%) patients that had not died have been censored at last known date alive. In two cases, the cause of death was listed as unknown. These patients have been censored on their last available date. In another patient, the date of death is before the start date of treatment. *Overall survival* (OS), defined as the time, in months, from the initiation of combined Dabrafenib and Trametinib or Dabrafenib as monotherapy to the date of death due to any cause, is shown in **Figure 10-3**. Median OS was estimated in 29.1 months (95% CI, 4.6-53.7 months).

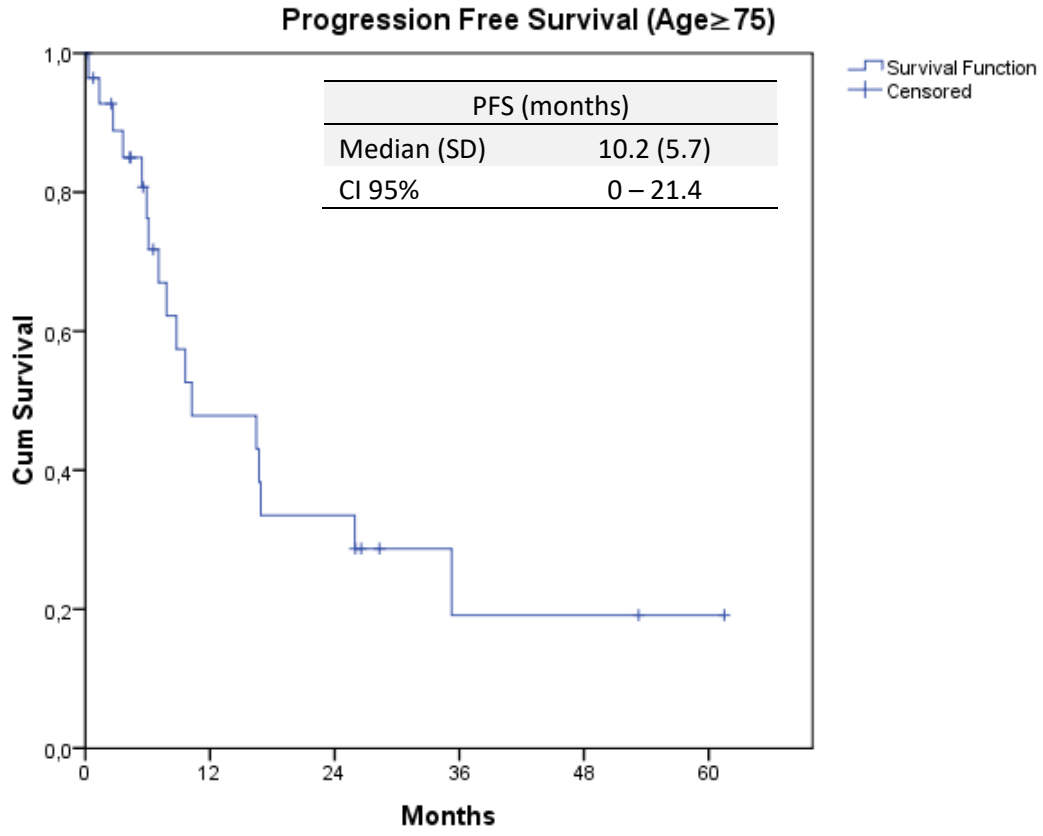
Figure 10-3: Overall Survival (OS) (AGE ≥75 years)



OS= Overall Survival; SD= Standard Deviation; CI= Confidence Interval

Progression-Free Survival (PFS) was defined as the time, in months, from the initiation of combined Dabrafenib and Trametinib or Dabrafenib as monotherapy to the date of first documented tumor progression (by RECIST v1.1) or death to any cause, whichever occurs first. Median PFS and the 95%CI the number of events and patients censored are shown in **Figure 10-4**. Patients who did not progress or die has been censored on the date of their last evaluable tumor assessment. Median PFS was estimated in 10.2 months (CI 95% 0-21.4 months).

Figure 10-4: Progression-Free Survival (PFS) (AGE ≥75 years)

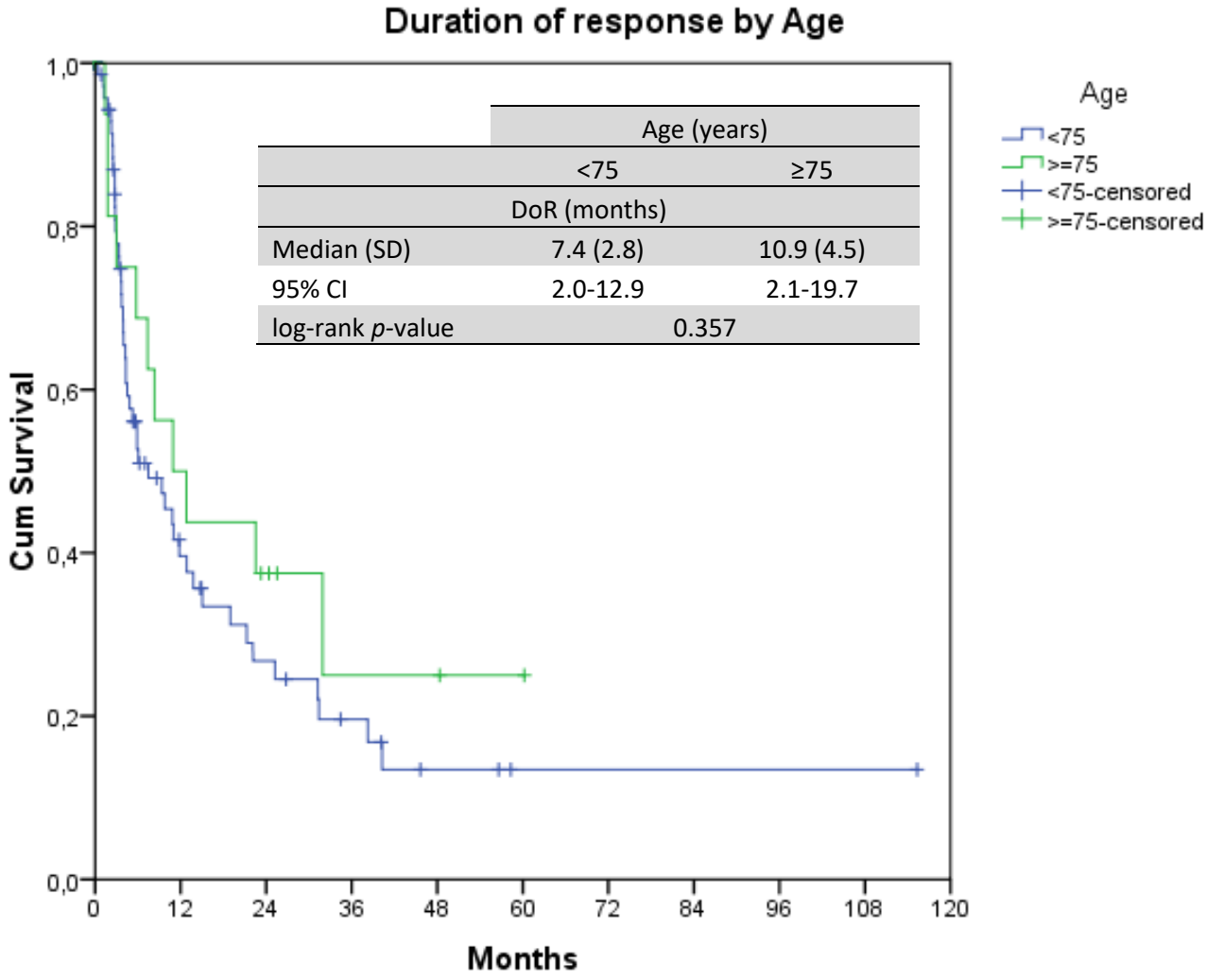


PFS= Progression-free Survival; SD= Standard Deviation; CI= Confidence Interval

Differences in efficacy depending on age and treatment dose-intensity

The Kaplan-Meier results for DoR, OS and PFS comparing subgroups of patients by age (<75 years and ≥75 years) are depicted graphically in **Figures 10-5 to 10-7**, together with a summary of Median (SD), Mean (SD) and 95% CI and log-rank p-value, in each case. Differences among age groups did not show statistically significance in any of the analyses.

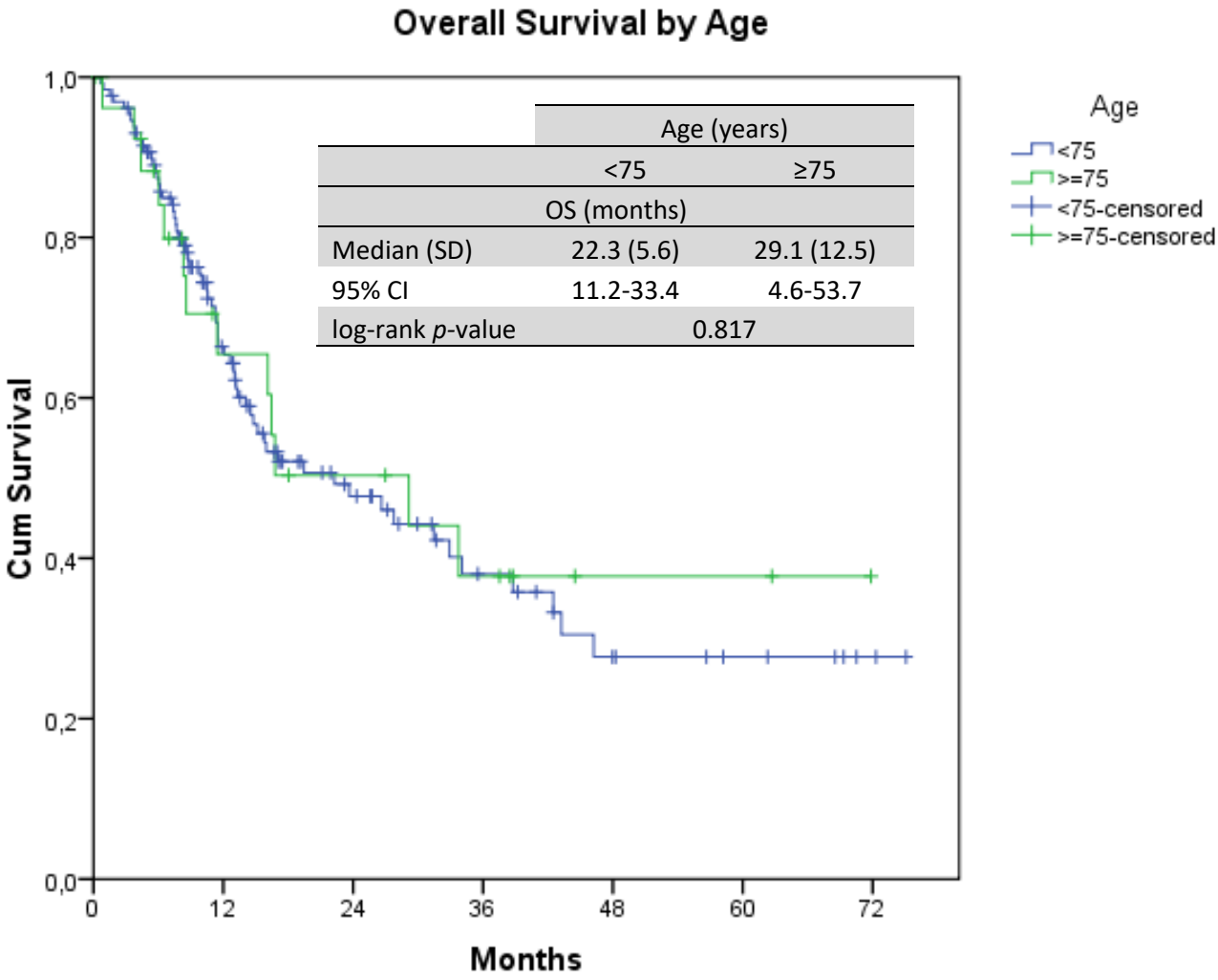
Figure 10-5: Duration of Response (DoR) comparing by age (<75 years and ≥75 years)



	Age (years)	
	<75	≥75
	DoR (months)	
Median (SD)	7.4 (2.8)	10.9 (4.5)
95% CI	2.0-12.9	2.1-19.7
log-rank *p*-value	0.357	

DoR= Duration of Response; SD= Standard Deviation; CI= Confidence Interval

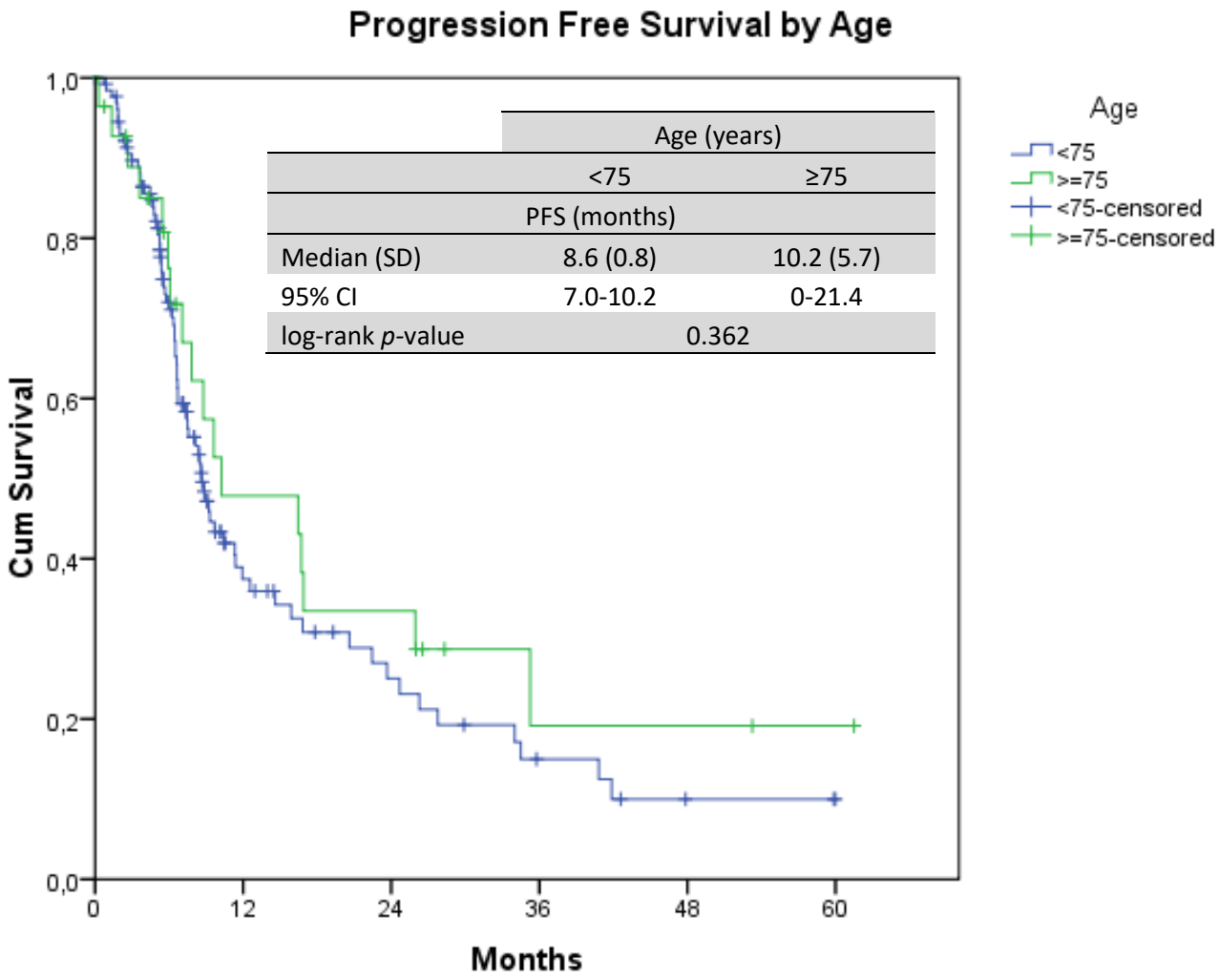
Figure 10-6: Overall Survival (OS) comparing by age (<75 years and ≥75 years)



	Age (years)	
	<75	≥75
	OS (months)	
Median (SD)	22.3 (5.6)	29.1 (12.5)
95% CI	11.2-33.4	4.6-53.7
log-rank *p*-value	0.817	

OS= Overall Survival; SD= Standard Deviation; CI= Confidence Interval

Figure 10-7: Progression-free survival comparing by age (<75 years and ≥75 years)

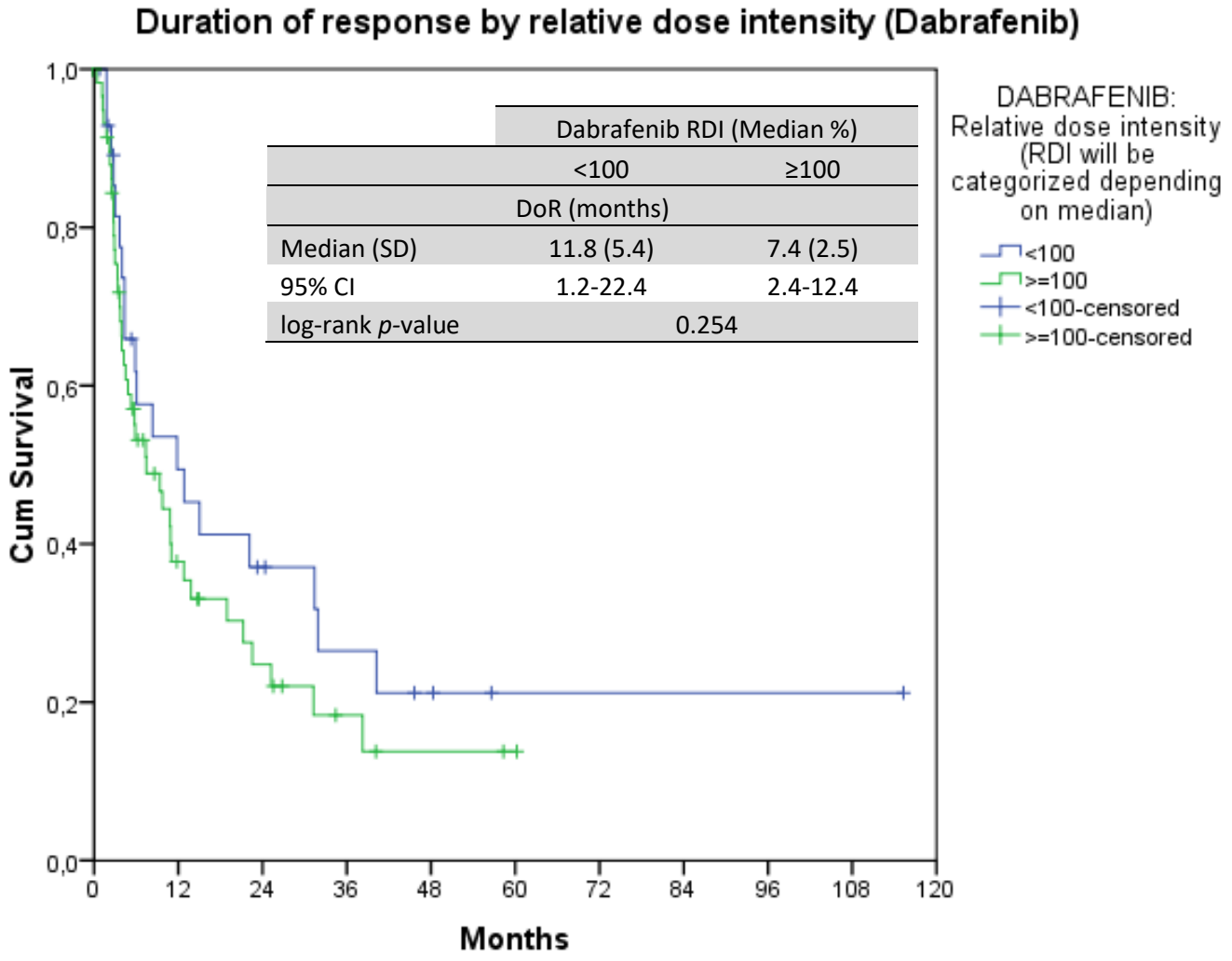


	Age (years)	
	<75	≥75
	PFS (months)	
Median (SD)	8.6 (0.8)	10.2 (5.7)
95% CI	7.0-10.2	0-21.4
log-rank *p*-value	0.362	

PFS= Progression-free Survival; SD= Standard Deviation; CI= Confidence Interval

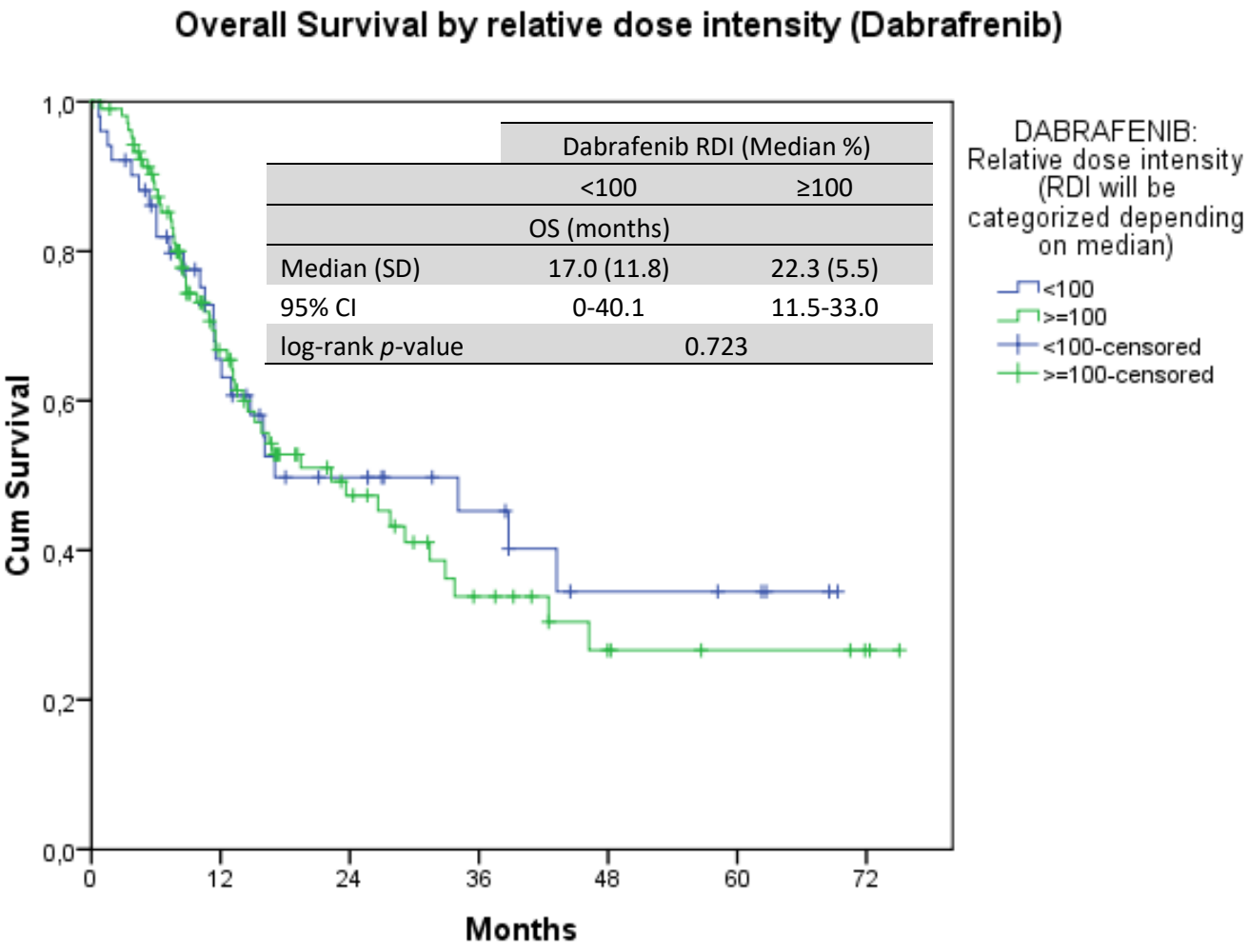
The Kaplan-Meier results for DoR, OS and PFS and comparison between subgroups of patients by Dabrafenib or Trametinib RDI (<100% or ≥100%) did not show statistically significant differences either, as can be observed in **Figures 10-8 to 10-13**.

Figure 10-8: Duration of Response (DoR) comparing by Dabrafenib relative dose intensity (RDI) (<100% and ≥100%)



RDI= Relative Dose Intensity; DoR= Duration of Response; SD= Standard Deviation; CI= Confidence Interval

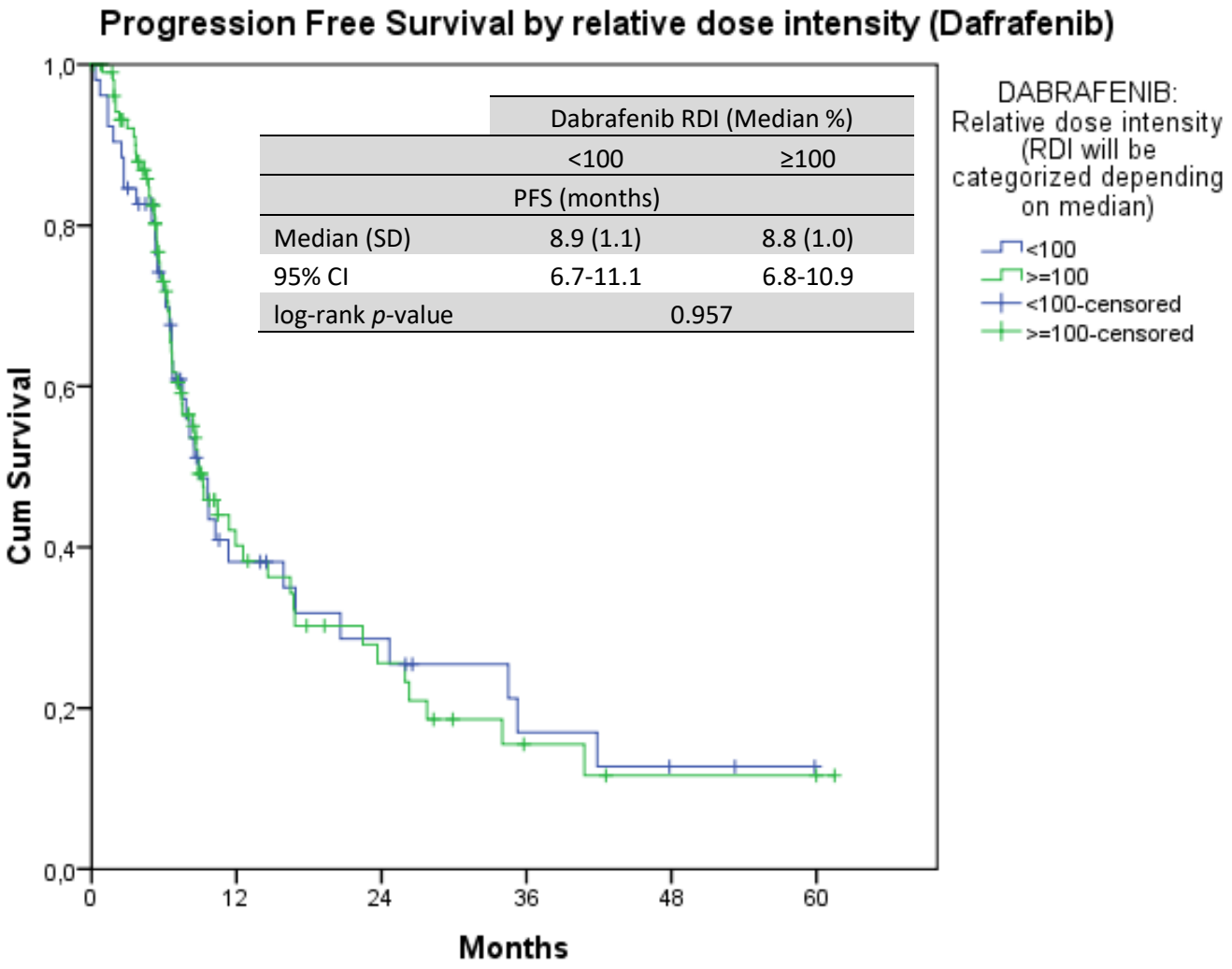
Figure 10-9: Overall Survival (OS) comparing by Dabrafenib relative dose intensity (RDI) (<100% and ≥100%)



	Dabrafenib RDI (Median %)	
	<100	≥100
	OS (months)	
Median (SD)	17.0 (11.8)	22.3 (5.5)
95% CI	0-40.1	11.5-33.0
log-rank *p*-value	0.723	

RDI= Relative Dose Intensity; OS= Overall Survival; SD= Standard Deviation; CI= Confidence Interval

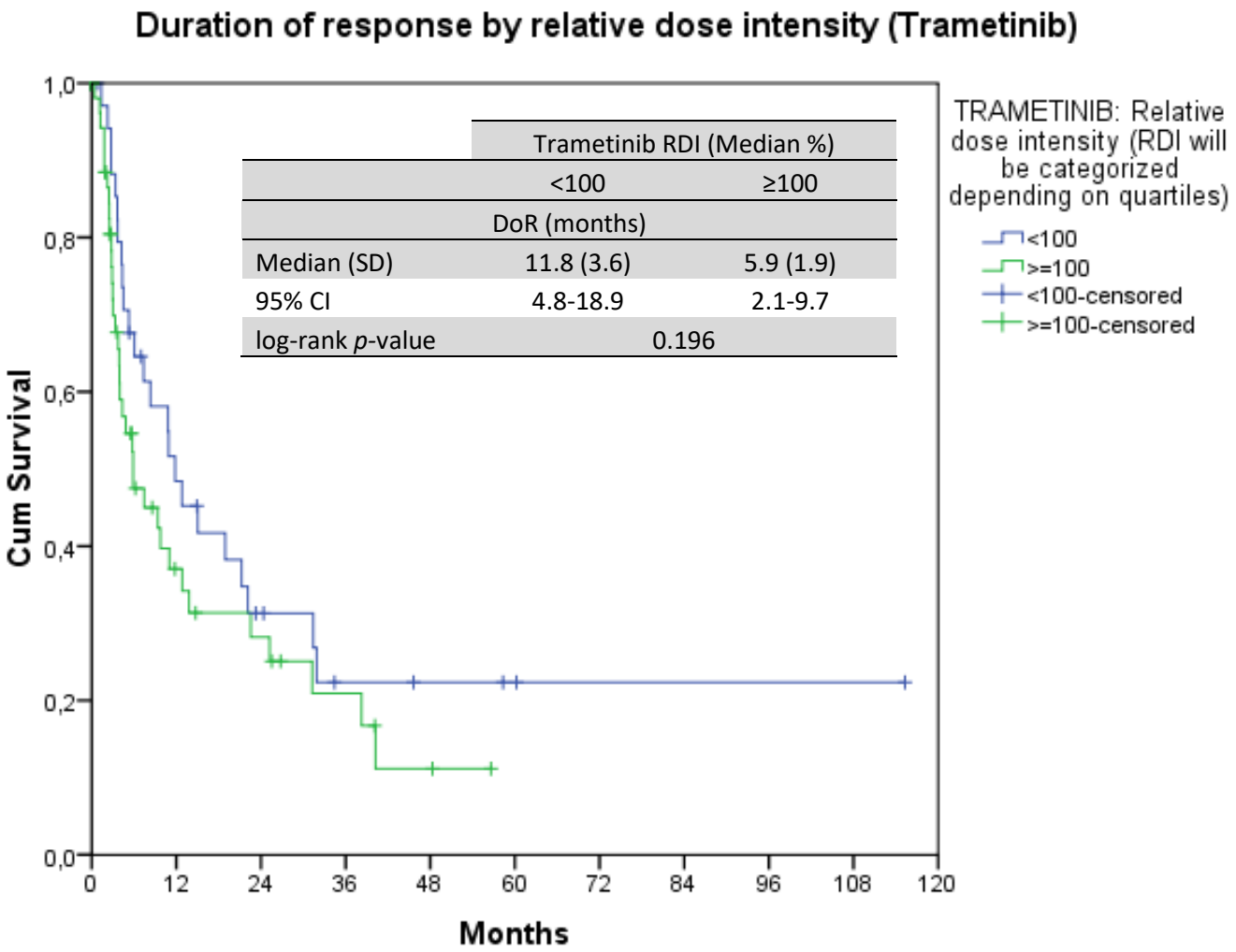
Figure 10-10: Progression-free Survival (PFS) comparing by Dabrafenib relative dose intensity (RDI) (<100% and ≥100%)



	Dabrafenib RDI (Median %)	
	<100	≥100
	PFS (months)	
Median (SD)	8.9 (1.1)	8.8 (1.0)
95% CI	6.7-11.1	6.8-10.9
log-rank *p*-value	0.957	

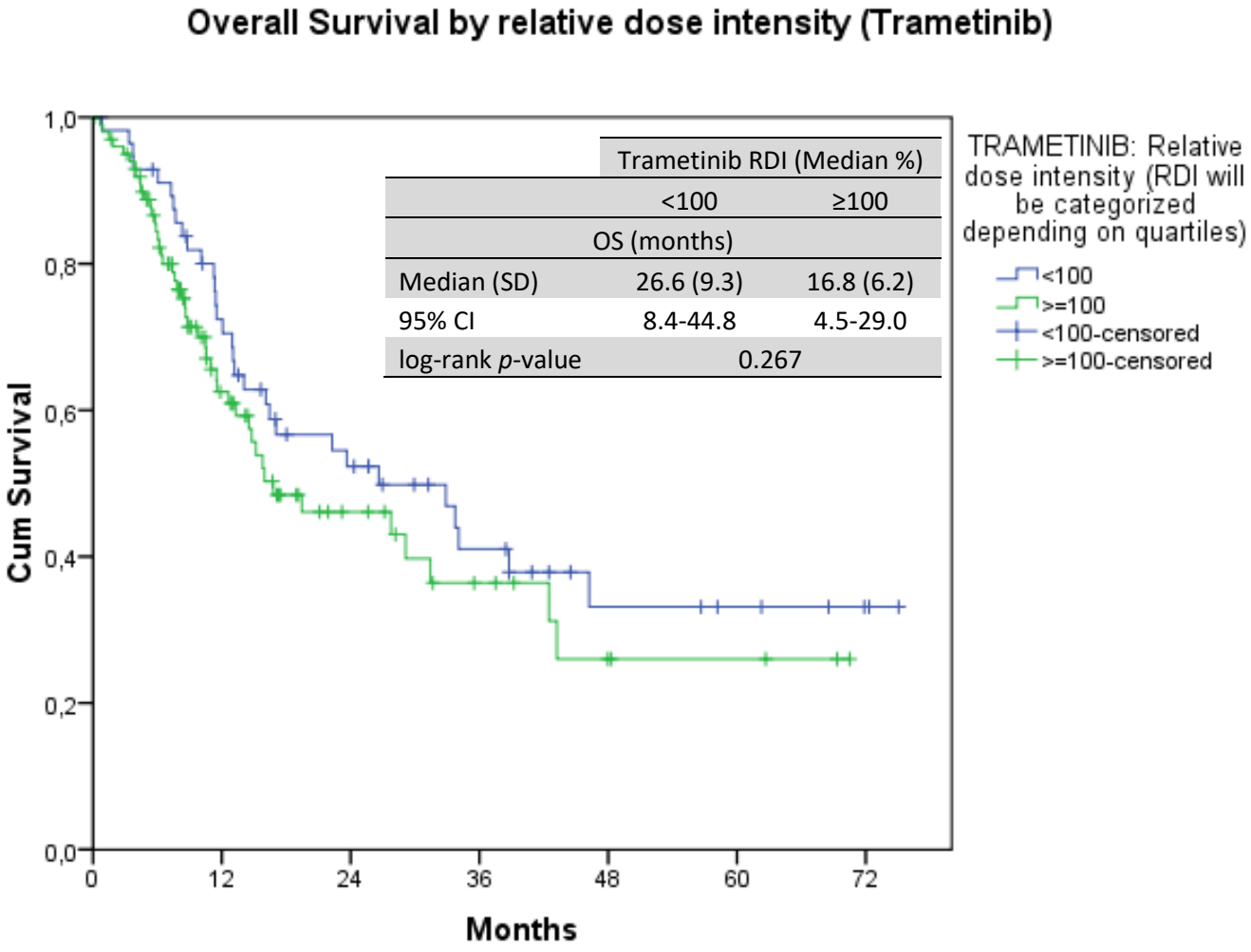
RDI= Relative Dose Intensity; PFS= Progression-free Survival; SD= Standard Deviation; CI= Confidence Interval

Figure 10-11: Duration of Response (DoR) comparing by Trametinib relative dose intensity (RDI) (<100% and ≥100%)



RDI= Relative Dose Intensity; DoR= Duration of Response; SD= Standard Deviation; CI= Confidence Interval

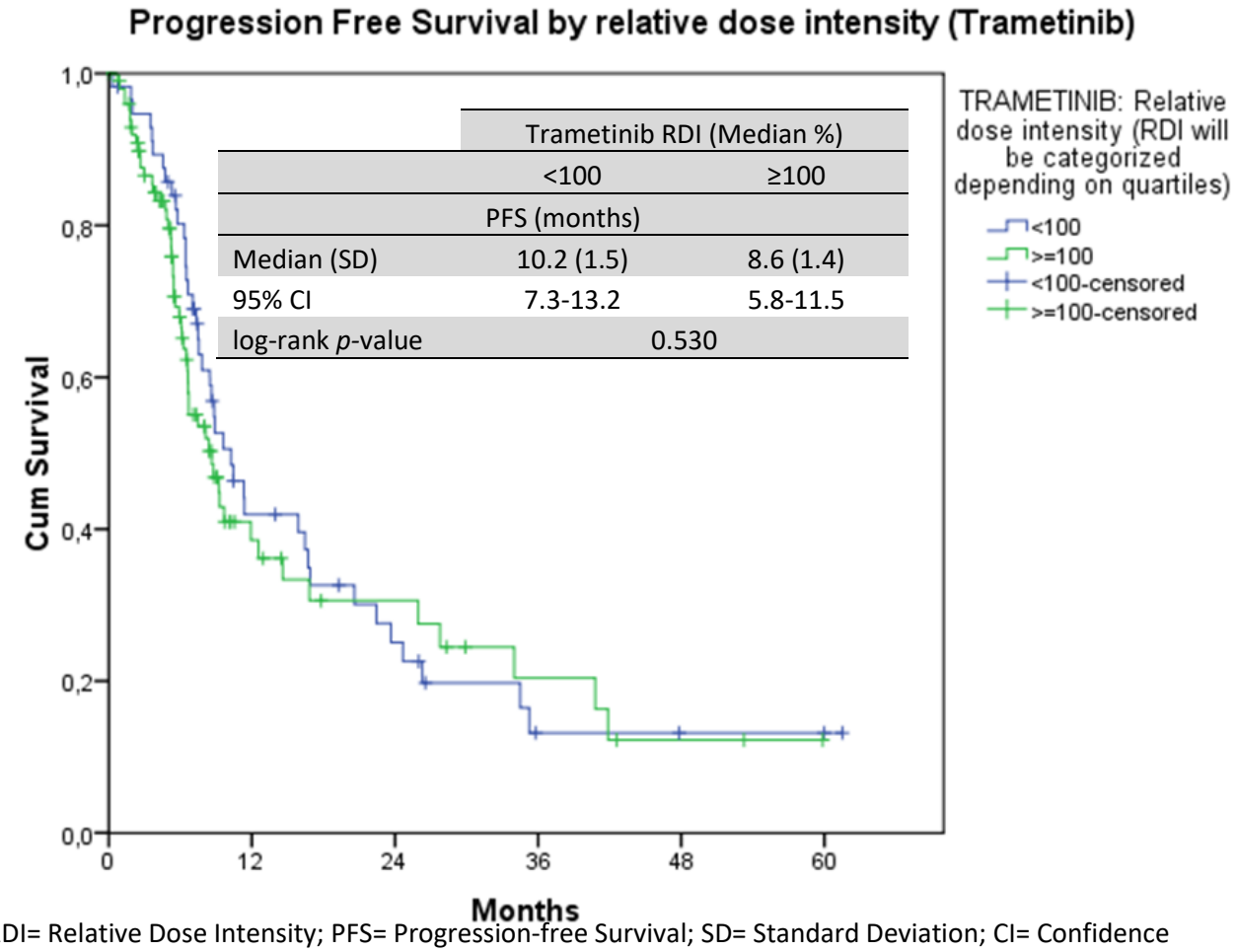
Figure 10-12: Overall survival (OS) comparing by Trametinib relative dose intensity (RDI) (<100% and ≥100%)



	Trametinib RDI (Median %)	
	<100	≥100
	OS (months)	
Median (SD)	26.6 (9.3)	16.8 (6.2)
95% CI	8.4-44.8	4.5-29.0
log-rank *p*-value	0.267	

RDI= Relative Dose Intensity; OS= Overall Survival; SD= Standard Deviation; CI= Confidence Interval

Figure 10-13: Progression-free survival comparing by Trametinib relative dose intensity (RDI) (<100% and ≥100%)



	Trametinib RDI (Median %)	
	<100	≥100
	PFS (months)	
Median (SD)	10.2 (1.5)	8.6 (1.4)
95% CI	7.3-13.2	5.8-11.5
log-rank *p*-value	0.530	

RDI= Relative Dose Intensity; PFS= Progression-free Survival; SD= Standard Deviation; CI= Confidence Interval

Factors associated with initial-dose decision and safety

To describe the clinical variables that influence on the initial-dose decision and safety, we performed a multivariate analysis. Firstly, we analysed the influence of several independent variables on the initial Dabrafenib dose. Bivariate analysis showed that ECOG status; Stage (IIIc+M1a as reference), Heart disease and Renal disease presented a p-value <0.200. However, adjusting all possible models with these variables, the optimal model did not show statistically significant variables.

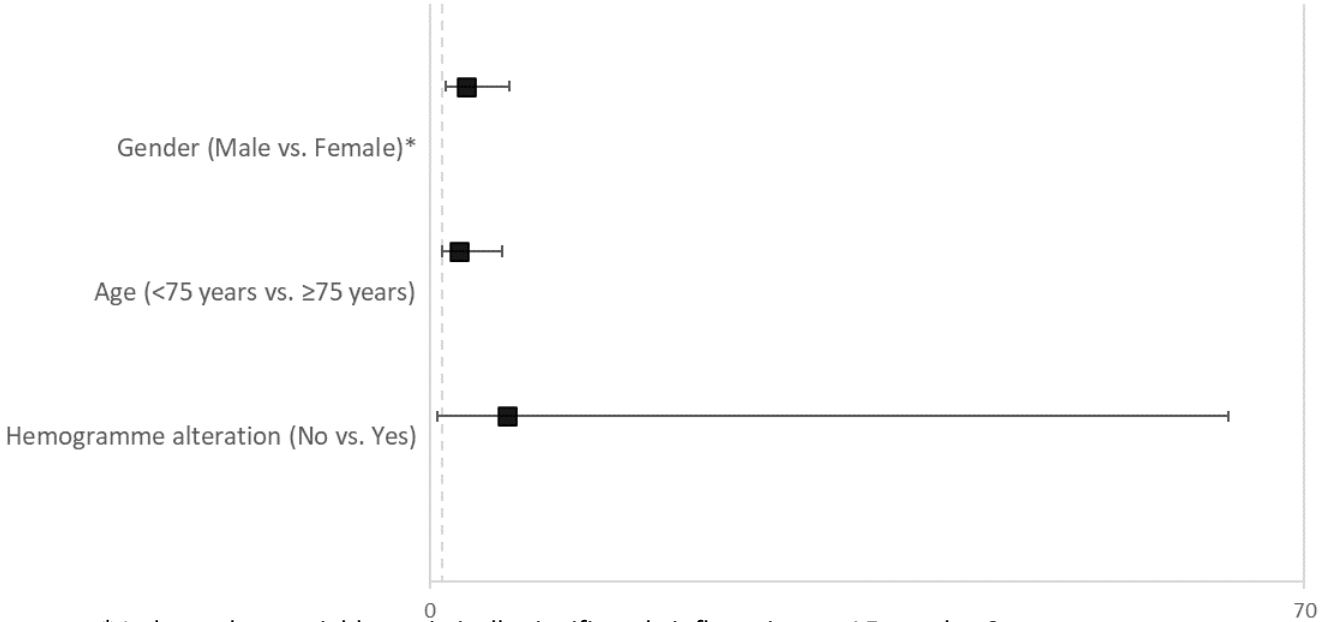
In a second analysis, also including all patients, the variable Age showed a statistically significant impact on initial Trametinib dose (p=0.004). Age (<75 years vs. ≥75 years) was the strongest predictor with b=-0.284, ranging -0.476 to -0.092.

Regarding multivariate analysis of independent variables that influence on safety, we determined which clinical variables could be influencing AEs rate. Bivariate analysis showed only one variable that had a p-value <0.200. Due to this we can assumed that the multivariate model does not fit.

Concerning influence on AE grade ≥3 rate, bivariate analysis showed that independent variables Gender; Age; Stage (IIIc+M1a as reference); ECOG status; Number of comorbidities and Hemogram alteration presented a p-value <0.200. These variables have been included in the multivariate analysis, which optimal model results are shown in **Figure 14**. Gender (males vs. females) (OR, 2.86; 95% CI, 1.29-6.32; p=0.01) was independently associated with an increased rate of AE grade ≥3. According this result, Females have more odds of presenting AEs grade ≥3.

Figure 10-14: Odds Ratios (OR) independent variables influencing on AEs grade ≥3

Variable	OR (95% CI)	p-value
Gender (Male vs. Female)*	2.86 (1.29-6.32)	0.010
Age (<75 years vs. ≥75 years)	2.36 (0.96-5.83)	0.062
Hemogramme alteration (No vs. Yes)	6.17 (0.59-63.93)	0.127

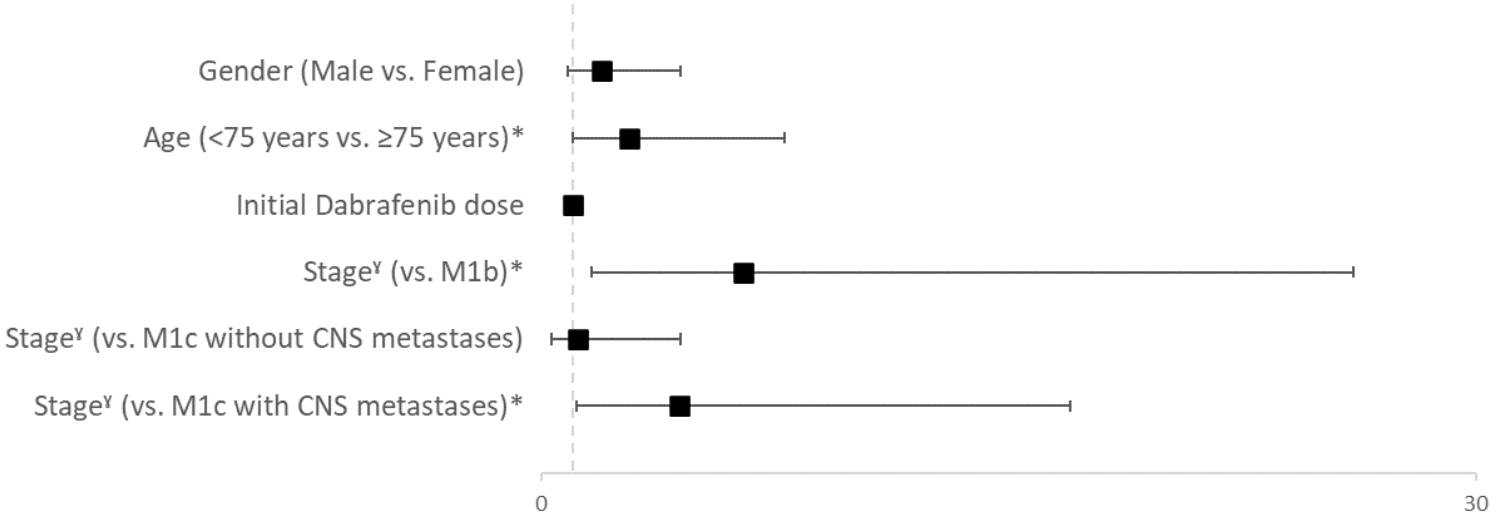


* Independent variable statistically significantly influencing on AEs grade ≥3

Two optimal multivariate analysis models were evaluated regarding independent variables influencing on SAEs rate (No vs. Yes). First model showed that Gender; Age; Stage (IIIc+M1a reference); ECOG Status; Number of comorbidities; Heart disease; Hemogram alteration and Initial Dabrafenib dose variables presented a p-value <0.200. Adjusting these variables included in the multivariate analysis showed an optimal model presented in **Figure 15**. Patients ≥75 years (vs. <75 years), with Stage M1b and Stage M1c with CNS metastases (vs. Stage IIc+M1a), have more odds of presenting SAEs.

Figure 10-15: Odds ratios (OR) independent variables influencing on serious AEs (Model 1)

Variable	OR (95% CI)	p-value
Gender (Male vs. Female)	1.94 (0.84-4.47)	0.121
Age (<75 years vs. ≥75 years)*	2.82 (1.02-7.79)	0.046
Initial Dabrafenib dose	1.01 (1-1,03)	0.140
Stage IIIc+M1a vs. M1b*	6.46 (1.60-26.06)	0,009
Stage IIIc+M1a vs. M1c without CNS metastases	1.19 (0.31-4.48)	0.801
Stage IIIc+M1a vs. M1c with CNS metastases*	4.41 (1.15-16.97)	0.031



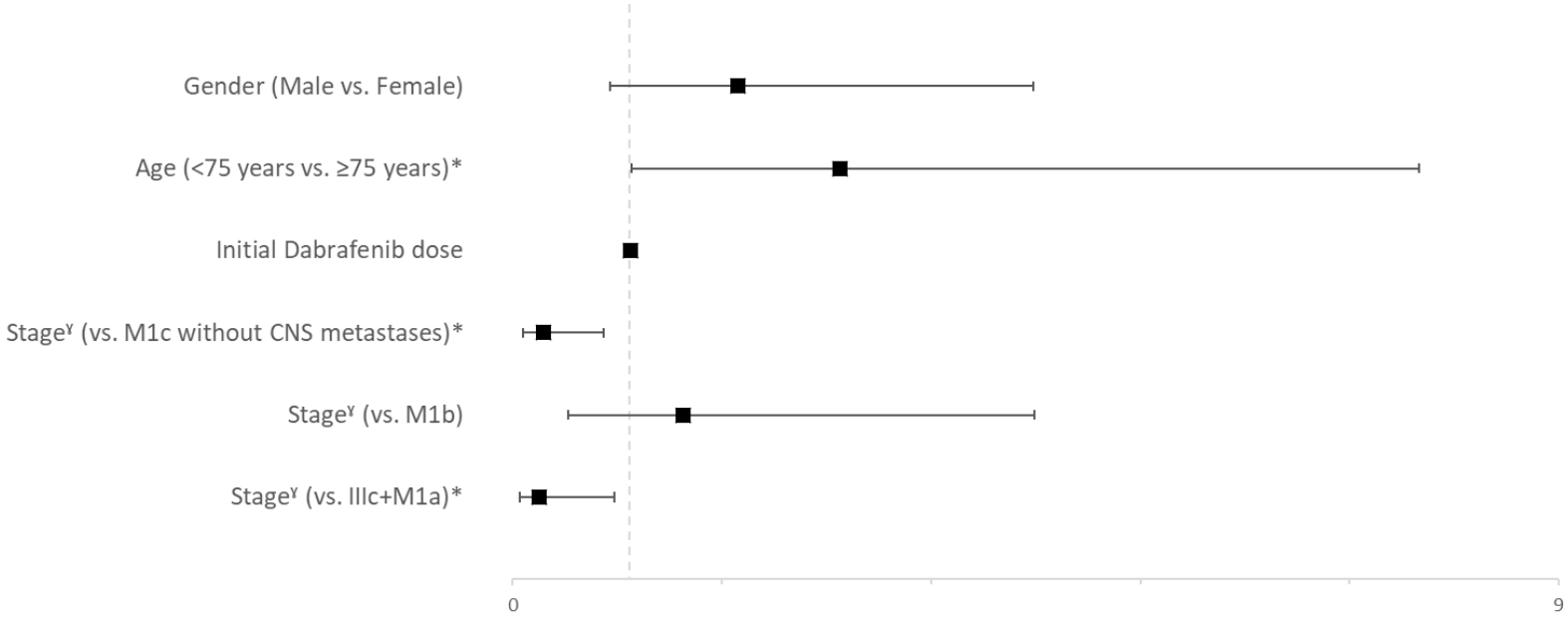
*Independent variables statistically significantly influencing on serious AEs.

ʏStage IIIc+M1a as reference

Second model showed that Gender; Age; Stage (M1c with CNS metastases as reference); ECOG Status; Number of comorbidities; Heart disease; Hemogram alteration and Initial Dabrafenib dose variables presented a p-value <0.200. Adjusting these variables included in the multivariate analysis presented an optimal model showed in **Figure 16**. Patients ≥75 years (vs. <75 years) have more odds of presenting SAE, whereas patients on Stage M1c without CNS metastases or Stage IIc+M1a (vs. Stage M1c with CNS metastases) have less probabilities of presenting SAE.

Figure 10-16: Odds ratios (OR) independent variables influencing on serious AEs (Model 2)

Variable	OR (95% CI)	p-value
Gender (Male vs. Female)	1.94(0.84-4.47)	0.121
Age (<75 years vs. ≥75 years)	2.82 (1.02-7.79)	0.046
Initial Dabrafenib dose	1.01 (1-1,03)	0.140
Stage M1c with CNS metastases vs. M1c without CNS metastases	0.27 (0.09-0.78)	0.016
Stage M1c with CNS metastases vs. M1b	1.46 (0.48-4.48)	0.505
Stage M1c with CNS metastases vs. IIIc+M1a	0.23 (0.06-0.87)	0.031



*Independent variables statistically significantly influencing on serious AEs.

ʏStage M1c with CNS metastases as reference

Independent effect on efficacy of treatment dose intensity and age

The multivariate analysis by Cox regression is shown in **Table 8**, including hazard ratio (HR), 95% CI and p-value. The results did not identify relative treatment dose intensity and age as significant statistically prognostic factors in terms of the time (months) of survival of the patient (OS); the time from the initiation of treatment (combination or Dabrafenib monotherapy) to the date of first documented tumour progression (by RECIST v1.1) or death from any cause (PFS); and from first documented evidence of CR or PR until disease progression or death (DoR).

Table 10-8: Cox regression analysis of treatment (Dabrafenib / Trametinib) relative dose intensity or relative dose intensity and age.

		HR	95% CI	p-value
OS				
RDI	Dabrafenib	1.00	0.99-1.01	0.679
	Trametinib	1.005	1.00-1.01	0.150
RDI and Age (<75 years vs. ≥75 years)	Dabrafenib	1.00	0.99-1.015	0.702
	Age	0.95	0.52-1.74	0.866
	Trametinib	1.005	1.00-1.01	0.155
	Age	1.00	0.545-1.83	0.996
PFS				
RDI	Dabrafenib	1.00	0.99-1.01	0.769
	Trametinib	1.01	1.00-1.01	0.091
RDI and Age (<75 years vs. ≥75 years)	Dabrafenib	1.00	0.99-1.01	0.857
	Age	0.79	0.46-1.34	0.378
	Trametinib	1.005	1.00-1.01	0.121
	Age	0.85	0.495-1.45	0.540
DoR				
RDI	Dabrafenib	1.01	0.995-1.02	0.221
	Trametinib	1.005	1.00-1.01	0.091
RDI and Age (<75 years vs. ≥75 years)	Dabrafenib	1.01	0.995-1.02	0.221
	Age	0.74	0.38-1.42	0.363
	Trametinib	1.005	1.00-1.01	0.128
	Age	0.815	0.42-1.59	0.551

OS= Overall Survival; HR= Hazard Ratio; RDI= Relative Dose Intensity; PFS= Progression-free Survival; DoR= Duration of Response; CI= Confidence Interval

10.5 Other analyses

No analyses other than those planned as primary and secondary objectives in the study protocol have been performed.

10.6 Adverse events/adverse reactions

At least one adverse event was reported in 120 patients (92.3%) in the <75 years group and in 27 (93.1%) in the ≥75 years group (**Table 9**). Serious adverse events occurred in 24 patients (18.5%) and 9 patients (31%) in the <75 years and ≥75 years groups, respectively. Three fatal grade 3 serious adverse events were reported in two patients in group <75 years (general physical health deterioration and pain, and urinary tract infection, respectively), but they were not related with the studied treatments. Of the adverse events that occurred in more than 10% of total number of patients, the most common were pyrexia (maximum grade adverse event in 4 patients (13.8%) in ≥75 years group), asthenia (maximum grade AE in 13 patients (44.8%) in ≥75 years group) and arthralgia (maximum grade AE in 2 patients (6.9%) in ≥75 years group). Most frequent AEs by grade and age (<75 years and ≥75 years) are shown in **Table 10**. In both groups the most common AEs that occurred in more than 5% were Grade ≤3. There were no adverse events grade 5.

Table 10-9: Adverse events (AEs)

	All N=159	Age (years) <75 N=130	Age (years) ≥75 N=29	*p*-value
Patients with AEs, N (%)				
Patient with AEs	147 (92.5)	120 (92.3)	27 (93.1)	>0.999
Patients with SAEs	33 (20.8)	24 (18.5)	9 (31)	0.203
Patients with related SAEs	20 (12.6)	14 (10.8)	6 (20.7)	0.210
Patients with AEs grade≥3[a]	39 (24.5)	28 (21.5)	11 (37.9)	0.093
Patients with AEs fatal outcome[a]	2 (1.3)	2 (1.5)	0 (0)	>0.999
Most frequent AEs, N (%)				
Pyrexia	91 (57.2)	85 (65.4)	6 (20.7)	<0.001
Asthenia	61 (38.4)	42 (32.3)	19 (65.5)	0.001
Arthralgia	40 (25.2)	38 (29.2)	2 (6.9)	0.010
Diarrhoea	25 (15.7)	21 (16.2)	4 (13.8)	>0.999
Fatigue	25 (15.7)	20 (15.4)	5 (17.2)	0.782
Rash	19 (11.9)	15 (11.5)	4 (13.8)	0.753
Maximum grade by patient, N (%)				
Pyrexia	59 (37.1)	55 (42.3)	4 (13.8)	0.005
Asthenia	46 (28.9)	33 (25.4)	13 (44.8)	0.044
Arthralgia	31 (19.5)	29 (22.3)	2 (6.9)	0.070
Diarrhoea	21 (13.2)	17 (13.1)	4 (13.8)	>0.999
Fatigue	19 (11.9)	15 (11.5)	4 (13.8)	0.753
Rash	18 (11.3)	14 (10.8)	4 (13.8)	0.745

AE= Adverse Event; SAE= Serious Adverse Event

[a]CTCAE (Common Terminology Criteria for Adverse Events) Grade Classification

Table 10-10: Most frequent adverse events (AEs) by grade and age (<75 years and ≥75 years)

	Severity (Grade CTCAE)		
	Grade 1	**Grade 2**	**Grade 3**
Age <75 years			
Maximum grade by patient, N (%)			
Pyrexia	35 (26.9)	15 (11.5)	5 (3.8)
Asthenia	17 (13.1)	14 (10.8)	2 (1.5)
Arthralgia	23 (17.7)	6 (4.6)	0 (0)
Diarrhoea	11 (8.5)	5 (3.8)	1 (0.8)
Fatigue	13 (10)	2 (1.5)	0 (0)
Rash	11 (8.5)	3 (2.3)	0 (0)
Oedema peripheral	9 (6.9)	1 (0.8)	0 (0)
Nausea	8 (6.2)	1 (0.8)	0 (0)
Neutropenia	3 (2.3)	3 (2.3)	2 (1.5)
Myalgia	6 (4.6)	2 (1.5)	0 (0)
Age ≥75 years			
Maximum grade by patient, N (%)			
Asthenia	3 (10.3)	7 (24.1)	3 (10.3)
Decreased appetite	2 (6.9)	3 (10.3)	0 (0)
Diarrhoea	2 (6.9)	2 (6.9)	0 (0)
Fatigue	3 (10.3)	1 (3.4)	0 (0)
Pyrexia	2 (6.9)	1 (3.4)	1 (3.4)
Urinary tract infection	1 (3.4)	1 (3.4)	2 (6.9)
Rash	2 (6.9)	1 (3.4)	1 (3.4)
Constipation	2 (6.9)	1 (3.4)	0 (0)
Nausea	2 (6.9)	1 (3.4)	0 (0)
Vomiting	2 (6.9)	0 (0)	1 (3.4)

CTCAE= Common Terminology Criteria for Adverse Events Grade Classification

A total number of 120 patients (75.5%) had at least one treatment related AE (**Table 11**). In <75 years and ≥75 years group, 98 patients (75.4%) (mainly Grade 1 or 2) and 22 patients (75.9%) (5 patients Grade 1, 10 patients Grade 2 and 7 patients Grade 3), respectively, had at least one treatment related AE. In the same way as it was reported in the case of general AEs, the most common treatment related AEs were pyrexia, arthralgia and asthenia, in both age groups. Most of the treatment-related reported records were in patients treated with Dabrafenib (107 records (36.4%) in <75 years group and 34 records (43%) in ≥75 years group) or the

combination of Dabrafenib and Trametinib (173 records (58.8%) and 39 records (49.4%), respectively). No action was taken with respect Dabrafenib or Trametinib treatment in the majority of the cases (110 records (84.6%) and 22 records (75.9%) in each age group, respectively). The adjustment or interruption of treatment were reported in 45 records (34.6%) in <75 years group and 17 records (63.6%). Ultimately, treatment discontinuation was reported in 14 cases (10.8%) and 2 cases (6.9%) in each age group, respectively.

Table 10-11: Treatment-related adverse events

		Age (years)		
	All N=159	**<75 N=130**	**≥75 N=29**	***p*-value**
Patients with at least 1 related AEs, N (%)	120 (75.5)	98 (75.4)	22 (75.9)	>0.999
Severity 1[a]	50 (31.4)	45 (34.6)	5 (17.2)	0.079
Severity 2[a]	45 (28.3)	35 (26.9)	10 (34.5)	0.494
Severity 3[a]	25 (15.7)	18 (13.8)	7 (24.1)	0.169
Most common related AEs by patient, N (%)				
Pyrexia	54 (34)	50 (38.5)	4 (13.8)	0.016
Arthralgia	23 (14.5)	21 (16.2)	2 (6.9)	0.255
Asthenia	29 (18.2)	18 (13.8)	11 (37.9)	0.006
Treatment-related AEs, records (%)	373 (100)	294 (100)	79 (100)	
Dabrafenib	141 (37.8)	107 (36.4)	34 (43)	
Trametinib	20 (5.4)	14 (4.8)	6 (7.6)	0.258
Dabrafenib + Trametinib	212 (56.8)	173 (58.8)	39 (49.4)	
Outcome by patient, N (%)[b]				
Not recovered/Not resolved	37 (23.3)	31 (23.8)	6 (20.7)	0.812
Recovered/Resolved	135 (84.9)	109 (83.8)	26 (89.7)	0.572
Recovering/Resolving	22 (13.8)	20 (15.4)	2 (6.9)	0.372
Recovered with sequelae	4 (2.5)	4 (3.1)	0 (0)	>0.999
Fatal	2 (1.3)	2 (1.5)	0 (0)	>0.999
Action taken with respect studied treatment, by patient, N (%)				
No action	132 (83)	110 (84.6)	22 (75.9)	0.277
Treatment adjusted	27 (17)	22 (16.9)	5 (17.2)	>0.999
Treatment interrupted	35 (22)	23 (17.7)	12 (41.4)	0.011
Treatment discontinued	16 (10.1)	14 (10.8)	2 (6.9)	0.738

AEs= Adverse Events

[a]CTCAE (Common Terminology Criteria for Adverse Events) Grade Classification

[b]Data were unknown in 5 cases (<75 years) (3.8%)

No adverse events other than those already known have been reported for the products analyzed in the study.

11 Discussion

11.1 Key results

- Clinical characteristics of elderly melanoma patients treated with Dabrafenib plus Trametinib in Spain are the presence of 3 or more comorbidities (mainly hypertension), 3 or more concomitant medications and having an ECOG status of 0-1.
- Regarding melanoma status, the majority of the patients had V600E or V600K BRAF-mutants melanoma; IIIc/M1a or M1b disease stage; without CNS metastases; and less than 3 disease sites.
- Real-world management of combined Dabrafenib and Trametinib in the elderly (≥75 years) Spanish population was mainly used in first line-treatment, as well as for patients under 75 years of age.
- Dabrafenib (monotherapy or in combination) and Trametinib initial doses were slightly lower in elderly patients than in patients <75 years. This observation was also obtained in the case of dose intensity (DI) and relative dose intensity (RDI).
- Regarding treatment modification, the main reason of the elderly patients who discontinued Dabrafenib and Trametinib treatment was progression of disease. Appearance of adverse events was mostly the reason for delaying treatment or modifying doses.
- Elderly patients' mean treatment duration was slightly longer or very similar than in the group of patients <75 years, for Dabrafenib in monotherapy or plus Trametinib, respectively.
- Median Overall Survival (OS) of elderly patients (≥75 years) was estimated in 29.1 months (95% CI, 4.6-53.7 months); Progression-free Survival (PFS) in 10.2 months (CI 95% 0-21.4 months); and Duration of Response (DoR) in 10.9 months (CI 95% 2.1-19.7 months). Complete response (CR) was achieved in 31% of elderly patients; partial response (PR) in 31%; and stable disease (SD) in 13.8%, whereas progressive disease (PD) was observed in 3.4% of the patients in the group of ≥75 years.
- Differences in efficacy among age groups and treatment dose-intensity did not show statistically significance in any of the analyses.
- Most of the patients reported at least one adverse event regardless age, although the majority were grade ≤3. There were no adverse events grade 5 and the three fatal grade

3 serious adverse events occurred in two patients <75 years and were Dabrafenib and Trametinib treatment-unrelated.

- The most common adverse events in overall population of the study were pyrexia, asthenia and arthralgia, but in the elderly group of patients most frequent adverse events were asthenia, decreased appetite and diarrhoea.
- Approximately 75% of patients had at least one treatment related adverse event, mainly related with Dabrafenib (in monotherapy or plus Trametinib), regardless age. The most common treatment related adverse events were pyrexia, arthralgia and asthenia, as in the case of general adverse events. However, in the majority of the cases no action was taken with respect delay, discontinuation or interruption of the treatment.
- Gender (male vs. female) was independently associated with an increased rate of AE grade≥3, while age and stage were independently associated with increased rate of SAEs. In this sense, elderly and M1b or M1c with CNS metastases stage patients have more odds of presenting SAEs. But, M1c without CNS metastases or IIIc+M1a stage patients have less probabilities of presenting SAEs.
- Treatment dose intensity and age were not identified as significant statistically prognostic factors in terms overall survival, progression-free survival or duration of response.

11.2 Limitations

This is a real-world research having the inherent limitations of observational studies, whose data were 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. Most data of interest in this study were registered in medical records as they are part of the routine clinic follow-up of the patients, however, in some patients this information was unknown, which has been noted in the results for each specific case.

Included patients comprised a heterogeneous population barely selected, with the only inclusion criteria of having received at least one dose of dabrafenib or combination with trametinib. The site selection process ensured that the participant sites had a proportion of elderly patients treated with dabrafenib and trametinib of 15-40% and more than 12 patients treated with combined dabrafenib and trametinib. Finally, the number of patients ≥75 years was 29, which

represents 18.2% of the total number of patients included (vs. 130 patients under 75 years old (81.8%)). This percentage is within the requirements previously established for the selected centers, reflecting the usual practice in the treatment of the type of melanoma analysed in the study, but it may represent a certain limitation for the statistical analysis of some of the objectives.

11.3 Interpretation

The results presented in this study provide a description of the clinical characteristics; melanoma status; Dabrafenib treatment management (in monotherapy or plus Trametinib); and general and treatment-related adverse effects, in real-world clinical practice in Spain.

The percentage of patients ≥75 years is lower than in the group of younger patients, but it is within the 15-40% range that is usually part of the typical treatment consultation for this type of melanoma. Therefore, the results allow a real life practice description. In that sense, the results seem to be very similar compared with the management and characteristics of patients <75 years with the same type of melanoma candidate to the treatment with Dabrafenib monotherapy or plus Trametinib.

It is important to note that no severe adverse events (grades 4 and 5) were observed in the population analyzed and most reported adverse events did not require any specific action or were resolved with usual clinical practice.

11.4 Generalizability

The analysis presented here has been performed with data from the medical records of patients in Spanish centers experienced using Dabrafenib in monotherapy or in combination with Trametinib in the management of BRAF-mutated melanoma. Therefore, the study offers an accuracy overview of the real clinical practice for the management of these treatments in Spain.

12 Other information

None

13 Conclusion

Analysis of the real-life management of Dabrafenib treatment (in monotherapy or in combination with Trametinib) in mutated BRAF melanoma indicates that the clinical characteristics of elderly patients are similar to the general population that is a candidate for this treatment. Elderly patients benefit from the treatment with Dabrafenib plus Trametinib in

terms of efficacy, without great treatment management modifications with an adequate and manageable safety profile.

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Appendices

Annex 1 – List of stand-alone documents

Annex 2 – Additional information

Study information

Protocol and protocol amendments

Sample case report forms

List of Independent Ethics Committees or Institutional Review Boards

List and description of investigators and other important participants in the study

Documentation of statistical methods

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Listings