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Adjuvant dabrafenib and trametinib for patients with resected *BRAF*-mutated melanoma: DESCRIBE-AD real-world retrospective observational study

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BRAF and MEK inhibitor, dabrafenib plus trametinib, adjuvant therapy is effective for high-risk resected melanoma patients with *BRAF*-^{V600} mutations. However, real-world evidence is limited. We aimed to determine the feasibility of this therapy in routine clinical practice. DESCRIBE-AD, a retrospective observational study, collected real-world data from 25 hospitals in Spain. Histologically confirmed and resected *BRAF*-mutated melanoma patients aged ≥18 years who were previously treated with dabrafenib plus trametinib adjuvant therapy, were included. The primary objectives were treatment discontinuation rate and time to discontinuation. The secondary objectives included safety and efficacy. From October 2020 to March 2021, 65 patients were included. Dabrafenib and trametinib discontinuation rate due to treatment-related adverse events (TRAEs) of any grade was 9%. Other reasons for discontinuation included patients' decisions (6%), physician decisions (6%), unrelated adverse events (3%), disease progression (5%), and others (5%). The median time to treatment discontinuation was 9 months [95% confidence interval (CI), 5–11]. G3–4 TRAEs occurred in 21.5% of patients, the most common being pyrexia (3%), asthenia (3%), and diarrhoea (3%). Unscheduled hospitalisations and clinical tests occurred in 6 and 22% of patients, respectively. After 20-month median follow-up (95% CI, 18–22), 9% of patients had exitus due to disease progression, with a 12-month relapse-free survival and overall survival rates of 95.3% and 100%, respectively. Dabrafenib and trametinib adjuvant therapy proved effective for melanoma patients in a real-world setting, with a manageable toxicity profile. Toxicity frequencies were low leading to low incidence of unscheduled medical visits, tests, and treatment discontinuations. *Melanoma Res* 33: 388–397

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Introduction

The incidence of cutaneous malignant melanoma is estimated at 8.8/100 000 people per year in Spain [1,2]. Surgical resection is the standard of care for early-stage melanoma [3]. Unfortunately, there is a high risk of

recurrence in patients with stage III melanoma, regional lymph node involvement, or the presence of in-transit metastases. Adjuvant therapy following surgical resection of the primary tumour reduces the probability of relapse and is encouraged, especially for high-risk patients [4].

The implementation of targeted therapy, with combinations of BRAF and MEK inhibitors, and immune checkpoint inhibitors, including those for anti-programmed death 1 (anti-PD-1) or cytotoxic T-lymphocyte antigen 4, in the adjuvant setting for melanoma patients has led to an increase in relapse-free survival (RFS) [5–12].

Approved adjuvant immunotherapies such as ipilimumab, pembrolizumab, or nivolumab, reported 1-year RFS of 63.5%, 75.4%, and 70.5%, respectively [5–11].

In *BRAF*-mutated melanoma patients, dabrafenib and trametinib combination have shown efficacy in the adjuvant setting in clinical trials [11–13]. The phase III clinical trial COMBI-AD reported an RFS rate at 1-year of 88% in the adjuvant setting with a manageable toxicity profile, which is of utmost reference for adjuvant therapies; 21.5% of patients experienced grade 3–4 treatment-related adverse events (TRAEs) and 26% discontinued therapy due to toxicity [11].

In the real-world context, anti-PD-1 adjuvant treatment led to grade 3–4 TRAEs in 16% of patients, and 22% treatment discontinuation due to toxicity, while reaching a 30-month (2.5 years) overall survival (OS) rate of 78% [14,15]. Evidence from routine clinical care for adjuvant dabrafenib and trametinib combination is limited.

Due to the current variety of approved therapies in the adjuvant setting, validation of results reported in clinical trials is required in a real-world context to enable a comprehensive therapeutic assignment that ensures patient well-being and optimises healthcare resources.

We sought to determine whether dabrafenib and trametinib would achieve relapse control while being safe and feasible therapy in the real world.

Patients and methods

Study design

DESCRIBE-AD was an observational, retrospective study including *BRAF*-mutated melanoma patients treated with dabrafenib plus trametinib in the adjuvant setting in 25 hospitals in Spain associated with the Grupo Español Multidisciplinar de Melanoma.

The study used secondary data retrieved from the medical records. The assignment of a patient to a specific therapeutic strategy was already decided in advance by the routine clinical practice of medicine and clearly dissociated from the decision to include a patient in the study. No additional interventions to the usual care were applied to the patients, either for diagnostic or follow-up reasons. Survival was updated prospectively at the end of the study to prolong the follow-up. Epidemiological methods were used to analyse the data.

Patients

Histologically confirmed and completely resected *BRAF*-mutated melanoma patients, aged ≥18 years, treated with dabrafenib plus trametinib in the adjuvant setting were included. Patients should have started dabrafenib plus trametinib at least 1 year prior to enrolment to ensure an adequate retrospective follow-up. Patients completed adjuvant treatment with dabrafenib plus trametinib at the time of study initiation. Only previous surgeries for melanoma were allowed. No other prior local (i.e. radiotherapy) or systemic anti-cancer therapy for melanoma was permitted.

Ethics and regulatory requirements

Patients provided written informed consent to participate, although informed consent exemption was considered in those cases for which the effort to obtain informed consent was beyond feasible (i.e. death patients).

This study was carried out in compliance with local regulations, the International Conference Harmonisation guidelines, and the principles derived from the Helsinki declaration and its latest update (Fortaleza 2013). The study was classified as non-interventional study with other designs (EPA-OD) by the competent authority in Spain and was granted approval by the Ethics committee of Institut Català d`Oncologia – Hospital Universitari Germans Trias i Pujol in March 2020 (Reference: PI-20-036).

Objectives and endpoints

The primary objective was to describe the discontinuation frequency and time to discontinuation of dabrafenib plus trametinib in the adjuvant setting in the real world. The frequency of discontinuation was measured as the rate of treatment discontinuation due to unacceptable toxicity and the rate of discontinuation due to other causes.

Descriptive baseline characteristics included demographic and pathologic endpoints.

Secondary objectives were to describe the safety profile, efficacy, and health resources used.

Secondary endpoints for safety included the rate of dose interruptions, dose modifications, and the rate of TRAEs. Data for adverse events were classified and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.03.

The study recorded indirect pharmacoeconomic endpoints such as health resources in terms of hospital visits (urgency, oncologist, primary care), hospital admissions

and their duration, need for new pharmacological treatments, concomitant therapies, management of adverse events, and medical tests.

Efficacy endpoints included RFS, defined as the time from the start of dabrafenib plus trametinib until disease recurrence or death related to melanoma progression, and OS, defined as the time from dabrafenib plus trametinib initiation to death from any cause.

The frequency of assessments was determined by the standard clinical practice at each hospital.

Preventive measures to identify and control patient duplicates were implemented into variables such as birth date, sex, centre, or diagnosis.

Statistical analysis

Continuous variables were summarised using descriptive statistics. Frequency counts and percentages of subjects within each category were provided for categorical data. The response percentages were estimated using 95% confidence intervals (CIs) or full-range intervals. The time-to-event endpoints were estimated using the Kaplan–Meier method and Cox regression analysis to obtain hazard ratios and CIs. Patients without documented progression or death at the time of analysis were censored at the last date of tumour evaluation. All statistical analyses were performed with R [version 3.6.3 (2020-02-29) 'Holding the Windsock', The R Foundation for Statistical Computing, Vienna, Austria] and SPSS (IBM SPSS Statistics Version 26, Armonk, New York, USA). Figures and tables were generated using RStudio (Version 1.2.5033 2009-2019 RStudio, Inc., Boston, Massachusetts, USA). Statistical tests were two-tailed, $P < 0.05$, for significance.

The trial was expected to include a number of 40–60 patients. There was no formal statistical assumption to calculate the sample size; this project was purely descriptive.

Results

Patient enrolment

Between October 2020 and March 2021, 74 patients with *BRAF*-^{V600} mutations were screened, 65 included. Our population was older, with a median age of 58 years (range: 30–84), and included fewer patients with multiple lymph node affection (83.1% vs. 93%) and in-transit metastasis (10.8% vs. 12%) than those in the phase III COMBI-AD trial (Table 1). Three patients with stage I–II [American Joint Committee on Cancer (AJCC) classification 7th and 8th editions] who had a high tumour burden (T3) and two patients with stage IV having resectable distant metastasis were selected for adjuvant treatment following the physician independent criteria. *BRAF*-^{V600} mutations had a similar frequency to the described frequency in melanoma patients (Fig. 1b).

Treatment compliance

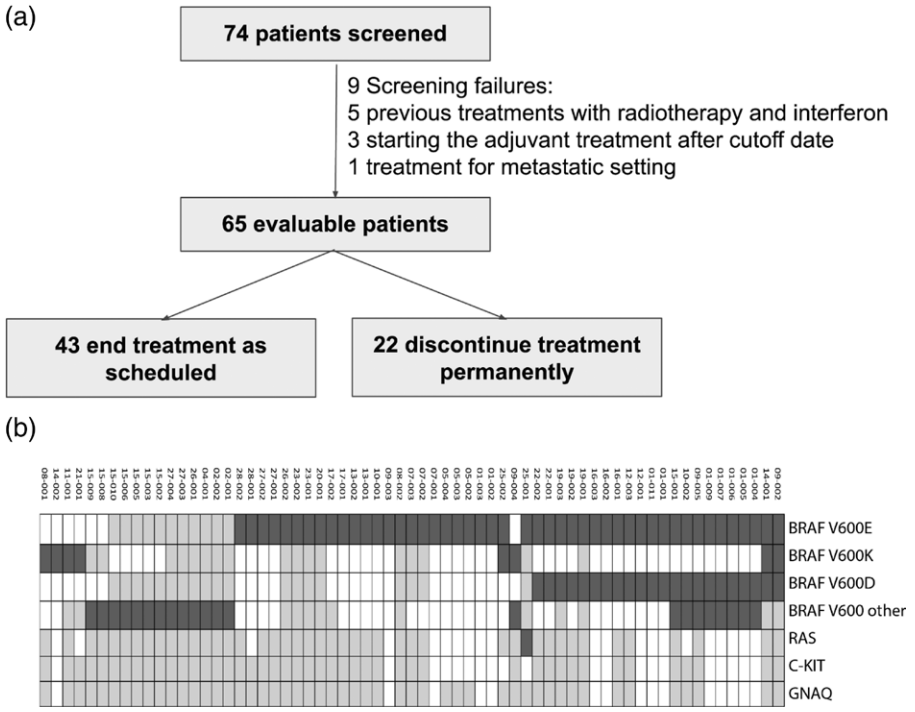
All patients were no longer receiving dabrafenib plus trametinib; 43 (66.2%) patients completed the adjuvant treatment as scheduled, and 22 (43.8%) discontinued treatment prematurely: 6 (9.2%) due to unacceptable toxicity, one of which was due to treatment-related pyrexia (Fig. 2). Other reasons for treatment discontinuation included patient decision (6.2%), disease relapse (4.6%), physician criteria (4.6%), non-related adverse events (4.6%), and other (4.6%) (Fig. 2). No adverse events were reported for those patients who discontinued due to patient or investigator criteria. Other causes

Table 1 Baseline patient characteristics for the melanoma patients enrolled in the DESCRIBE-AD study and in the phase III clinical trial COMBI-AD, that led to approval of dabrafenib plus trametinib in the adjuvant setting for melanoma

Characteristic	Unit	Describe-AD	COMBI-AD
Median age (range)	Years	58 (30–84)	50 (18–89)
Sex			
Male	*n* (%)	36 (55.4)	195 (45)
Female	*n* (%)	29 (44.6)	243 (55)
BRAF mutation status			
BRAF wild	*n* (%)	0 (0)	0 (0)
BRAF-mutated	*n* (%)	65 (100)	438 (100)
uk	*n* (%)	0 (0)	0 (0)
ECOG performance status			
0	*n* (%)	39 (60)	402 (92)
1	n (%)	16 (24.6)	33 (8)
3	*n* (%)	1 (1.5)	0 (0)
uk	*n* (%)	9 (13.8)	3 (1)
Disease stage AJCC 7th ed			
I–II	*n* (%)	3 (4.6)	0 (0)
IIIA	*n* (%)	19 (29.2)	83 (19)
IIIB	*n* (%)	18 (27.7)	169 (39)
IIIC	*n* (%)	22 (33.8)	181 (41)
IV	*n* (%)	2 (3.1)	0 (0)
uk	*n* (%)	1 (1.5)	5 (1)
Disease stage AJCC 8th ed.			
I–II	*n* (%)	3 (4.6)	0 (0)
IIIA	*n* (%)	13 (20)	50 (11.4)
IIIB	*n* (%)	15 (23.1)	145 (33.1)
IIIC	*n* (%)	31 (47.7)	217 (49.5)
IIID	*n* (%)	0 (0)	22 (5)
IV	*n* (%)	2 (1.5)	0 (0)
uk	*n* (%)	1 (7.7)	4 (1)
Number of affected lymph nodes			
0	*n* (%)	5 (7.7)	0 (0)
1	*n* (%)	37 (56.9)	177 (40)
2 or 3	*n* (%)	12 (18.5)	158 (36)
≥4	*n* (%)	5 (7.7)	73 (17)
uk	*n* (%)	6 (9.2)	30 (7)
Type of lymph node involvement			
Microscopic	*n* (%)	29 (44.6)	152 (35)
Macroscopic	*n* (%)	23 (35.4)	158 (36)
na (i.e. nodes 0)	*n* (%)	5 (7.7)	0 (0)
uk	*n* (%)	8 (12.3)	128 (29)
Breslow			
<2	*n* (%)	15 (23.1%)	–
≥2	*n* (%)	46 (70.8)	–
uk	*n* (%)	0 (0)	–
Primary tumour ulceration			
Yes	*n* (%)	26 (40)	179 (41)
No	*n* (%)	35 (53.8)	253 (58)
uk	*n* (%)	4 (6.2)	6 (1)
In-transit metastasis			
Yes	*n* (%)	7 (10.8)	51 (12)
No	*n* (%)	50 (76.9)	387 (88)
uk	*n* (%)	8 (12.3)	0 (0)

AJCC, American Joint Committee on Cancer; uk, unknown.

Fig. 1



(a) Patient flowchart and (b) mutational status at baseline. In the heatmap, dark grey colour indicates presence of a mutation and light grey not determined value.

included diagnosis of second tumour, surgery, and one not specified. Dabrafenib and trametinib were discontinued simultaneously in all cases. There was no correlation between treatment discontinuation and disease stage at diagnosis (Supplementary Table S1, Supplemental digital content 1, *http://links.lww.com/MR/A317*).

The median duration of treatment was 12 months (95% CI, 11.4–12.1). The median duration of treatment for those patients who discontinued treatment prematurely due to unacceptable toxicity was 9 months (range 4.5–15.6) (Fig. 2). Dabrafenib and trametinib doses were reduced in 14 (21.2%) patients, and interrupted in 10 (15.4%) to manage toxicities.

Safety

In total, 50 (76.9%) patients experienced at least one TRAE, the most frequent were: fever 23 (35.4%), fatigue 19 (29.2%), diarrhoea 12 (18.5%), and arthralgia 10 (15.4%) (Table 2).

Grade 3–4 TRAEs (grade 3–4) were reported at least once in 14 patients (21.5%), the most frequent being increased levels of creatine phosphokinase (4.6%) (Table 2). Eight serious adverse events (SAEs) were reported, affecting 7 (10.8%) patients, most related to infection processes (4.6%), and vascular incidents (4.6%). All SAEs were resolved by data cut-off (Table 2). Most toxicities were reversible, 2 (3.1%) patients reported worsening condition, and 2 (3.1%) presented minor sequelae due to neutropenia and fatigue. During treatment, 39 (60%) patients required concomitant or rescue medication to manage TRAE, omeprazole 8 (12.3%) and paracetamol 7 (10.8%) being the most common drugs (Supplementary Table S2, Supplemental digital content 1, *http://links.lww.com/MR/A317*).

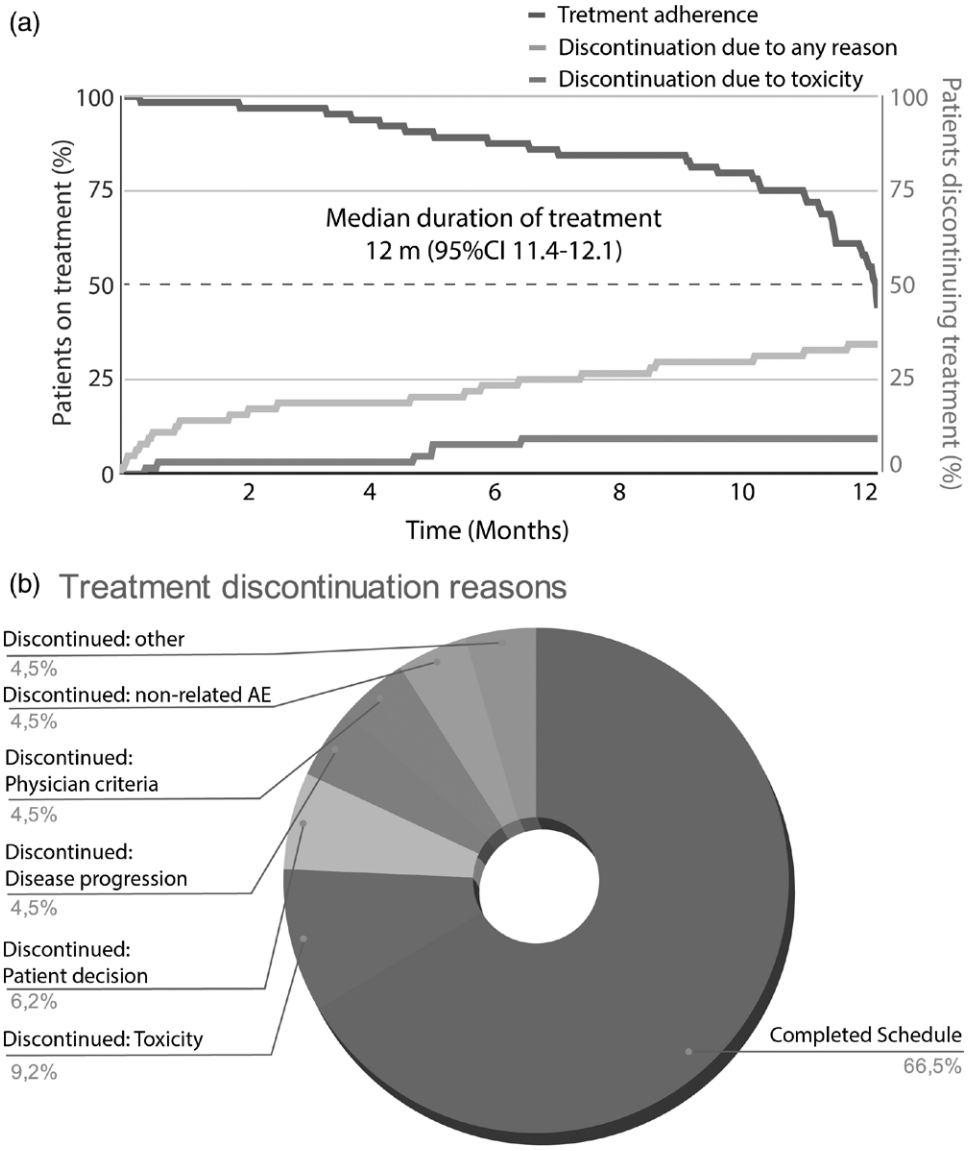
Healthcare system resources

As a consequence of the medical condition and the aforementioned toxicities, 24 (36.9%) patients had unscheduled medical visits (Fig. 3), with a median per patient of 1.5 (95% CI, 1–4); a total of 60 visits. The most frequent unscheduled visits were consultations with oncologists 26 (43.3%), emergency visits 17 (28.3%), and consultations with dermatologists 9 (15.0%) (Fig. 3). Four (6.7%) patients required unscheduled hospitalisation once.

Fourteen (21.5%) patients required unscheduled medical tests, with a median of 2.00 tests (95% CI, 1–5) per patient. There were 44 unscheduled medical tests reported, the most frequent: blood analysis 14 (31.8%), and chest/thorax radiodiagnostic determinations 12 (27.3%) (Fig. 3). There were 3 (6.8%) unscheduled CT scans.

Burden of pyrexia-related events was assessed using a composite endpoint accounting with the grade 3–4 pyrexia, hospitalisation events due to pyrexia, and treatment permanent discontinuations caused by pyrexia

Fig. 2



Dabrafenib and trametinib treatment compliance. (a) Treatment adherence. The percentage of patients who remain on treatment, the percentage of patients who experienced an unscheduled treatment discontinuation and the percentage of patients discontinuing treatment due to toxicity throughout the 1-year scheduled adjuvant scheme is represented. (b) Percentage of patients who completed the treatment scheduled as expected and who discontinued treatment by different reasons: toxicity, patient decision, progressive disease, physician criteria, non-related adverse event and other.

[16]. The composite rate was 7.7%, with 3 (4.6%) patients experiencing grade 3 fever, 1 (1.5%) hospitalised, and 1 (1.5%) who permanently discontinued treatment due to pyrexia (Fig. 3g and h).

Efficacy

After a median follow-up of 19.7 months (95% CI, 18.3–22.5), the median RFS was not reached. The percentage of patients alive or without relapse at 12 and 24 months was 95.3% (95% CI, 90.3–100) and 72.9% (95% CI, 61.3–86.8), respectively (Fig. 4a).

Survival status was updated at the end of the study, with a median follow-up of 36.2 months (range: 13–51.1). Throughout the study period, 11 (16.9%) patients died, 10 due to disease progression and one due to coronavirus disease 2019 (see Supplementary Table S3, Supplemental digital content 1, *http://links.lww.com/MR/A317* for baseline characteristics of these patients). Median OS was not reached. The overall OS rates at 1 year, 2 years, and 3 years were 100% (95% CI, 100–100), 90.6% (95% CI, 83.8–98.1), and 83.2% (95% CI, 74.1–93.4), respectively (Fig. 4b). According to AJCC 7th ed. stage at diagnosis,

Table 2 Toxicity profile, summarising the treatment-related adverse events classified according to their grade (National Cancer Institute Common Toxicity Criteria for Adverse Events v4.03) and seriousness

	Any grade	Grade 3–4	SAE
Event	*n* (%)	*n* (%)	*n* (%)
All patients	50 (76.9)	14 (21.5)	7 (10.8)
Fever	23 (35.4)	2 (3.1)	1 (1.5)
Fatigue	19 (29.2)	2 (3.1)	–
Diarrhoea	12 (18.5)	2 (3.1)	–
Arthralgia	10 (15.4)	–	–
Nausea	7 (10.8)	–	–
Myalgia	6 (9.2)	–	–
Headache	6 (9.2)	–	–
Vomiting	5 (7.7)	–	–
Skin disorders	5 (7.7)	–	–
Rash	4 (6.2)	–	–
Musculoskeletal disorders – CPK increased	4 (6.2)	3 (4.6)	1 (1.5)
Gastrointestinal disorders	4 (6.2)	–	–
Anorexia	4 (6.2)	–	–
Abdominal pain	4 (6.2)	1 (1.5)	–
Chills	1 (1.5)	1 (1.5)	–
Colonic haemorrhage	1 (1.5)	1 (1.5)	1 (1.5)
Neutropenia	1 (1.5)	1 (1.5)	–
Febrile neutropenia	1 (1.5)	1 (1.5)	–
Oedema	1 (1.5)	1 (1.5)	1 (1.5)
Lung infection	1 (1.5)	1 (1.5)	1 (1.5)
Thromboembolic event	1 (1.5)	1 (1.5)	1 (1.5)
Urinary tract infection	1 (1.5)	–	1 (1.5)

For all grades events are reported with a 5% threshold despite those cases in which the events were grade 3–4 or were notified as serious adverse event.
CPK, creatine phosphokinase; SAE, serious adverse event.

the 3-year OS rate was 95.2% (95% CI, 86.6–100), 75% (56–100), and 76.8% (60.7–97.2) for stage II–IIIA, IIIB, and IIIC–IV respectively ($P = 0.334$) (Fig. 3c).

Discussion

To our knowledge, DESCRIBE-AD reported for the first time the efficacy, safety, and use of healthcare resources of adjuvant treatment with dabrafenib plus trametinib in a population of patients with resected melanoma in Spain.

Adjuvant dabrafenib plus trametinib proved a manageable toxicity profile while being highly effective for *BRAF-V600* mutated melanoma patients in phase III clinical trials [11–13,16,17] and in this real-world study.

According to our results, the frequency of TRAEs in the real world was lower than the benchmark study COMBI-AD, with rates of 76.9% and 97%, respectively (Supplementary Table S4, Supplemental digital content 1, *http://links.lww.com/MR/A317*). Grade 3–4 TRAEs were also less common, 21.5% vs. 41%, respectively, and led to less treatment discontinuation due to toxicity, 9.2% vs. 26% (Supplementary Table S4, Supplemental digital content 1, *http://links.lww.com/MR/A317*). or dose reductions (21.2% vs. 38%) [11]. The impact of pyrexia-associated symptoms was quite low, in line with previous reports [16]. Our results are in line with previous retrospective observational studies that reported a discontinuation rate due to toxicity of 13% [18]. The differences observed in the incidence of discontinuations due to toxicity may reflect the cumulative experience in handling specific treatment-related events and the management strategies implemented in routine clinical practice. The strict monitoring and drug management imposed in clinical trials may have also impacted the discontinuation rate.

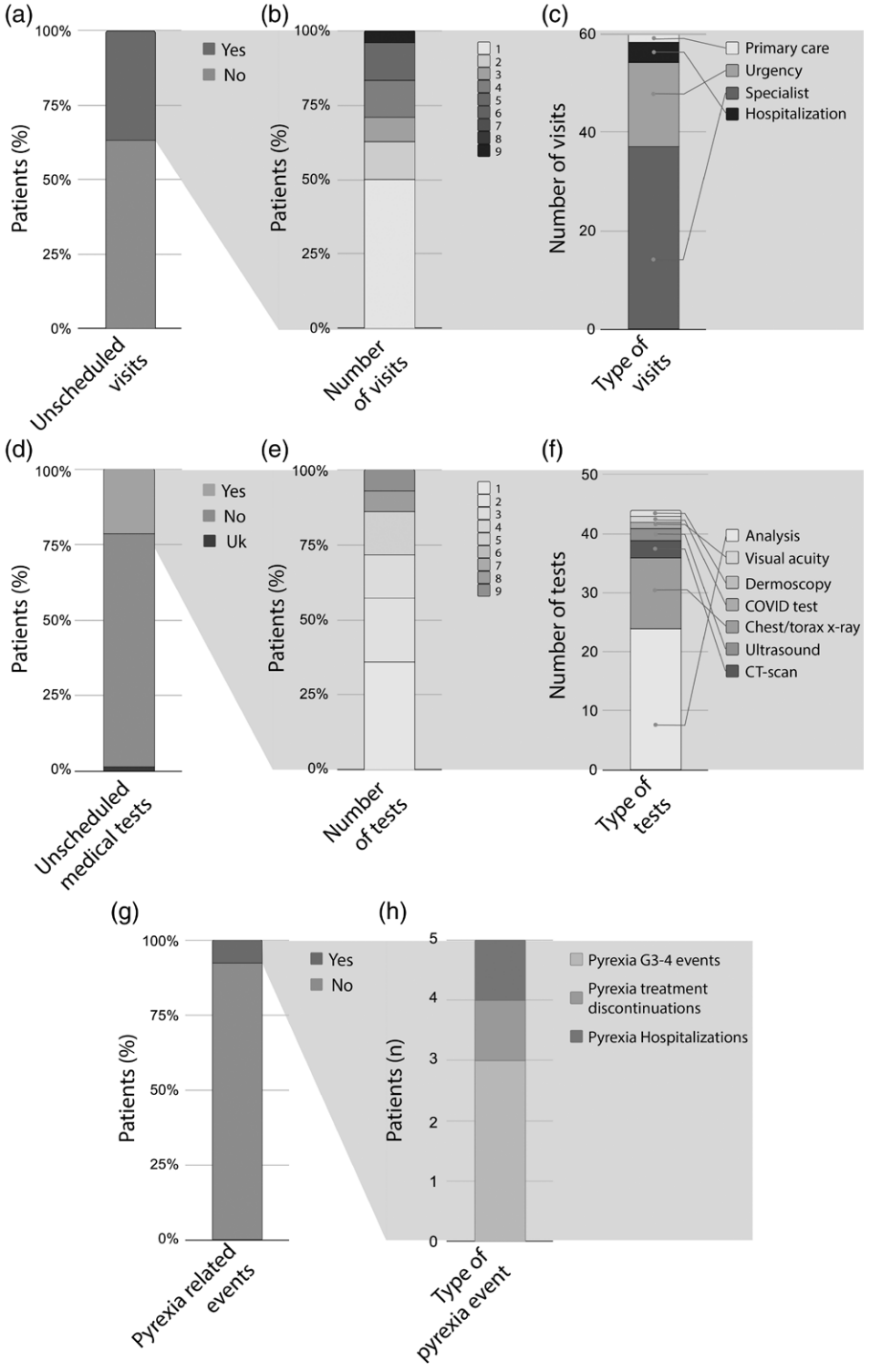
The discontinuation rate due to adverse events with nivolumab ranged from 9.7 to 18% [10,19], and with pembrolizumab 12.2% [7], whereas ipilimumab at a dose of 10 mg/kg of body weight reported a discontinuation rate of up to 54%, which was substantially higher [5,9]. In the real-world context, immunotherapies reported a discontinuation rate due to toxicity that ranged from 22 to 32% [14,20]. Thus, the management of dabrafenib and trametinib discontinuations seems feasible in the real-world context.

The number of unscheduled hospitalisations (6.7%) was lower than the rates from clinical trials of dabrafenib and trametinib in the current setting, which reported up to 25 and 11% of patients requiring hospitalisation due to SAEs or pyrexia, respectively [11]. Comorbidities did not differ greatly from that expected for the population of patients enrolled, and were easily handled.

In perspective, low-dose ipilimumab reported hospitalisation rates as high as 17.2% in a real-world retrospective study [20], whereas the incidence of hospitalisations for nivolumab was estimated by Wahler *et al.* at 3.8% [21]. The hospitalisation incidence in our population was in the range of immune checkpoint inhibitors. Nevertheless, dabrafenib and trametinib are mostly associated with an increased frequency of pyrexia, and gastrointestinal events, whereas immunotherapy is associated with endocrine dysfunction, diarrhoea, skin, immune-mediated, and infusion reactions [7]. The differences in the toxicity profile may be relevant for optimal treatment assignment and also from the pharmacoeconomic perspective, as events associated with immunotherapy such as endocrine disorders may become chronic and often imply more unscheduled hospitalizations [21].

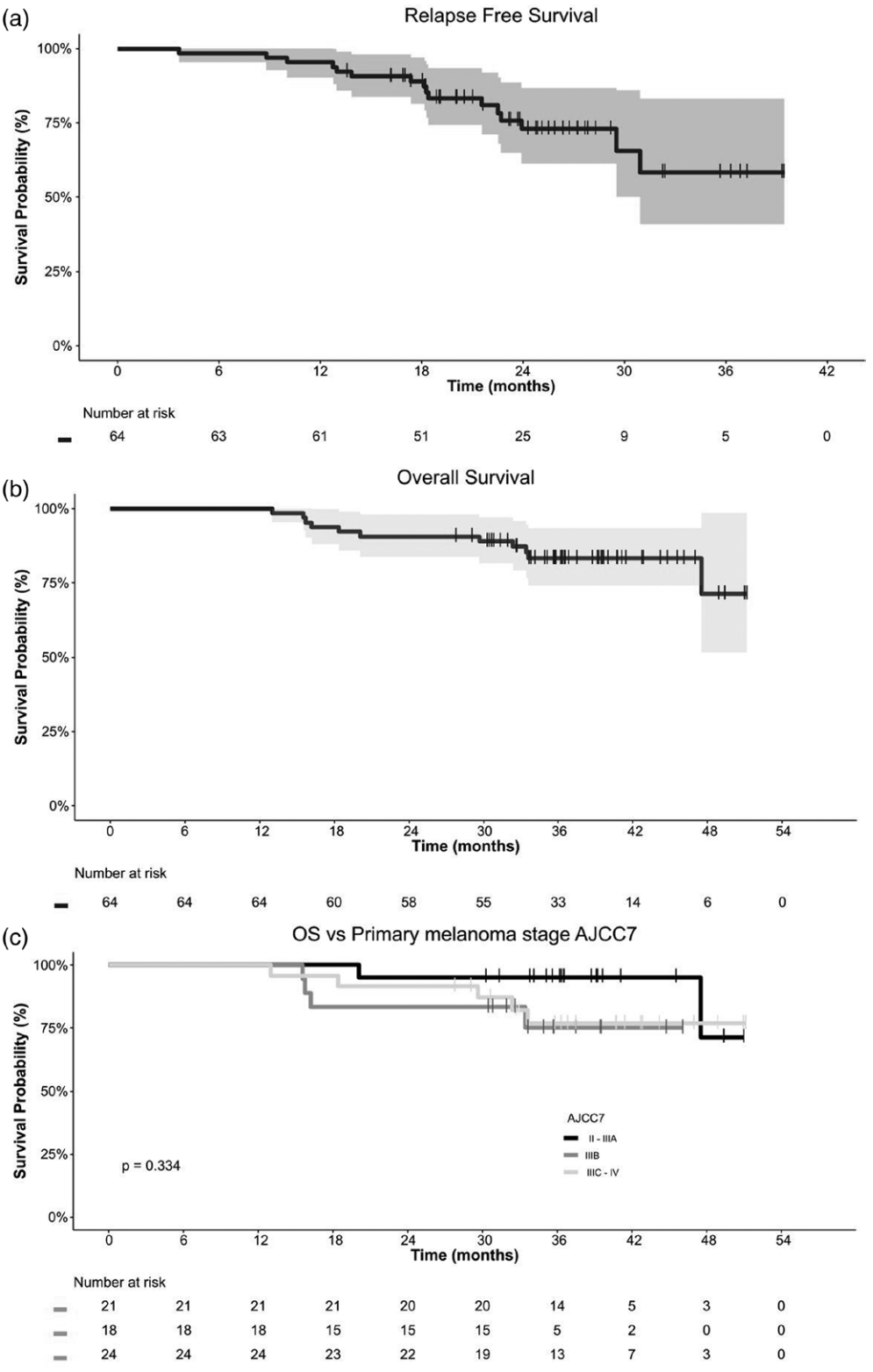
The COMBI-AD trial reported an RFS rate at 1 year of 88% [11–13]. In line with this, the RFS reached a 1-year rate of 95.3% in our cohort, validating the efficacy in the real-world (Supplementary Table S3, Supplemental digital content 1, *http://links.lww.com/MR/A317*). The RFS in DESCRIBE-AD was higher when indirectly compared to other adjuvant treatments [5,7,11]. Dabrafenib plus trametinib also achieved high OS rates regardless of stage, while recent reports pointed out a limited benefit of adjuvant immunotherapy in low-risk patients (i.e. stages IIIA and IIIB) in the real-world context [15]. Better treatment adherence during the study may explain the increase in RFS regarding COMBI-AD, although the inclusion of patients with better prognosis (i.e. lower stage, less lymph node affectation, or in-transit metastasis) might also have an impact. For instance, our cohort included fewer patients with stage IIIC (32.3% vs. 41%), and fewer patients with multiple affected lymph nodes (25.5% vs. 53%) [5,7,11].

Fig. 3



Healthcare resources-related indicators. The healthcare resources associated with dabrafenib and trametinib treatment were analysed by (a and d) the number of unscheduled visits and unscheduled medical tests, (b and e) the number of these unscheduled visits and medical tests per patients and (c and f) the type of these unscheduled visits and medical tests. Percentage of patients suffering from (g) pyrexia-related events and (h) their number by pyrexia event type. Colour scales for both unscheduled visits and unscheduled medical tests are representative of the estimated indirect relative costs for the healthcare system based on median cost for healthcare published by Spanish Health Ministry (https://www.sanidad.gob.es/estadEstudios/estadisticas/inforRecopilaciones/anaDesarrolloGDR.htm). The higher saturation of the colour indicates a greater cost of the visit and medical test, although the scale is not linearly proportional to the cost and remains an estimation to ease the visualisation of the frequency of those events with higher impact on the healthcare system budget.

Fig. 4



Dabrafenib plus trametinib efficacy. Relapse-free survival, defined as the time elapsed from the first dose of dabrafenib and trametinib to the date of relapse, or (a) death due to PD and (b) overall survival, defined as the time elapsed from the first dose of dabrafenib and trametinib to the date of death by any cause or lost to follow-up for the full dataset or (c) stratified by stage at diagnosis. The graphs represent the percentage of patients without events (relapse, death) over time. The patient diagnosed with stage I melanoma was not included within the survival analysis, as prognosis in stage I melanoma differs significantly from the other subgroups. PD, progressive disease.

The main caveats of this study were related to the intrinsic limitations of non-controlled and retrospective observational studies, which may lead to a higher rate of missing data. Follow-up information was also limited, with a high number of censures from 12 months after the end of treatment. However, most variables had more than 90% of data availability, and the study achieved sufficient data completion to ensure solid conclusions.

Conclusion

The low frequency and severity of toxicities led to an amenable number of treatment discontinuations and unscheduled medical visits and tests; together with a great RFS, indicate that dabrafenib and trametinib is a feasible treatment for melanoma patients. This therapy implied a low use of unscheduled healthcare resources in the real world and may be implemented for routine clinical management of *BRAF-*^{V600} melanoma patients, especially for those not eligible for immunotherapy.

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Conflicts of interest

J.M.-L. has received lecture fees from Astellas, Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Pfizer, Roche, and Sanofi; advisory fees from Bristol-Myers Squibb, Highlight Therapeutics, Novartis, Pierre Fabre, Roche, and Sanofi; research grants from Sanofi; and travel grants from Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Pfizer, Roche, and Ipsen. M.Q. has received lecture fees from Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Roche, Sanofi, GSK; Astra-Zeneca, and Clovis; advisory fees from Bristol-Myers Squibb, Novartis, Roche, GSK, Astra-Zeneca, and MSD; and travel grants from MSD, Novartis, Pierre Fabre, GSK, and Astra-Zeneca. L.F.-M. has received lecture fees from Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, and Roche; and advisory fees from Novartis. J.R.M. has received advisory boards and consulting fees from BMS, Amgen, Novartis, Rainier, Janssen, and Pierre Fabre; speaker honoraria from Roche, BMS, Novartis, MSD, Janssen, Pfizer, and Astra-Zeneca; travel, accommodations, expenses from Astellas, Novartis, Roche, BMS, Pfizer, MSD, and Astra-Zeneca; and Corporate-sponsored research grants from Astra-Zeneca, BMS, Amgen, Roche, Novartis, MSD, Janssen, Pfizer, Astellas, GSK, PharmaMar, Ipsen, Tesaro, Abbvie, Aprea Therapeutics, Eisai, Bayer, Merck, IOVANCE, and Nektar. J.M.M. has received advisory boards and consulting fees from BMS, Novartis, Pierre Fabre, and Sanofi; speaker honoraria from Roche, BMS, Novartis, and MSD; travel, accommodations, expenses from Novartis, Roche, BMS, Ipsen, and MSD. P.C.-F. has received advisory boards and consulting fees from BMS, MSD, Novartis, Pierre Fabre, Roche, Sanofi, and SunPharma; travel, accommodations, expenses from BMS, MSD, Novartis, Pierre Fabre, Sanofi, and SunPharma. L.E.F. and G.B.F. declared to be employed by Novartis. For the remaining authors, there are no conflicts of interest.

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