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► **To cite this version:**

Caroline Dutriaux, Caroline Robert, Jean-Jacques Grob, Laurent Mortier, Olivier Dereure, et al.. An open label, non-randomised, phase IIIb study of trametinib in combination with dabrafenib in patients with unresectable (stage III) or distant metastatic (stage IV) BRAF V600-mutant melanoma: A subgroup analysis of patients with brain metastases. *European Journal of Cancer*, 2022, 175, pp.254-262. 10.1016/j.ejca.2022.07.035 . hal-03888969

HAL Id: hal-03888969

<https://hal.science/hal-03888969>

Submitted on 8 Feb 2023

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Original Research

An open label, non-randomised, phase IIIb study of trametinib in combination with dabrafenib in patients with unresectable (stage III) or distant metastatic (stage IV) BRAF V600-mutant melanoma: A subgroup analysis of patients with brain metastases



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Received 5 May 2022; received in revised form 6 July 2022; accepted 20 July 2022

Available online 25 September 2022

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<https://doi.org/10.1016/j.ejca.2022.07.035>

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KEYWORDS

Dabrafenib;
 Trametinib;
 BRAFV600-mutation;
 Melanoma;
 Brain metastases

Abstract Background: Despite the poor prognosis associated with melanoma brain metastases (BM), data concerning these patients and their inclusion in clinical trials remains scarce. We report here the efficacy results of a subgroup analysis in patients with BRAFV600-mutant melanoma and BM treated with BRAF and MEK inhibitors dabrafenib (D) and trametinib (T).

Patients and methods: This phase IIIb single-arm, open-label, multicenter, French study included patients with unresectable stage IIIc or IV BRAFV600-mutant melanoma with or without BM. The present analysis focuses on patients with BM. Response rates were determined clinically and/or radiologically as per standard clinical practice. Progression-free survival (PFS) was estimated using the Kaplan Meier analysis and modelled with multivariate Cox regression model. Risk subgroups were identified using an exponential regression tree analysis. Significance was set at $p < 0.05$.

Results: Between March 2015 and November 2016, 856 patients were included and 275 (32%) patients had BM. Median PFS was 5.68 months (95% confidence interval [CI], 5.29–6.87). Significant independent factors associated with shorter PFS were ECOG ≥ 1 , elevated serum lactate dehydrogenase (LDH), ≥ 3 metastatic sites, and non-naïve status. The binary-split classification and regression tree modelling identified baseline LDH and ECOG status as major prognostic factors.

Conclusion: This is to date the largest, close to real-world, study in advanced BRAFV600-mutant melanoma patients with BM treated with D+T. ECOG > 1 , ≥ 3 metastatic sites and elevated LDH were associated with shorter PFS, a finding previously demonstrated only in patients without BM. Further studies are warranted to determine the optimal treatment sequence in this population.

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1. Introduction

An estimated 2% of patients with cutaneous melanoma and 40% of patients with metastatic disease develop brain metastases (BM) at some point in the course of their disease. These numbers are expected to rise due to an increasing incidence of melanoma diagnoses and longer survival due to the developments of efficient treatments during the last decade.

Historically, the management of melanoma-related BMs has been limited to local therapies including surgical resection and radiation therapy and median overall survival ranged from 4 to 5 months.

Despite the poor prognosis and the lack of alternatives, most pivotal phase 3 clinical trials have excluded patients with clinically active BM [1], and the data concerning these patients are scarce.

Emerging treatment strategies for BRAF-mutated metastatic melanoma include immunotherapy and targeted therapies.

Recent studies have demonstrated the safety and efficacy of immune checkpoints, including anti-PD-1 and anti-CTLA-4 therapy in patients with BM. Notably, the combination of anti-PD-1 and anti-CTLA-4 therapy has been shown to lead to 46% and 52% intracranial response rates in treatment naïve patients [2,3].

Regimens combining BRAF and MEK inhibitors have shown potential for the treatment of patients with unresectable (stage III) or distant

metastatic (stage IV) BRAF V600-mutant cutaneous melanoma and BM.

The COMBI MB study was the first phase 2 trial evaluating the combination of BRAF inhibitor dabrafenib plus trametinib in patients with BRAF V600-mutant melanoma that had metastasized to the brain and remains, to date, the largest with 125 patients [4].

The trial showed that patients with BM respond to treatment with BRAF and MEK inhibitors [4]. In addition, one previous retrospective study (DESCRIBE II) gathered real-world data in a large cohort of 271 patients with unresectable or distant metastatic BRAF V600-mutant cutaneous melanoma, including 99 patients with BM, treated with combination dabrafenib and trametinib [5]. Another retrospective case series investigation of 24 patients with stage IV BRAF-mutant BMs treated with encorafenib plus binimetinib reported a clinical benefit rate of 63% [3]. Last, recent preliminary results of the GEM1802/EBRAIN-MEL phase II trial in 63 patients have shown intracranial response rates of 64.3% in asymptomatic patients (among 14 evaluable patients) and of 63.6% in symptomatic patients (among 11 evaluable patients) [6].

In March 2015, given that trametinib was not yet commercially available in France, a study was launched to grant a large number of patients (including patients with BM) access to trametinib, based on the benefit of dabrafenib–trametinib combination. An earlier analysis

provided efficacy and safety results of dabrafenib and trametinib in the overall population. Here we report an exploratory subgroup analysis to describe the response of patients with BM and assess factors associated with response in close to ‘real life’ conditions.

2. Methods

2.1. Participants

The study included patients aged 18 years and older with histologically confirmed melanoma BRAF V600 positive mutation either unresectable (stage III) or distant metastatic (stage IV) (American Joint Committee on Cancer [AJCC] 7th edition) and with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0–2 and in stable clinical condition (defined as not needing any urgent treatment). Patients who had received previous advanced melanoma treatments (except BRAFi + MEKi combination) were allowed. Main exclusion criteria were history of malignancy other than melanoma within 3 years, history of hepatitis B or C virus and any other serious or unstable pre-existing medical conditions. Some cardiovascular medical history (e.g. abnormal or non-available electrocardiogram or echocardiogram values) were permitted. Patients with active BM were eligible if they did not require or were ineligible for immediate local treatment. The present subgroup exploratory analysis focuses only on patients from the study with BM at the time of study inclusion.

The study was conducted according to the ethical principles of the Declaration of Helsinki and its amendments and Good Clinical Practice guidelines. The study protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each study site. Patients were enrolled in the program after providing signed and dated informed consent.

2.2. Study design and treatment

This was a single-arm, open-label, multicentre, non-randomised, access study. Patients received trametinib 2 mg orally once daily and, where appropriate, in combination with dabrafenib 150 mg orally twice daily. Treatment continued until a safety event warranting discontinuation occurred, until disease progression, until the patient withdrew consent or until trametinib was granted authorisation to be reimbursed when used in combination with dabrafenib (study termination). For patients who were unable to tolerate the protocol-specified dosing scheme, dose adjustments and interruptions were permitted in order to keep the patient on study drug.

Response to treatment was assessed every 4 weeks during the first 2 months, then every 8 weeks or as per

standard clinical treatment. It was recommended to monitor blood chemistry/biology, blood pressure and temperature every 4 weeks during the first 6 months and every 8 weeks thereafter. Safety was monitored throughout the study and adverse events/severe adverse events were collected up to 28 days after discontinuation of the study.

2.3. End-points

The end-points presented here include the response rates to treatment determined clinically and/or radiologically by the investigator as per standard clinical practice and evaluated by the investigator (RECIST criteria were proposed but not mandatory), progression-free survival (PFS) rates, the prognostic value of individual factors and risk groups using an exponential regression tree analysis model.

2.4. Statistical analysis

Categorical variables were reported as frequency and percentage, while continuous variables were reported as mean, standard deviation, median and range values.

Overall response rate (ORR) was defined as the percentage of subjects achieving a complete response or partial response from the start of treatment until disease progression or end of the study.

Median follow-up time was calculated using the reverse Kaplan–Meier method. PFS was defined as the interval of time (in months) between the start date of trametinib and disease progression or death due to any cause, whichever occurred first. Patients without events were censored at the time of last known visit (including those withdrawn from the study due to authorisation of trametinib). PFS was estimated using the Kaplan–Meier method, presented as median and survival rates in percentages, both with the 95% confidence interval (CI). The prognostic value of individual factors (LDH, ECOG status, number of metastatic sites, naïve versus non-naïve status, prior immunotherapy treatment [interferons, monoclonal antibodies, other antineoplastic agents]) was assessed using the univariate Cox proportional hazards model with a backward procedure. Variables significant on univariate analysis or clinically relevant were included in the multivariate Cox proportional hazard model. Hazard ratios with their 95% CIs were calculated to display risk changes. We used regression tree modelling to identify patients with the highest risk of progression depending on factor combinations. The regression tree analysis recursively partitioned patients into binary subgroups that best maximised differences between outcomes. All possible splits for each factor were assessed at each partition using a forward stepwise splitting procedure to select the most significant split and divide data into two risk groups when determining the next split in the Cox model. Splits had to include at least

10% of all subjects treated patients [7]. The process was then repeated in each subset of the data recursively until either a small-sized group was obtained or no additional splitting was available (no important covariate remains). A restriction was imposed on the tree construction so that terminal subgroups resulting from any given split had to have at least 20 patients [8]. We included the missing data in the analysis for homogeneity of the studied population.

All p values reported were two-sided, and the significance level was set at 5% ($p < 0.05$). Statistical analysis was performed using the SAS[®] software (version 9.4).

2.5. Sample size

This was an access study. The nature and purpose of the study precluded the *a priori* specification of a sample size. It was estimated that between 300 and 1000 patients would be enrolled depending on the duration of the study.

3. Results

3.1. Patients

Between March 2015 and November 2016, 856 patients with melanoma received trametinib in combination with dabrafenib [7]. Of the 856 patients, 617 patients had M1c status, 275 of whom presented with brain metastasis (BM). Baseline demographic and clinical characteristics for patients with BM are presented in Table 1.

3.2. Efficacy

3.2.1. Response to treatment

Median follow-up of the study was 5.63 months (range, 0.03–20.53). ORR was 41.5%. Median PFS was 5.68 months (95% CI 5.29–6.87). There were 164 progression events (disease progression or death, see Table 2).

3.2.2. Survival according to previous treatments

Median PFS of patients that had received previous treatment was 4.96 months [95% CI, 4.04–5.78] versus 7.23 months [95% CI, 5.68–8.02] for those who had not (HR = 1.60; 95% CI, 1.14–2.25; $p = 0.0061$).

Median PFS for patients that had previously received treatment by gamma knife was 4.86 months [95% CI, 2.17–11.83] compared to 5.98 months [95% CI, 5.32–7.06] in patients that had not received any radio-surgery treatment (HR = 1.10; 95% CI, 0.63–1.90; $p = 0.7350$).

There was no statistically significant difference in the median PFS of patients having received or not prior immunotherapy (5.32 months [95% CI, 3.78; 6.87] versus 5.98 months [95% CI, 5.29; 7.16], respectively) (HR = 1.04 [95% CI; 0.67–1.63]; $p = 0.8456$).

Table 1

Patient demographic and clinical characteristics at baseline.

Characteristics	Total (N = 275)
Age, years, mean (SD)	57.6 (14.8)
Gender male, n (%)	166 (60.4)
ECOG performance score, n (%)	
0	144 (52.4)
1	91 (33.0)
≥2	40 (14.6)
Type of BRAF mutation, n (%)	
E	229 (83.3)
K	33 (12.0)
Other	13 (4.7)
Number of metastatic sites, n (%)	
<3	84 (30.55)
≥3	191 (69.45)
Baseline mean (SD) LDH, ULN ^a	418.1 (579.5)
Baseline LDH (ULN) in classes, n (%)	
<1	115 (41.8)
[1–2[50 (18.2)
≥2	21 (7.6)
Missing	89 (32.4)
Status regarding previous systemic treatment	
Naive	121 (44.0)
Non-naive	154 (56.0)
Patients with prior ≥1 immunotherapy treatment ^b	
No	233 (84.7)
Yes	42 (15.3)
Previous treatment by gamma knife	
Yes	20 (7.3)
No	255 (92.7)

n, number of patients in a group; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; ULN, Over half the patients (154/275, 56.0%) had taken therapy for unresectable advanced or metastatic disease before participating in the study and 20 (7.3%) patients had received treatment by gamma therapy.

^a Based on patients with known LDH at baseline (n = 628).

^b Monoclonal antibodies (eg: ipilimumab, anti-PD1) (in 12.0% of the patients), alpha-interferon.

3.3. Multivariate analysis

LDH level, ECOG PS and the number of metastatic sites at baseline were found to be significant predictors of PFS after treatment with D + T in multivariate analysis (Table 3). Patients with LDH ≥2 ULN (versus <1 ULN; HR = 2.50; 95% CI; 1.37–4.58; $p = 0.0030$), patients with ECOG PS 2 (versus ECOG PS = 0; HR = 2.17; 95% CI; 1.37–3.44; $p = 0.0010$) and patients with ≥3 metastatic sites (versus <3 metastatic

Table 2

Efficacy outcomes.

End point	Total (N = 275)
ORR, n (%)	114 (41.5)
DCR, n (%)	194 (70.5)
Progression throughout the study, n (%)	164 (59.6)
Progression-free survival, months, median (95% CI)	5.68 (95% CI 5.29–6.87)

ORR = overall response rate; DCR = disease control rate; CI = confidence interval.

Table 3

Multivariate Cox proportional hazard analysis of PFS by prognostic factors (N = 275).

	Population (n)	mPFS (95% CI), months	Multivariate analysis	
			HR (95% CI)	p value
LDH at baseline^a				
<1 ULN	115	7.06 [5.13; 8.34]	1 (=ref)	–
[1; 2[ULN	50	4.90 [3.65; 6.70]	1.30 [0.83–2.04]	0.2473
≥2 ULN	21	2.89 [2.04; 7.23]	2.50 [1.37–4.58]	0.0030
Missing	89		1.44 [0.99–2.10]	0.0577
ECOG PS^a				
Stage 0	144	7.20 [5.68; 8.34]	1.00 (=ref)	–
Stage 1	91	5.55 [4.44; 6.21]	1.36 [0.94–1.96]	0.0995
Stage ≥ 2	40	3.88 [2.83; 4.93]	2.17 [1.37–3.44]	0.0010
Metastatic sites^a				
<3	84	7.36 [5.78; 9.10]	1.00 (=ref)	–
≥3	191	5.39 [4.67; 6.01]	1.58 [1.10–2.28]	0.0142
Status^a				
Naive	121	7.23 [5.68; 8.02]	1.00 (=ref)	–
Non-naive	154	4.96 [4.04; 5.78]	1.60 [1.14–2.25]	0.0061
Pts with ≥1 prior immunotherapy treatment				
No	233	–	1.00 (=ref)	–
Yes	42	–	0.84 [0.52–1.35]	0.4719

Prior immunotherapy treatment was included in the multivariate model even though it was not significant in univariate due to its clinical relevance.

ECOG PS = Eastern Cooperative Oncology Group Performance Status; BM = brain metastasis; PFS = progression-free survival, CI = confidence interval.

^a Factors included in the regression analysis.

sites; HR = 1.58; 95% CI, 1.10–2.28; p = 0.0142) had an increased risk of progression.

In addition, patients previously treated were 1.6 times as likely as naïve patients to progress, and the difference was statistically significant (95% CI, 1.14–2.25; p = 0.0061).

The classification and regression tree analysis was performed using the number of metastatic sites, ECOG PS, LDH category at baseline and the naïve/non-naïve status (Fig. 1).

The binary-split classification and regression tree modelling identified LDH levels and ECOG PS status at baseline as major prognostic factors. Patients with ECOG PS 0 and normal LDH had the lowest risk of progression at both 6 and 12 months (6-month PFS = 61%; 95% CI, 51–70 and 12-month PFS = 34 months; 95% CI, 24–45). On the other hand, patients with ECOG PS ≥1 and having been previously treated for the BM had the shortest median PFS (6-month PFS = 23%; 95% CI, 13–35 and 12-month PFS = 5 months; 95% CI, 0.5–17).

Fig. 2 presents the Kaplan–Meier curves for PFS in melanoma patients with BM according to baseline clinical characteristics.

4. Discussion

To our knowledge, this analysis reports on the largest cohort of patients with BRAF-mutated melanoma and with BM treated with a BRAF inhibitor. Data on prognosis and predictive factors of progression in melanoma patients with BM are scarce due to, mostly,

patients not having been allowed to participate in clinical trials.

The longer survival of patients with BM due to more effective systemic therapies has encouraged the recruitment of this subpopulation in clinical trials. However, inclusion criteria are often restraining and exclude many patients seen in clinical practice, including pre-treated patients, those with high ECOG or Karnofsky performance status scores [4] and patients with leptomeningeal involvement (which account for 5–7% of patients with melanoma [9]).

At the time in which we carried out this study, most reports also lacked data on the impact of previous systemic or local treatments for BM and of sequencing, either because the information was not collected or because patients previously treated were not included. While BMs are a common outcome among patients with melanoma, no standard of care existed until recently. Ongoing improvements in local therapies including stereotactic radiosurgery and hypofractionated stereotactic radiotherapy have led to improved tumour control and better outcomes [10,11]. In 2017, the European Association of Neuro-Oncology published evidence-based guidelines to aid in the treatment of patients with BM from solid tumours and stated that they could benefit from targeted agents including BRAF inhibitors [1].

While the results in COMBI MB suggested that, D + T had good clinical activity and safety profile, the study had some limitations as discussed by the authors. There was not enough information on the previous or subsequent local or systemic treatments, and the cohorts were small-sized.

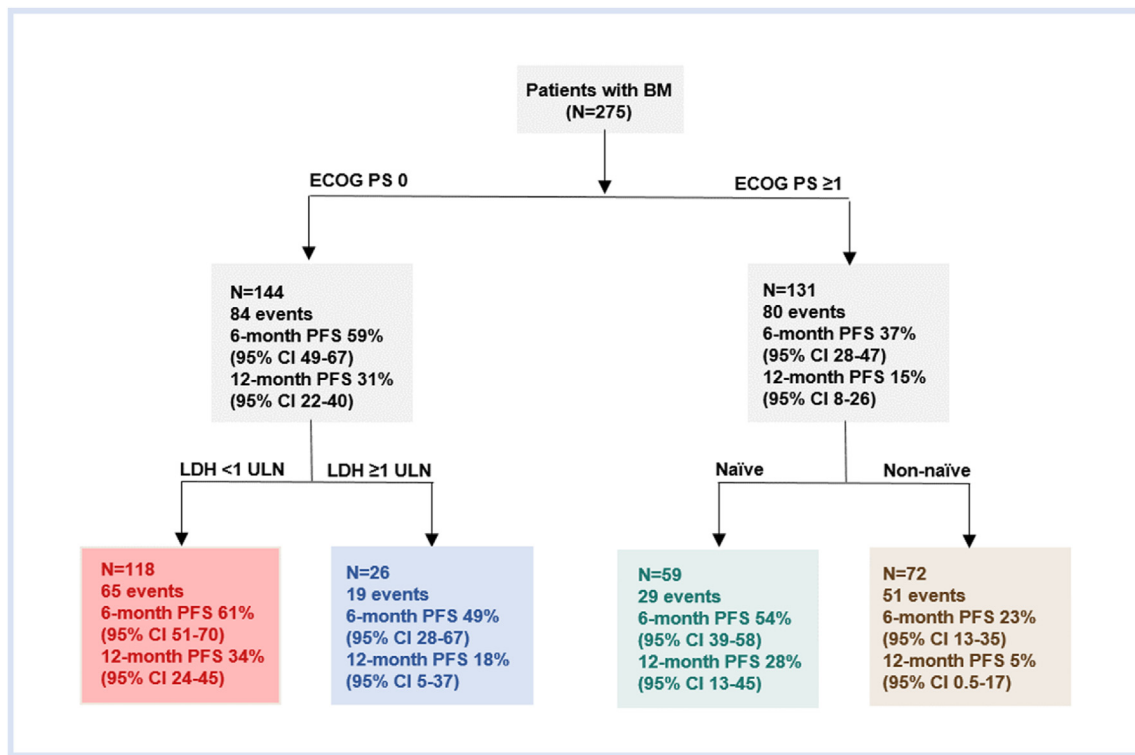


Fig. 1. Regression tree for progression-free survival, and 6- and 12-month survival rate estimates according to the Kaplan–Meier method (N = 275).

We report here the results of a subgroup analysis carried out in patients with melanoma and with BM that were treated with dabrafenib and trametinib in

conditions close to real life. The efficacy and safety of D + T in the overall population were reported recently [7]. In our study, median PFS was 5.68 months (versus

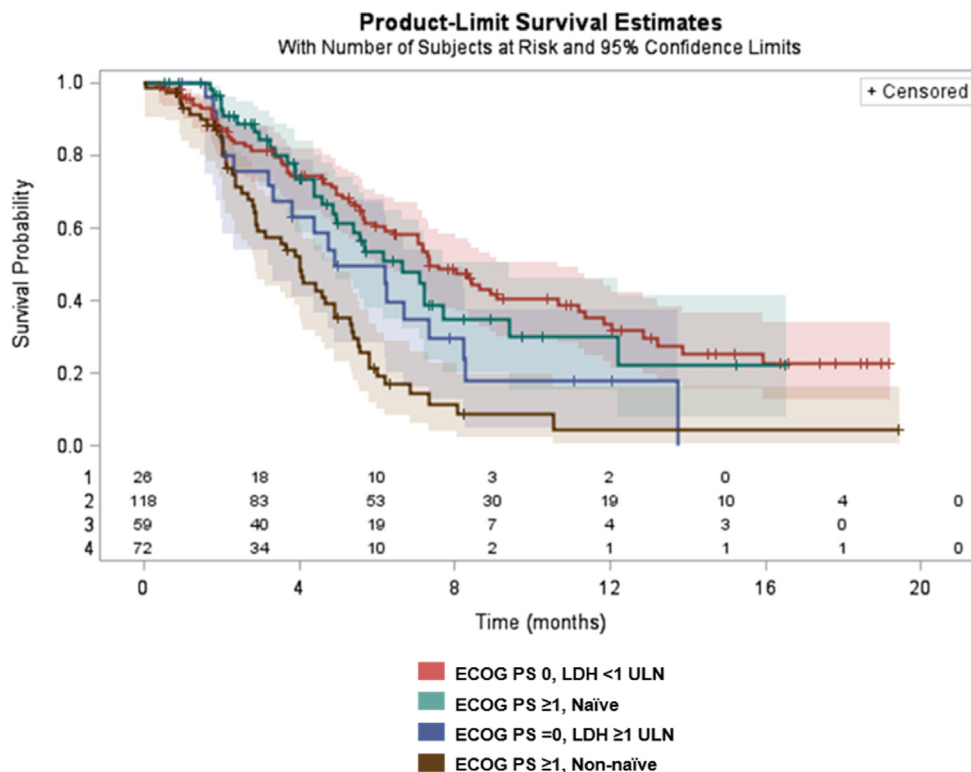


Fig. 2. Kaplan–Meier survival curves–PFS (N = 275). PFS, progression-free survival.

8.02 months in the overall population) and ORR 41.5%. In the DESCRIBE II study (36.5% of patients with BM), patients with known BM achieved a median PFS of 6.2 months. Our findings together with those from DESCRIBE II demonstrate that the combination of dabrafenib and trametinib provides clinical benefit to this subgroup of patients [5].

In the COMBI MB trial, patients in cohort A (without prior local brain-directed therapy) achieved a PFS of 5.6 months (95% CI 5.3–7.4) and those in cohort B (with prior local brain-directed therapy) achieved a PFS of 7.2 months (95% CI 4.7–14.6).

We assessed, for the first time, the predictive factors of PFS in patients treated with D + T in patients with melanoma metastasized to the brain. LDH level, ECOG PS and the number of metastatic sites at baseline were found to be significant predictors of PFS in patients being treated with D + T in multivariate analysis. These are known potential predictive factors of response to D + T in patients with BRAF-mutated melanoma. However, none of these have been validated as a discriminant factor for selection in patients with BM. The regression tree model allowed us to identify the hierarchy of baseline prognostic factors revealed and revealed that ECOG PS status as the most important predictor of PFS. For patients with an ECOG PS = 0, LDH level was the next most important factor, whereas for patients with ECOG PS >0, the naïve/non-naïve status was the most determining. The present model did not identify the number of metastatic sites, which was the most important predictor of PFS in the overall population of the study (including patients with and without BM) [7].

The present study was carried out in conditions close to real life and included patients with BM regardless of the number or the symptomatic/asymptomatic nature of metastases, ensuring the representativeness encountered in routine clinical practice. Given the increasing incidence of patients with BM, studies that include patients with poor prognosis (i.e. leptomeningeal involvement) are warranted to assess the benefits of such therapies in this subgroup of patients. One of the limitations of the study arose from the access study nature. Once trametinib was authorised, patients were withdrawn from the study, leading to short follow-up and insufficient data to evaluate the effect of treatment on overall survival. Also, information that would have been relevant for this subanalysis, such as concomitant treatment with stereotactic radiosurgery, was not collected as part of the study.

This study contributes to the field of metastatic melanoma by providing preliminary data on factors predictive of response to D + T in a subpopulation of patients with BRAF-mutated melanoma and with BM. Further studies should validate these factors for risk assessment and patient selection. The ESMO has recently issued some recommendations for the

management of metastatic melanoma, including patients with BMs. The chosen therapy should take into consideration the symptomatic nature of metastases. For instance, for patients with asymptomatic BMs (irrespective of BRAF mutational status), combination ipilimumab and nivolumab have been shown to provide disease control compared to targeted therapy. For patients with contraindication for immunotherapy or in need of rapid response, combination D + T is recommended [12]. However, strong evidence on the optimal synergies between different treatments is lacking. Clinical phase 3 trials should be performed to define the optimal combination of immunotherapy, targeted treatment and local treatments including stereotactic radiosurgery or surgery.

Funding

This work was supported by Novartis Pharma S.A.S., France.

Authorship file based on CRediT roles

Caroline Dutriaux: Conceptualisation, Methodology, Validation, Investigation, Resources, Writing – Original Draft, Writing – Review & Editing, Visualisation, Supervision.

Caroline Robert: Investigation, Resources, Writing – Review & Editing.

Jean-Jacques Grob: Investigation, Resources, Writing – Review & Editing.

Laurent Mortier: Investigation, Resources, Writing – Review & Editing.

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Alexandra Szenik: Conceptualisation, Resources, Writing – Original Draft, Writing – Review & Editing, Supervision, Project administration.

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Philippe Saiaq: Conceptualisation, Methodology, Validation, Investigation, Ressources, Writing – Review & Editing, Visualisation, Supervision.

Conflict of interest statement

The authors declare the following financial interests/ personal relationships which may be considered as potential competing interests:

Caroline Dutriaux has served as a member of an advisory board or as an investigator for Novartis.

Caroline Robert has acted as a consultant for BMS, MSD, Sanofi, Novartis, Roche and Amgen, and has served as a member of an advisory board and steering committee for Pierre Fabre.

Jean-Jacques Grob has received honoraria from BMS, MSD, Merck, Pfizer, Incyte, Novartis, Roche, Amgen and Pierre Fabre, has received travel grant support from BMS, MSD and Roche, has acted as a consultant and advisor for BMS, MSD, Roche, Novartis, Amgen, Merck, Pierre Fabre, Pfizer and Incyte.

Laurent Mortier has acted as a consultant and advisor for BMS, MSD, Roche, Novartis, Amgen, and Leo and has participated to clinical studies sponsored by Amgen, BMS, Roche, GSK/Novartis, Merck Serono, Leo, and MSD. He has received honoraria from Roche, BMS, MSD, Sanofi, Novartis, Amgen and Pierre Fabre.

Céléste Lebbe has received honoraria from BMS, MSD, Roche, Novartis, Amgen, Merck, Pierre Fabre, Pfizer and Incyte, has acted as a consultant or has served as a member of an advisory board for BMS, and has received travel grant support from BMS and MSD.

Sandrine Mansard has served as a member of an advisory board for Novartis.

Eve-Marie Neidhart has received honoraria from BMS.

Florent Grange has served as a member of an advisory board for Novartis.

Thierry Lesimple has served as a member of an advisory board for MSD, Incyte and Pierre Fabre; He has participated to research sponsored by Roche.

Christophe Bedane has served as a member of an advisory board for Novartis.

Sophie Dalac-Rat has served as a member of an advisory board for Novartis, Roche, BMS and Pierre Fabre.

Charlée Nardin has acted as a consultant for Novartis, BMS and MSD.

Alexandra Szenik and Amine Denden are employees of Novartis.

Olivier Dereure, Laurent Machet and Hervé Maillard have nothing to disclose related to this research.

Philippe Saiaq has received personal fees from Amgen, Bristol-Myers Squibb, MSD, Merck-Serono, Pfizer, Roche-Genentech, Pierre Fabre, Sanofi and Novartis; he has received nonfinancial support from Bristol-Myers Squibb, MSD, Roche-Genentech, and Novartis; and has received a funding grant from Roche-Genentech.

Acknowledgements

The authors would like to thank patients and families for having participated in the study, and Jone Iriondo-Alberdi, PhD, from ITEC Services, for medical editorial assistance.

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