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Clinical Trial

Efficacy, safety and factors associated with disease progression in patients with unresectable (stage III) or distant metastatic (stage IV) *BRAF* V600-mutant melanoma: An open label, non-randomized, phase IIIb study of trametinib in combination with dabrafenib



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KEYWORDS

Dabrafenib;
 Trametinib;
 BRAF V600-mutation;
 Melanoma;
 Regression tree

Abstract Background: BRAF and MEK inhibitors combination, including dabrafenib (D) and trametinib (T) have transformed the treatment of *BRAF V600*-mutant advanced melanoma patients, including patients with brain metastasis (BM). In a large phase IIIb, single-arm, open-label, multicenter French study, we assessed safety, response to treatment, progression-free survival (PFS) and factors associated with progression, and stratified the population into risk groups.

Methods: Patients with unresectable, advanced, *BRAF V600*-mutant melanoma were included, including those with the presence of BM, Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 2 , elevated lactate dehydrogenase (LDH) or previous melanoma treatments. Responses were determined locally, without central review. PFS was estimated using the Kaplan–Meier analysis and modelled with multivariate Cox model. Risk subgroups were identified using a regression tree analysis.

Results: Between March 2015 and November 2016, 856 patients received at least one D + T dose. Overall, 92% had stage IV melanoma, 38% ECOG PS ≥ 1 , 32% BM and 37.5% elevated LDH. Median PFS was 8.02 months (95% confidence interval [CI] 7.33–8.77). Significant factors associated with lower PFS were ECOG PS ≥ 1 , elevated LDH, ≥ 3 metastatic sites and presence of BM. Patients with < 3 metastatic sites, ECOG = 0 and no BM had the highest probability of PFS at 6 months (83%, 95% CI 76–87) and 12 months (56%, 95% CI 47–64), respectively.

Conclusions: This is the largest prospective study in advanced *BRAF V600*-mutant melanoma patients treated with D + T, conducted in conditions close to ‘real-world practice’. We confirm previous findings that LDH, ECOG PS and ≥ 3 metastatic sites are associated with shorter PFS, but the real-world setting introduces BM as a major prognostic factor.

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1. Introduction

Cutaneous melanoma is an aggressive skin cancer. In France in 2018, 7886 patients were diagnosed and 1135 died of the disease [1]. Approximately 40% of metastatic forms harbour a *BRAF V600* mutation resulting in constitutive activation of the Mitogen-Activated Protein Kinase (MAPK) pathway [2]. BRAF inhibitor monotherapy with dabrafenib or vemurafenib demonstrated improved progression-free survival (PFS) and overall survival (OS) compared with chemotherapy [3,4], but most patients experience resistance with reactivation of the MAPK pathway in tumour cells. The addition of an MEK inhibitor delays this reactivation, and abrogates the paradoxical activation of the MAPK pathway in normal cells which is associated with some adverse events (AEs) of BRAF inhibitors [5,6]. Several randomized controlled trials have demonstrated the benefits of the dabrafenib + trametinib (an MEK inhibitor) combination (D + T) over single-agent BRAF inhibitors [7–10] or chemotherapy regimens [11] in the treatment of unresectable (American Joint Committee on Cancer [AJCC] 7th edition, stage III) or distant metastatic (stage IV) *BRAF V600*-mutant cutaneous melanoma. This combination demonstrated increased PFS and OS, with a reduction of hyperproliferative cutaneous side-effects. Extended 3- and 5-year follow-up studies have confirmed the long-term beneficial outcomes in D + T treated patients

with *BRAF V600*-mutant advanced melanoma [3,12–14]. A pooled regression tree analysis of D + T treated patients from registration trials suggested that high lactate dehydrogenase (LDH) serum level, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 and ≥ 3 metastatic sites are associated with shorter PFS [15], but this finding has not been confirmed in an independent population.

In June 2014, trametinib received a marketing authorization approval in Europe for use as monotherapy treatment of unresectable or metastatic *BRAF V600*-mutated melanoma. However, unlike in other European countries, the drug was not available in France before its approval and reimbursement in combination with dabrafenib. This open-label access multicenter trial was thus launched in March 2015 to grant patients with advanced unresectable AJCC (7th ed) stage III-IV *BRAF V600* mutation-positive cutaneous melanoma access to trametinib, either as monotherapy or in combination with dabrafenib.

The real-world setting of this study allowed inclusion of patients with brain metastases (BMs) or with ECOG PS = 2, who are excluded from pivotal trials. The aim of this analysis is to confirm or infirm prognostic factors previously found in regression-tree analysis from registration trials [15], to add new prognostic markers and to identify eventually different prognostic groups using a regression tree analysis.

2. Methods

2.1. Participants

Eligible patients were aged ≥ 18 years, had adequate organ function and histologically confirmed *BRAF* V600-mutant advanced unresectable melanoma (AJCC 7th ed, stage III or IV) and ECOG PS of 0–2. Patients with asymptomatic or symptomatic BM were eligible if they did not require or were ineligible for immediate local treatment. Patients who had received either previous *BRAF* inhibitors as single agents or previous immunotherapy 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, or psychiatric disorders. Certain cardiovascular medical history (e.g. abnormal or non-available electrocardiogram or echocardiogram values) was permitted.

The study was conducted according to the 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 after providing signed and dated informed consent. This trial was registered in [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02416232) (NCT02416232).

2.2. Study design and treatment

This is a single-arm, open-label, multicentre, non-randomised, phase IIIb study aiming to provide access to trametinib, while dabrafenib was commercially available. Patients received trametinib 2 mg orally once daily 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 authorization to be reimbursed when used in combination with dabrafenib (study termination). Dose adjustments and interruptions were permitted according to protocol guidelines.

Evaluations were performed every 4 weeks during the first 2 months, then every 8 weeks ([Supplementary Fig. 1](#)). Response to treatment was determined in each centre by the investigators and reported as follows: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable and unknown. No central review of images was performed. Safety was monitored throughout the study and AEs/serious adverse events (SAEs) were collected up to 28 d after discontinuation of the study.

Patients were followed up until their withdrawal from study.

2.3. End-points

The end-points were the frequencies and proportion of AEs graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 of SAEs related to treatment or leading to treatment discontinuation, the response to treatment, the overall response rate (ORR, defined as the percentage of subjects achieving CR or PR at any time during the study) and PFS (defined as time from first dose to documented PD or death). The association of clinical and disease characteristics at inclusion with PFS was also evaluated.

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. Median follow-up time was calculated using the reverse Kaplan–Meier method. PFS was defined as the time interval (in months) between the start date of trametinib and disease progression or death due to any cause, whichever occurred first. PFS was estimated using the Kaplan–Meier method, presented as median with 95% confidence interval (CI), and survival rates in percentages with 95% CI. The prognostic value of individual clinical and disease factors was assessed using the univariate Cox proportional hazards model with a backward procedure. The following factors were included in univariate analysis: LDH, M1c status, ECOG status, number of metastatic sites, naïve versus non-naïve status, prior immunotherapy treatment (interferons, monoclonal antibodies, other antineoplastic agents) and presence of BM. Variables significant in univariate analysis or clinically relevant were included in the multivariate Cox proportional 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. Patients were recursively partitioned into binary subgroups that best maximised differences between outcomes. The most significant split at each partition was selected using a forward stepwise procedure. Splits had to include at least 10% of all treated patients [16]. The process was then repeated in each data subset recursively until either a small-sized group was obtained, or no additional splitting was available (i.e. no important covariate remained). Also, terminal subgroups resulting from any given split had to have at least 20 patients [17]. We included the missing data in the analysis for homogeneity of the population.

All *P* values reported were two-sided, and the significance level was set at $P < 0.05$. Statistical analysis was performed using SAS® (version 9.4).

As this is 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, 914 patients were screened in 40 French sites and 856 patients received D + T. Among the 856 patients who started treatment 59.1% of patients withdrew prematurely from the study. The remaining 40.9% of patients transitioned to marketed product. The main reasons for discontinuation were disease progression (63.2%), occurrence of an AE (18.8%) and death (5.3%). The median time between the first dose and withdrawal was 4.91 months (range 0.03–18.46) and between the first dose and transition to marketed product was 7.36 months (range 0.49–20.53). A total of 275 (32.1%) patients had BM at inclusion. Patient baseline characteristics are presented in Table 1. Over half the patients (47.5%) had received systemic therapy for unresectable advanced or metastatic disease before study inclusion: 4.2% received at least one cytotoxic chemotherapy treatment, 12.0% an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or anti-PD1 monoclonal antibody and 21.3% at least one targeted therapy.

3.2. Efficacy: response to treatment

Median follow-up was 5.63 months (range 0.03–20.53) and 21.1% of the patients reached a 48-week follow-up. ORR was 50.2%, and 15.3% of patients achieved CR (Table 2). There were 401 progression events (including death). Median PFS was 8.02 months (95% CI 7.33–8.77).

Factors associated with PFS in multivariate analysis are presented in Table 3. Significant baseline independent factors associated with lower PFS were ECOG PS ≥ 1 , elevated LDH, ≥ 3 metastatic sites and presence of BM.

The regression tree analysis was performed using the number of metastatic sites, ECOG PS, LDH category at baseline and presence of BM. The variable with the optimal first split was the number of metastatic sites, and 6 terminal subgroups were generated (Fig. 1). PFS curves corresponding to the 6 subgroups are presented in Fig. 2. Patients with < 3 metastatic sites, ECOG PS = 0 and absence of BM ($n = 232$) had the greatest 6-month and 1-year PFS rates (83% and 56%, respectively). On the other extreme, 6-month and 1-year PFS rates among patients with ≥ 3 metastatic sites, ECOG PS ≥ 1 and LDH $> N$ ($n = 156$) were the lowest (31% and 13%, respectively).

3.3. Safety

AEs of any grade, regardless of relationship to study drug, were observed in 93.9% of the patients and 18.8% were withdrawn from the study due to an AE/SAE. Overall, 29.4% of the patients presented at least one grade III AE, 3.2% of grade IV and 1.4% of grade V. Grade V events included confusion, septic shock, abdominal pain, sepsis, ischaemic stroke, hemiparesis, pneumonia, cerebral haematoma, anaemia, disease progression, death ($n = 1$ for each event) and general physical health deterioration ($n = 2$). Overall, 11.6% and 8.9% of the patients presented at least one AE that led to trametinib or dabrafenib withdrawal, respectively.

At least one SAE occurred in 28% of patients, 10.5% of which presented at least one SAE related to D + T as suspected by the investigator. The most frequent AEs were pyrexia/hyperthermia (38.2%), asthenia (36.8%),

Table 1
Patient demographic and clinical characteristics at baseline.

Characteristics	Total (N = 856)
Age (years), mean (SD)	58.5 (14.8)
Gender: male, n (%)	474 (55.4)
ECOG performance score, n (%)	
0	531 (62.0)
1	242 (28.3)
2	83 (9.7)
Disease stage at screening, n (%)	
Unresectable stage II	1 (0.1)
Unresectable stage III	67 (7.8)
IV	788 (92.1)
TNM stage (AJCC 7th ed.) at screening (M) ^a , n (%)	
M0	68 (8.0)
M1a	81 (9.5)
M1b	88 (10.3)
M1c	617 (72.2)
If M1c, presence of brain metastasis ^b	275 (44.6)
Type of BRAF V600 mutation, n (%)	
E	727 (84.9)
K	93 (10.9)
Other	36 (4.2)
Baseline serum LDH (ULN) in classes, n (%)	
< 1	366 (42.8)
$[1-2]$	160 (18.7)
≥ 2	61 (7.1)
Missing	269 (31.4)
Status regarding previous systemic anticancer treatment	
Naïve	449 (52.4%)
Non-naïve	407 (47.6%)
Patients with ≥ 1 prior immunotherapy treatment ^c	
No	740 (86.4%)
Yes	116 (13.6%)

n, number of patients in a group; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; ULN, upper limit normal; SD, standard deviation; TNM, tumour-node-metastasis; AJCC, American Joint Committee on Cancer; PD, progressive disease.

^a Data were missing for 2 patients.

^b Based on subjects with M1c at screening ($n = 617$).

^c Monoclonal antibodies (e.g. ipilimumab, anti-PD1) (in 12.0% of the patients), alpha-interferon.

Table 2
Efficacy outcomes.

End-point	Total (N = 856)
Best response, n (%)	
Complete response	122 (15.3) ^a
Partial response	315 (39.6) ^a
Stable disease	232 (29.1)
Progression	107 (13.4)
Not evaluable	15 (1.9)
Unknown	5 (0.6)
Missing	60 (7.0)
ORR, n (%)	430 (50.2) ^a
Duration of response (months), median (range)	4.3 (2.4–7.8)
DCR, n (%)	634 (74.1)
Progression event or death during study, n (%)	401 (46.8)
Median progression-free survival (months) (95% CI)	8.02 (7.33–8.77)

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

^a Seven patients achieved a response after progression and were not therefore included in the ORR.

diarrhoea (22.3%) and nausea (20.78%) (Supplementary Table 1).

Two patients reported a secondary melanoma that was treated by local excision. In both cases, the events

were related to D + T as suspected by the investigator. No actions were taken concerning treatment.

4. Discussion

To our knowledge, this is the largest prospective (856 patients) study including *BRAF V600*-mutant cutaneous melanoma patients treated with D + T. It had a recruitment close to the real-world setting, which is illustrated by 32.1% of patients with BM at inclusion. Patients who had received previous systemic melanoma treatment were also allowed in the study. However, it should be noted that, in contrast to current practice, the use of anti-PD1 was not standard of care in real-life and not readily available at the launch of the study, with only 13.6% of the patients having previously received immunotherapy. The median PFS for the overall population was 8.02 months and ORR was 50.2%.

To date, two other retrospective studies have gathered real-world data on melanoma treatment with D + T. The DESCRIBE II study included 271 patients with unresectable or distant metastatic *BRAF V600*-mutant cutaneous melanoma treated with D + T as part

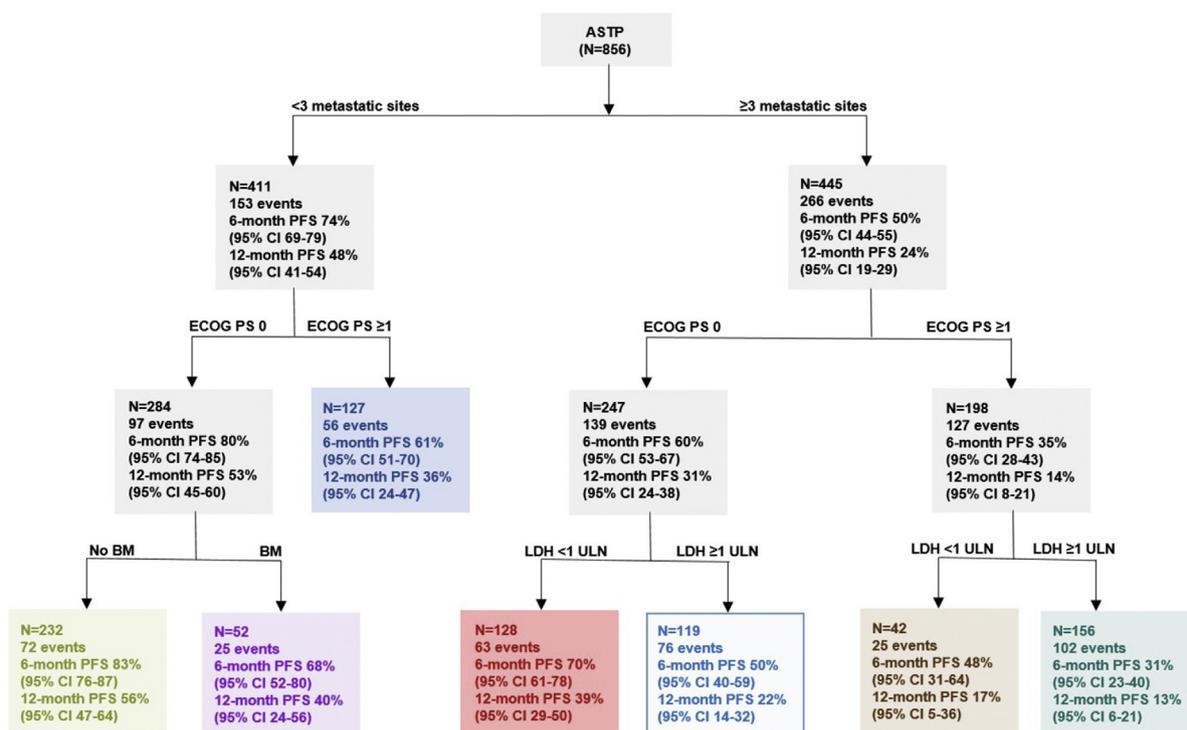
Table 3
Multivariate Cox proportional hazard analysis of PFS by prognostic factors - all subjects treated population (N = 856).

	Population (n)	Median PFS (months) (95% CI)	Multivariate analysis	
			HR (95% CI)	P value
LDH at baseline ^a				
<1 ULN	366	9.92 (8.77–13.01)	1.00 (reference)	–
[1; 2] ULN	160	6.21 (5.36–7.85)	1.64 (1.26–2.14)	0.0003
≥2 ULN	61	3.91 (2.89–5.52)	2.45 (1.70–3.53)	<0.0001
Missing	269		1.34 (1.05–1.71)	0.0167
M1c				
No	237	11.17 (9.30–18.07)	1.00 (reference)	–
Yes	617	7.06 (6.01–7.52)	1.20 (0.88–1.64)	0.2457
Missing	2		–	–
ECOG PS ^a				
0	531	9.59 (8.90–11.17)	1.00 (reference)	–
1	242	6.01 (5.55–7.36)	1.49 (1.19–1.87)	0.0005
≥2	83	3.88 (2.99–4.73)	2.32 (1.69–3.19)	<0.0001
Metastatic sites ^a				
<3	344	10.51 (9.10–13.50)	1.00 (reference)	–
≥3	445	5.95 (5.52–7.06)	1.61 (1.28–2.02)	<0.0001
Missing	67		1.05 (0.63–1.74)	0.8494
Status				
Naïve	449	8.61 (7.59–9.40)	1.00 (reference)	–
Non-naïve	407	6.87 (5.95–8.25)	1.21 (0.98–1.49)	0.0749
Patients with ≥1 prior immunotherapy treatment				
No	740	–	1.00 (reference)	–
Yes	116	–	0.94 (0.69–1.29)	0.7128
Presence of BM ^a				
No	579	–	1.00 (reference)	–
Yes	275	–	1.38 (1.11–1.71)	0.0043
Missing	2		–	–

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; HR, hazard ratio; LDH, lactate dehydrogenase; ULN, upper limit normal.

^a Factors included in the regression analysis.



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

Fig. 1. Regression tree for 6- and 12-month progression-free survival rates, all subjects treated population (N = 856). ASTP, all subjects treated population; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BM, brain metastasis; PFS, progression-free survival; CI, confidence interval; LDH, lactate dehydrogenase; ULN, upper limit normal.

of the combination Named Patient Program [18]: 92.6% had stage IV melanoma, and 36.5% BM at study entry. D + T was used in first line for 63.1% of patients and in second line for 29.5% of patients. Among BRAF inhibitor-naïve patients, the ORR was 67.3% and median PFS was 7.5 months. In a Japanese study [19] that included only 50 patients, the response rate was 72.3%, with CR achieved in 8 cases (17.0%), PR in 26 (55.3%), SD in 9 (19.1%) and PD in 4 (8.5%).

Robert *et al.* recently published extended survival data from the pooled analysis of 2 registration trials (COMBI-d and COMBI-v) involving previously untreated melanoma patients who had received D + T. The median follow-up was 22 months (range 0–76). The median PFS was 11.1 months (95% CI 9.5–12.8), and at 5 years, 34% (95% CI 30–38) of the patients were still alive.

No direct comparison of outcomes is possible because of the different populations enrolled in our study and this pooled analysis of registration trials. The median PFS is, as expected, shorter in our study, because our population is much closer to real-life than the population enrolled in COMBI-v and COMBI-d with strict exclusion criteria, such as absence of BM or of previous systemic melanoma treatment, or ECOG PS = 2.

Indeed, our population exhibited severe prognostic markers, with 72.2% of M1c stage IV patients, 37.5% of patients with LDH ≥1 upper limit normal (ULN) among those with measured LDH serum level, only 52.5% of treatment-naïve patients and, most importantly, 32.1% of patients with BM at baseline.

In the present study, baseline factors associated with PFS were LDH, ECOG, number of metastatic sites and the presence of BM. These results are consistent with the trend described by Long *et al.* in their analysis [15], and confirm previous findings from registration trials that LDH, ECOG and disease burden are associated with shorter PFS [20]. The ‘real-world’ setting of the study presented here introduces BM as a major prognostic factor. In multivariate analysis, patients with BM were 1.38 times as likely as those without to experience progression. Davies *et al.* [21] evaluated the use of dabrafenib and trametinib in patients with cutaneous melanoma metastatic to the brain in the phase 2 COMBI-MB trial. In this study, 125 patients were divided into 4 cohorts depending on baseline characteristics (LDH level, ECOG status, type of mutation, symptoms of BM). Median PFS ranged from 4.2 to 7.2 months and the duration of clinical response was generally shorter than that observed in melanoma

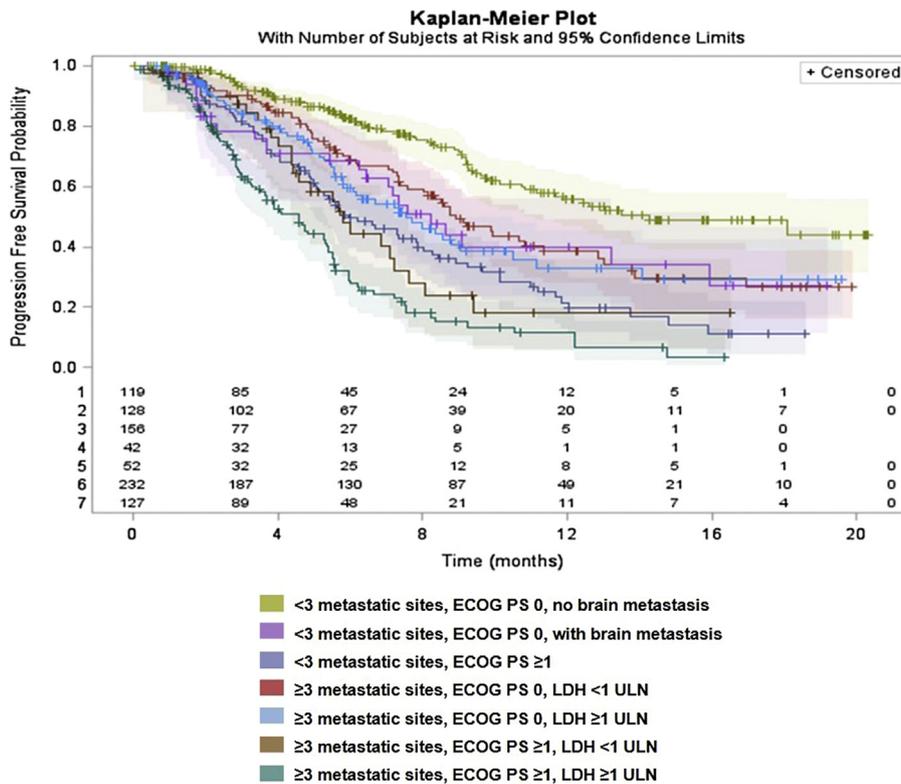


Fig. 2. Kaplan–Meier progression-free survival curves for different subgroups, all subjects treated population (N = 856). ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; ULN, upper limit normal.

patients without BMs (median duration of overall response ranged from 4.5 to 8.3 months). These results together with ours have important implications and reinforce the idea that better treatments for BM are a pressing need to improve outcomes of patients with melanoma and BMs. The regression tree analysis identified patients with <3 metastatic sites, ECOG PS 0 and no BM as having the longest duration of PFS, with 83% of the patients being progression-free at 6 months and 56% at 12 months. In contrast, among patients with ≥3 metastatic sites, ECOG PS ≥1 and LDH ≥1 ULN, 6-month and 1-year PFS rates were 31% and 13%, respectively. The main drivers of this regression tree are similar to those found in the pooled analysis, but the presence/absence of BM logically enters the tree, as expected for such an important factor. Thus, this tree is probably more meaningful for the real practice than the one obtained in pooled analysis of registration trials.

The safety profile of D + T in this study was similar to that reported in previous studies and no new safety signals were observed [20,22], although certain deviations were allowed, specially concerning cardiovascular medical history.

The major strength of this large study is the representativity of sample and the possibility to generalise the results. However, the fact that the study was a way to access to a drug not otherwise available, had several consequences on the follow-up and data collections. Patients were withdrawn from the study not only at

progression but also upon approval of trametinib. The follow-up during the study was therefore short, with lack of meaningful OS data, and the duration differed among patients. Moreover, the collection of LDH and type of mutation was implemented along the study following recommendations from the investigators, the data are therefore not available for all patients. Unlike in a controlled trial, there was no centralized assessment of radiological images. Strict adherence of investigators to the Response Evaluation Criteria in Solid Tumours version 1.1 evaluation criteria was not verified but seems plausible as the majority of patients were treated in centres which had included numerous patients in melanoma trials using those criteria.

In conclusion, this study contributes to the field of *BRAF V600*-mutant cutaneous melanoma by including the largest population to date in near real-world conditions, including patients with BM. The results not only confirm the clinical activity of D + T, but also provide realistic figures of ORR and PFS in a real-world setting, and provide clinicians with practical tools to predict the PFS when treated by D + T.

Authorship file based on CReDiT roles

Philippe Saiag: Conceptualisation, Methodology, Validation, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization, Supervision; **Caroline Robert:** Investigation, Resources,

Writing – review & editing; **Jean-Jacques Grob**: Investigation, Resources, Writing – review & editing; **Laurent Mortier**: Investigation, Resources, Writing – review & editing; **Olivier Dereure**: Investigation, Resources, Writing – review & editing; **Céléste Lebbe**: Investigation, Resources, Writing – review & editing; **Sandrine Mansard**: Investigation, Resources, Writing – review & editing; **Florent Grange**: Investigation, Resources, Writing – review & editing; **Eve-Marie Neidhart**: Investigation, Resources, Writing – review & editing; **Thierry Lesimple**: Investigation, Resources, Writing – review & editing; **Laurent Machet**: Investigation, Resources, Writing – review & editing; **Christophe Bedane**: Investigation, Resources, Writing – review & editing; **Hervé Maillard**: Investigation, Resources, Writing – review & editing; **Sophie Dalac-Rat**: Investigation, Resources, Writing – review & editing; **Charlée Nardin**: Investigation, Resources, Writing – review & editing; **Alexandra Szenik**: Conceptualization, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration; **Amine Denden**: Conceptualisation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration; **Caroline Dutriaux**: Investigation, Resources, Writing – review & editing.

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Conflict of interest statement

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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.

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Appendix A. Supplementary data

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