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Dabrafenib plus trametinib for compassionate use in metastatic melanoma

A STROBE-compliant retrospective observational postauthorization study

Salvador Martín Algarra, MD[a,*], Virtudes Soriano, MD[b], Luis Fernández-Morales, MD[c], Miguel-Ángel Berciano-Guerrero, MD[d], Karmele Mujika, MD[e], José Luis Manzano, MD[f], Teresa Puértolas Hernández, MD[g], Ainara Soria, MD[h], Delvys Rodríguez-Abreu, MD[i], Enrique Espinosa Arranz, MD[j], Javier Medina Martínez, MD[k], Ivan Márquez-Rodas, MD[l], Jordi Rubió-Casadevall, MD[m], María Eugenia Ortega, MD[n], José Miguel Jurado García, MD[o], María José Lecumberri Biurrun, MD[p], Isabel Palacio, MD[q], María Rodríguez de la Borbolla Artacho, MD[r], Javier Pérez Altozano, MD[s], Victoria Eugenia Castellón Rubio, MD[t], Almudena García, MD[u], Pablo Luna, MD[v], Anabel Ballesteros, MD[w], Ovidio Fernández, MD[x], Jose Antonio López Martín, MD[y], Alfonso Berrocal, MD[z], Ana Arance, MD[aa]

Abstract

The main objective of the study was to evaluate the efficacy and safety of dabrafenib alone or combined with trametinib for compassionate use in patients with metastatic melanoma.

This retrospective, observational study involved 135 patients with unresectable stage IIIC or stage IV melanoma from an expanded-access program at 30 Spanish centers.

Forty-eight patients received dabrafenib monotherapy and 87 received combination dabrafenib and trametinib; 4.4% and 95.6% of the patients had stage IIIC and IV melanoma, respectively. All patients showed *BRAF* mutations in their primary or metastatic lesions; 3 were positive for V600K while the remainder had V600E or V600+. A positive response to treatment was reported in 89.3% of the patients. Overall survival rates at 12 and 24 months were 59.6% (95% confidence interval [CI], 52.5–68.9%) and 36.4% (95% CI, 27.8–45%), respectively. Progression-free survival rates at 12 and 24 months were 39.3% (95% CI, 31.1–47.5%) and 21.6% (95% CI, 14.5–28.7%), respectively. Fifty-seven patients (42.2%) reported cutaneous toxicity of any type, mainly hyperkeratosis (14.8%) and rash (11.9%). The most frequent adverse events were pyrexia (27.4%), asthenia (19.3%), arthralgia (16.9%), and diarrhoea (13.2%).

Our results suggest that both dabrafenib alone or in combination with trametinib are effective for compassionate use in terms of response and/or survival rates. However, differences in patients' prognostic features ought to be considered. No new findings were revealed regarding the safety profiles of either regimen. This is the first study to evaluate the efficacy of these 2 selective BRAF and mitogen-activated extracellular signal-regulated kinase inhibitors in a real-world setting in Spain.

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[a] Medical Oncology, Clínica Universidad de Navarra, Pamplona, [b] Instituto Valenciano de Oncología, Valencia, [c] Medical Oncology, Parc Taulí Sabadell Hospital Universitario, Sabadell, [d] Oncología Intercentros, Hospitales Universitarios Regional y Virgen de la Victoria (HURyVV) and Instituto de Investigación Biomédica de Málaga (IBIMA), Málaga, [e] Onkologikoa, Instituto Oncológico de Kutxa, San Sebastian, [f] Instituto Catalán de Oncología, ICO-Badalona, Hospital Germans Trías I Pujol, Barcelona, [g] Medical Oncology, Hospital Universitario Miguel Servet, Zaragoza, [h] Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, [i] Medical Oncology, Complejo Hospitalario Universitario Insular—Materno Infantil de Gran Canaria, Las Palmas de Gran Canaria, [j] Medical Oncology, Hospital Universitario La Paz, Madrid, [k] Medical Oncology, Hospital Virgen de la Salud, Toledo, [l] Medical Oncology, Hospital General Universitario Gregorio Marañón, Madrid, [m] Instituto Catalán de Oncología Girona, Girona, [n] Medical Oncology, Hospital Universitario Arnau de Vilanova, Lleida, [o] Medical Oncology, Hospital Universitario San Cecilio, Granada, [p] Medical Oncology, Complejo Hospitalario de Navarra, Pamplona, [q] Medical Oncology, Hospital Universitario Central de Asturias, Oviedo, [r] Medical Oncology, Hospital Universitario Nuestra Señora de Valme, Sevilla, [s] Medical Oncology, Hospital General Universitario de Elche, Alicante, [t] Medical Oncology, Complejo Hospitalario Torrecárdenas de Almería, Almería, [u] Medical Oncology, Hospital Marqués de Valdecilla, Santander, [v] Medical Oncology, Hospital Universitario Son Espases, Palma de Mallorca, [w] Medical Oncology, Hospital Universitario La Princesa, Madrid, [x] Medical Oncology, Complejo Hospitalario Universitario Ourense, Ourense, [y] Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, [z] Medical Oncology, Hospital General Universitario de Valencia, Valencia, [aa] Medical Oncology, Hospital Clínic Barcelona, Barcelona, Spain.

[*] Correspondence: Salvador Martín Algarra, Clinica Universitaria de Navarra, Pamplona, Spain (e-mail: secretaria@groupgem.org).

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Abbreviations: AEs = adverse events, CI = confidence interval, ECOG PS = Eastern Cooperative Oncology Group performance status, LDH = lactate dehydrogenase, MEK = mitogen-activated extracellular signal-regulated kinase, ORR = overall response rate, OS = overall survival, PD = progression of disease, PFS = progression-free survival.

Keywords: BRAF, BRAF inhibitors, compassionate use, dabrafenib, metastatic melanoma, trametinib

1. Introduction

Cutaneous melanoma is the most frequent type of malignant melanoma,[1] with incidence and mortality rates of approximately 13.0 and 2.2 per 100,000 inhabitants, respectively, in European countries.[2] Sun exposure, host characteristics (such as the numbers and types of nevi or skin phototypes) and specific environmental factors have been clearly associated with an increased risk for the development of this disease.[3] Evidence suggests that 15% to 25% of patients with a primary tumor will develop metastasis, with 5-year survival rates of less than 15%.[4,5] In cases of metastatic melanoma, the tumor location as well as other variables such as the Eastern Cooperative Oncology Group performance status (ECOG PS) and serum lactate dehydrogenase (LDH) levels have been identified as prognostic factors.[6] Current treatment strategies include surgery (for isolated lesions), targeted therapies, immunotherapy, and palliative radiotherapy. Chemotherapy is currently reserved for further lines of treatment; however, most regimens are frequently associated with the development of adverse events (AEs) and the deterioration of the quality of life.[7] The discovery that approximately half of melanomas harbor mutations in the *BRAF* oncogene has changed the paradigm of treatment in patients with advanced stages.[8–10] The presence of such mutations has also been associated with worse outcomes in patients with metastatic melanoma.[11] The use of selective BRAF inhibitors, such as dabrafenib and vemurafenib, has achieved response rates of approximately 50%, and has also prolonged overall survival (OS) compared with dacarbazine, in patients with the BRAF V600E mutation.[12–14] Dabrafenib, whose activity inhibits the mitogen-activated extracellular signal-regulated kinase (MEK) 1 and 2, is currently indicated as a monotherapy or in combination with trametinib for the treatment of adult patients with unresectable metastatic melanoma and confirmed *BRAF* V600 mutation[15]; vemurafenib and cobimetinib are similarly indicated.[16] Based on currently published data of dabrafenib and trametinib use in metastatic melanoma, these targeted therapies have been introduced in compassionate use programs in different countries, including Spain. Currently, data regarding the use of dabrafenib in a real-world setting, with or without trametinib, are scarce.[17–23] Therefore, the Spanish Melanoma Group (Grupo Español Multidisciplinar de Melanoma) has developed a centralized database documenting the clinical experiences of both dabrafenib in monotherapy and in combination with trametinib for compassionate use in patients with metastatic melanoma treated in Spain. The main objective of this study was to evaluate the efficacy and safety of compassionate-use dabrafenib alone or in combination with trametinib for the treatment of metastatic melanoma in an expanded access program in Spain.

2. Materials and methods

This retrospective observational expanded access program study involved 149 patients with metastatic melanoma from 30 Spanish medical centers (Table 1). Patients considered for chart review included those diagnosed with an unresectable stage IIIC/IV melanoma and who commenced treatment any time before April 30, 2014 with at least 1 dose of dabrafenib alone or in combination with trametinib as part of the compassionate use program. Criteria for exclusion were the absence of a complete clinical history, treatments administered outside of the previously established time-frame, and absence of informed consent to participate. The study was performed between September 2014 and March 2016 in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and applicable regulatory requirements; the protocol was approved by both the Ethical Committee of the Hospital Clinic Barcelona and each of the committees at the participating sites. All treatment-related decisions were according to the discretion of the *physician*.

2.1. Endpoints and study variables

Primary endpoints included the overall response rate (ORR) of both treatment alternatives, as well as the safety profiles of both dabrafenib alone or when combined with trametinib. The ORR was defined as the best tumor response (according to the Response Evaluation Criteria in Solid Tumours version 1.1) that was observed between the time of first treatment dose and the last available evaluation or the date of commencing a new treatment. Patients with positive responses to treatment included all those with complete response, partial response, and stable disease as documented in their clinical records. Secondary endpoints included progression-free survival (PFS) and OS. The PFS was calculated as the time between the initial administration of treatment and the date of detection of progression of disease (PD) or death by any cause; OS was calculated as the time between the initial administration of treatment and death by any cause. Both variables were analyzed and classified based on: the treatment strategy (dabrafenib monotherapy, dabrafenib plus trametinib initiated simultaneously, and combination therapy with dabrafenib preceding trametinib); whether the patient had undergone previous therapy, and the number of previous lines of therapy (1, 2, 3, or >3).

OS data of patients who were alive at the end of follow-up or whose follow-up information was unavailable were censored. PFS data of patients with no PD at the time of analysis were also censored. Other results, such as serum LDH levels and ECOG PS at 6 and 12 months, were assessed. The AEs were graded according to the Common Terminology Criteria for AEs, version 3.0. Because of their relevance to this field of the study, cutaneous toxicities were analyzed independently of other AEs.

2.2. Statistical analyses

Categorical variables were expressed as absolute and relative frequencies (%), and continuous variables as medians and ranges (minimum–maximum values). Percentages were compared by using the Chi-squared test, *t* test, and Fisher or Mann–Whitney *U* test. Kaplan–Meier survival curves were used to estimate OS,

Table 1

Total patients screened and included at each participating site.

	Eligible, N (%)	Included, N (%)
Clínica Universidad Navarra, Pamplona	3 (2.0)	3 (2.2)
Hospital Clínic Barcelona, Barcelona	13 (8.7)	12 (8.9)
Instituto Valenciano de Oncología, Valencia	13 (8.7)	12 (8.9)
Hospital Universitario 12 de Octubre, Madrid	1 (0.7)	1 (0.7)
Onkologicoa, Instituto Oncológico de Kutxa, San Sebastián	8 (5.4)	8 (5.9)
Hospital Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria	5 (3.4)	5 (3.7)
Corporació Sanitaria Parc Taulí, Barcelona	11 (7.4)	11 (8.1)
Hospital Universitario Miguel Servet, Zaragoza	7 (4.7)	7 (5.2)
Hospital Universitario La Paz, Madrid	5 (3.4)	5 (3.7)
Hospital Can Misses Ibiza/Hospital Son Espases, Mallorca	3 (2.0)	2 (1.5)
Hospital Universitario Ramón y Cajal, Madrid	8 (5.4)	6 (4.4)
Hospitales Universitarios Regional y Virgen de la Victoria, Málaga	12 (8.1)	11 (8.1)
Hospital Virgen de la Salud, Toledo	7 (4.7)	5 (3.7)
ICO Girona, Girona	4 (2.7)	4 (3.0)
Hospital Universitari Arnau de Vilanova, Lleida	4 (2.7)	4 (3.0)
ICO Badalona, Barcelona	9 (6.0)	8 (5.9)
ICO L'Hospitalet de Llobregat, Barcelona	1 (0.7)	0 (0.0)
Hospital Universitario La Princesa, Madrid	2 (1.3)	1 (0.7)
Hospital General Universitario de Valencia, Valencia	1 (0.7)	1 (0.7)
Hospital de Navarra, Pamplona	3 (2.0)	3 (2.2)
Hospital Universitario Central de Asturias, Asturias	4 (2.7)	3 (2.2)
Hospital Universitario Nuestra Señora de Valme, Sevilla	3 (2.0)	3 (2.2)
Hospital General Universitario de Elche, Alicante	3 (2.0)	3 (2.2)
Hospital Torrecárdenas, Almería	3 (2.0)	3 (2.2)
Hospital Universitario Gregorio Marañón, Madrid	5 (3.4)	5 (3.7)
Hospital Marqués de Valdecilla, Santander	3 (2.0)	3 (2.2)
Complejo Hospitalario Universitario Ourense, Ourense	2 (1.3)	2 (1.5)
Hospital Universitario San Cecilio, Granada	6 (4.0)	4 (3.0)
Total	149 (100.0)	135 (100.0)

ICO = Institut Català d'Oncología/Oncology Catalán Institute.

expressed as means and the 95% confidence intervals (CIs). A P value of $<.05$ was considered statistically significant. All statistical procedures were performed using the SPSS 21.0 software for Windows (IBM, Chicago, IL).

3. Results

3.1. Patient characteristics

Of the 149 patients initially screened, 14 did not meet the inclusion criteria; therefore, data from 135 patients were analyzed (Table 2). Forty-eight patients (35.6%) received dabrafenib monotherapy and 87 (64.4%) were treated with combination dabrafenib and trametinib. Eighty patients (58.8%) initiated dabrafenib and trametinib simultaneously, while 7 (5.1%) initiated dabrafenib 1.1 to 13 days before trametinib. Overall, patients had a median age of 55.2 years (range: 24.8–84.3 years; Table 2). The most frequent locations of the primary tumors were the trunk (44.4%) and extremities (25.9%); furthermore, 4.4% and 95.6% of the patients had stage IIIC and IV melanoma, respectively. All patients treated with the combined regimen had stage IV melanoma, as did 87.5% of the patients in the dabrafenib monotherapy group. The remaining patients had stage IIIC melanoma.

All patients had a BRAF mutation in their primary or metastatic melanoma; 3 patients were positive for V600K, while the remainder had V600E or V600+. The percentage of patients who underwent previous therapies was 68.9% (72.9% from the dabrafenib monotherapy group and 66.7% from the combination group); details are shown in Table 2. The median LDH level at baseline was 281.0 IU/L (range: 137.0–2353.0 IU/L), and 63.0% of the patients had an ECOG PS of 0; neither of these variables significantly changed after 6 or 12 months of treatment (LDH: 250.5 [131–1714] and 282 [139–1714] IU/L, respectively; ECOG PS 0: 68% and 62.4%, respectively). The median length of treatment was 7.2 months (range: 0.1–24.7 months). Surgical rescue of residual disease after treatment was performed in 12.6% of the patients (10.4% and 13.8% in the monotherapy and combined groups, respectively).

3.2. Efficacy analyses

The treatment ORRs are shown in Table 3. Complete response, partial response, and stable disease were achieved in 19.1%, 48.9%, and 21.4% of all patients, respectively. A clinical benefit was observed in 89.3% of patients (89.4% in the monotherapy group and 89.3% in the combined group).

PD was observed in 10.7% of patients (10.6% and 10.7% in the monotherapy and combined therapy groups, respectively). Information regarding the radiological response to treatment was not available for 4 patients. Survival (Fig. 1) at 12 months was 60.5% (95% CI, 52.2–68.8%): 59.6% (95% CI, 45.6–73.6%) in patients who received dabrafenib monotherapy and 60.9% (95% CI, 50.6–71.2%) in patients who received combination therapy. Survival at 24 months (Fig. 1) was 36.4% (95% CI, 27.8–45.0%): 39.7% (95% CI, 25.5–53.9%) in patients treated with dabrafenib monotherapy, and 34.0% (95% CI, 23.1–44.9%) in those who received combination therapy. The median OS was 15.3 months (range: 0.2–33.2 months): 17.5 months (range: 0.85–31.5 months) with dabrafenib monotherapy and 15.3 months (range: 10.1–20.5 months) with dabrafenib plus trametinib. Survival beyond 2 years was reported in 32.7% and 14.9% of patients in the monotherapy combination groups, respectively. A total of 61.5% of patients died (59.2% in the monotherapy and 62.1% in the combination therapy groups). The median follow-up was 15.0 months (range: 0.2–33.2 months), 15.4 months (range: 0.8–31.5 months) for dabrafenib, and 15.0 months (range: 0.2–33.2 months) for dabrafenib plus trametinib.

Among patients who started dabrafenib and trametinib simultaneously, 11.3% were alive 2 years after the onset of treatment, whereas the percentage was 57.1% in patients who first started treatment with dabrafenib. Moreover, in treatment-naïve patients, survival at 12 months was observed in 58.3% (95% CI, 30.4–86.2%) and 58.6% (95% CI, 40.7–76.5%) of patients who received monotherapy and combined treatment, respectively; a similar trend was observed when patients were

Table 2

Baseline demographic and clinical characteristics of patients.

	Dabrafenib monotherapy (N = 49)	Dabrafenib plus trametinib (N = 87)	Total (N = 135)
Gender, male, N (%)	30 (62.5)	41 (47.1)	71 (52.6)
Age, median years (range)	56.8 (26.2–84.3)	53.2 (24.8–81.3)	54.8 (24.8–84.3)
Fitzpatrick skin phototype, N (%)			
Type I	2 (4.2)	10 (11.5)	12 (8.9)
Type II	13 (27.1)	22 (25.3)	35 (25.9)
Type III	14 (29.2)	16 (18.4)	30 (22.2)
Type IV	2 (4.2)	6 (6.9)	8 (5.9)
Unknown	17 (35.4)	33 (37.9)	50 (37.0)
History of primary melanoma			
Main localizations, N (%)			
Trunk (cheek and axilla)	21 (43.8)	39 (44.8)	60 (44.4)
Extremities	14 (29.2)	21 (24.1)	35 (25.9)
Head and neck	5 (10.4)	15 (17.2)	20 (14.8)
Breslow's thickness, mm			
≤1	3 (6.3)	4 (4.6)	7 (5.2)
1–2	4 (8.3)	15 (17.2)	19 (14.1)
2–4	12 (25.0)	15 (17.2)	27 (20.0)
>4	15 (31.3)	25 (28.7)	40 (29.6)
Lymph node involvement, N (%)	23 (52.3)	35 (42.2)	58 (45.7)
Ulceration, N (%)	18 (41.9)	23 (28.4)	41 (33.1)
Mitotic rate, median mitoses/mm^2 (range: minimum–maximum)	7.0 (2.0–2.1)	6.0 (1.0–37.0)	7.0 (1.0–37.0)
Baseline metastatic melanoma			
Tumor stage, N (%)			
IIIC	6 (12.5)	0 (0.0)	6 (4.4)
IV	42 (87.5)	87 (100.0)	129 (95.6)
Metastasis stage, N (%)			
M1a	7 (16.3)	12 (13.8)	19 (14.6)
M1b	8 (18.6)	19 (21.8)	27 (20.8)
M1c	28 (65.1)	56 (64.4)	84 (64.6)
ECOG performance status, N (%)			
0	28 (58.3)	57 (65.5)	85 (63.0)
1	12 (25.0)	26 (29.9)	38 (28.1)
2	7 (14.6)	2 (2.3)	9 (6.7)
3	1 (2.1)	2 (2.3)	3 (2.2)
LDH levels, median IU/L (range)	285.0 (141.0–2275.0)	280.0 (137.0–2353.0)	281.0 (137.0–2353.0)
BRAF mutation status, N (%)			
V600E	34 (70.8)	39 (44.8)	73 (54.1)
V600	14 (29.2)	44 (50.6)	58 (43.0)
V600K	0 (0.0)	3 (3.4)	3 (2.2)
Previous therapies, N (%)			
No previous treatment, N (%)	13 (27.1)	29 (33.3)	42 (31.1)
1 previous line, N (%)	15 (31.3)	39 (44.8)	54 (40.0)
2 previous lines, N (%)	6 (12.5)	17 (19.5)	23 (17.0)
3 previous lines, N (%)	8 (16.7)	1 (1.1)	9 (6.7)
>3 previous lines, N (%)	6 (12.6)	1 (1.1)	7 (5.1)
Number of previous lines, median (range)	1.0 (0.0–10.0)	1.0 (0.0–7.0)	1.0 (0.0–10.0)
Chemotherapy	9 (18.8)	14 (16.1)	23 (17.0)
Radiotherapy	9 (18.8)	13 (14.9)	22 (16.3)
Immunotherapy	11 (22.9)	8 (9.2)	19 (14.1)
Length of treatment, median months (range)	6.4 (0.6–24.3)	7.3 (0.1–24.7)	7.2 (0.1–24.7)

ECOG PS = Eastern Cooperative Oncology Group performance status, IU = international units, LDH = lactate dehydrogenase, N % = total patients (percentage).

Table 3

Response rates achieved during the treatment period.

	Dabrafenib monotherapy (N = 48)	Dabrafenib plus trametinib (N = 84)	Total (N = 132)
Best response to treatment, N (%)			
Complete response	7 (14.9)	18 (21.4)	25 (19.1)
Partial response	21 (44.7)	43 (51.2)	64 (48.9)
Stable disease	14 (29.1)	14 (16.7)	29 (22.0)
Progressive disease	5 (10.6)	9 (10.7)	14 (10.6)
Clinical benefit, N (%)	43 (89.6)	75 (89.3)	117 (89.3)
Time from onset of treatment to best response, median months (range)	2.8 (0.8–27.4)	2.8 (0.1–21.2)	2.8 (0.1–27.4)

N = total patients.

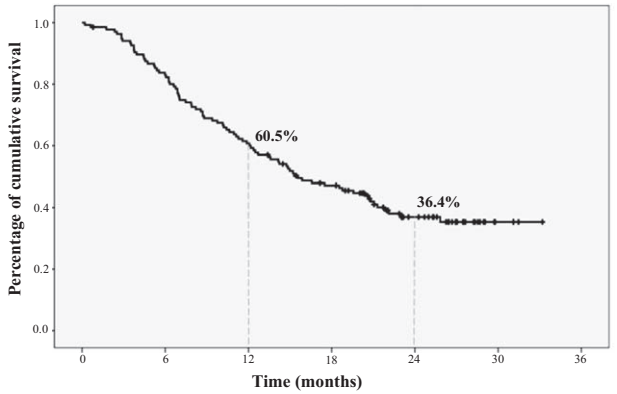

Figure 1. Overall survival for patients receiving dabrafenib in monotherapy or in combination with trametinib.

classified according to their history of previous therapy with 1 to 2 lines, with 52.4% (95% CI, 31.0–73.8%) alive with monotherapy and 62.5% (95% CI, 49.8–75.2%) alive with the combined treatment.

Global PFS rates at 12 and 24 months was 38.8% (95% CI, 30.5–47.1%) and 20.9% (95% CI, 13.9–27.9%), respectively (Fig. 2). The PFS rates at 12 and 24 months were 33.3% (95% CI, 20.0–46.6%) and 20.8% (95% CI, 9.3–32.3%), respectively, in patients receiving dabrafenib; and 42.5% (95% CI, 32.1–52.9%) and 21.8% (95% CI, 12.8–30.8%), respectively, in those treated with the combination regimen. The median global PFS was 9.5 months (range: 0.1–31.8 months); PFS rates were 8.1 months (range: 0.8–31.5 months) for the dabrafenib monotherapy group and 10.2 months (range: 0.1–31.8 months) for the combination dabrafenib plus trametinib group. Other data of postoncological treatments were also recorded: therapy of any line was prescribed for 64 patients, chemotherapy (32 patients) and immunotherapy (77 patients) were the most frequently used.

3.3. Safety profile

Cutaneous toxicity of any type was reported in 42.2% of patients overall (58.3% and 33.3% in the monotherapy and combination groups, respectively). The toxicity profiles are shown in Table 4. The most frequent cutaneous toxicities were hyperkeratosis (14.8%) and rash (11.9%). The most frequent AEs were pyrexia (27.4% of patients), asthenia (19.3%), arthralgia (17.0%), and diarrhea (13.2%). In total, 18.5% of patients (18.8% and 18.4% from the monotherapy and combination groups, respectively) experienced at least a single grade 3/4 AE; however, each of these events was reported in at least 2 patients.

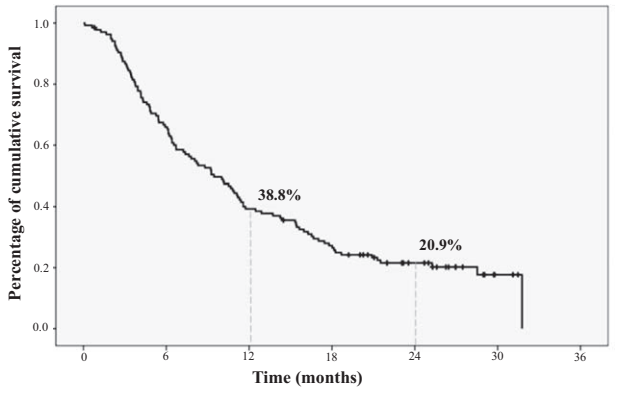

Figure 2. Progression-free survival for patients receiving dabrafenib in monotherapy or in combination with trametinib.

4. Discussion

Dabrafenib and trametinib, used as single agents or in combination, have produced a significant improvement on the outcomes of patients with metastatic melanoma harboring *BRAF* mutations, and have changed the scope of treatment in this setting.[24]

The impressive results of the early studies with dabrafenib, as well as the subsequent phase II–III clinical trials,[13,14] demonstrated significant improvements in PFS and OS rates compared with conventional chemotherapy; however, tumor progression occurred in approximately 50% of patients by 6 months after commencing treatment.[14]

The reactivation of the mitogen-activated protein kinase pathway through various mechanisms of drug resistance has been implicated in recurrence,[25,26] and combining BRAF and MEK inhibitors was therefore postulated to avoid or delay the development of treatment refractoriness, as well as to prolong survival.[27] To that end, combining dabrafenib and trametinib has shown promising results in randomized phase III trials, including improved and prolonged PFS and OS when compared to monotherapy with dabrafenib or vemurafenib.[28,29]

The COMBI-d multicenter double-blinded phase-III clinical trial of 423 patients with *BRAF* V600E or V600K stage IIIC or IV unresectable melanoma, who had not undergone previous systemic therapy, showed a 3-year PFS of 22% with dabrafenib plus trametinib versus 12% with monotherapy; the 3-year OS rates were 44% versus 32%, respectively.[30]

Dabrafenib alone or in combination with trametinib expanded access programs were initiated in Spain following their subsequent approval by the European Medical Agency, and make the basis for this retrospective, observational study. This early, multicenter and standard clinical-setting experience, with unselected series of BRAFV600E/K melanoma patients, are consistent with the efficacy and toxicity data previously described in the pivotal trials,[29,30] However, comparison between these treatments was not, indeed, considered at the time of study design, neither as objective of this retrospective and real-life series of patients. Differences in results should take into account the recruitment procedures and the variability of experience among the recruiting centers.

Given these factors, data revealed a PFS rate of 8.1 months for the dabrafenib monotherapy group and of 10.8 months for the combination group of patients. These results are similar to those described in the COMBI-d trial (8.8 and 11.0 months, respectively).

Contrary to the PFS, the OS results obtained in our series cannot be compared with those reported in the COMBI-d trial (in our study, 60.3% and 60.4%, dabrafenib and combined therapy at 12 months, respectively; 68% and 74% for the COMBI-d trial); this is not only because of the above-mentioned factors, but also because patients in our study received prior lines of treatments, and also because our study was observational and based on real-life settings. Notably, 14% of our patients previously received immunotherapy and 40.5% (out of 84 patients with any metastasis) had brain metastases when treatment was initiated. However, even considering these high-

Table 4

Description of adverse events reported during the treatment period.

	Dabrafenib monotherapy (N = 49)			Dabrafenib plus trametinib (N = 87)			Total (N = 136)		
	G1	G2	G3/4	G1	G2	G3/4	G1	G2	G3/4
Cutaneous toxicity, N (%)	19 (3.6)	6 (12.5)	3 (6.3)	17 (19.5)	10 (11.5)	2 (2.3)	36 (26.7)	16 (11.9)	4 (3.0)
Hyperkeratosis	14 (29.2)	2 (4.2)	1 (2.1)	3 (3.4)	0 (0.0)	0 (0.0)	17 (12.6)	2 (1.5)	1 (0.7)
Rash	4 (8.3)	2 (4.2)	0 (0.0)	8 (9.2)	2 (2.3)	0 (0.0)	12 (8.9)	4 (3.0)	0 (0.0)
Most frequent AEs, N (%)									
Pyrexia	11 (22.9)	0 (0.0)	0 (0.0)	14 (16.1)	11 (12.6)	1 (1.1)	25 (18.5)	11 (8.1)	1 (0.7)
Arthralgia	9 (18.8)	1 (2.1)	0 (0.0)	11 (12.6)	2 (2.3)	0 (0.0)	20 (14.8)	3 (2.2)	0 (0.0)
Asthenia	9 (18.8)	2 (4.2)	1 (2.1)	10 (11.5)	4 (4.6)	0 (0.0)	19 (14.1)	6 (4.4)	1 (0.7)
Diarrhea	6 (12.5)	0 (0.0)	0 (0.0)	10 (11.5)	2 (2.3)	0 (0.0)	16 (11.9)	2 (1.5)	0 (0.0)
Alopecia	4 (8.3)	1 (2.1)	0 (0.0)	2 (2.3)	0 (0.0)	0 (0.0)	6 (4.4)	1 (0.7)	0 (0.0)
Hand–foot syndrome	2 (4.2)	2 (4.2)	2 (4.2)	1 (1.1)	2 (2.3)	0 (0.0)	3 (2.2)	4 (3.0)	2 (1.5)

AEs = adverse events, G = grade of toxicity, N = number of patients.

risk factors, our OS results were similar to those of an earlier trial[30] that investigated 78 patients with *BRAF* V600 mutation-positive metastatic melanoma who were naïve to previous *BRAF* inhibitors and who received dabrafenib plus trametinib; their PFS rates were 44%, 22%, and 18% at 12, 24, and 36 months of treatment, respectively.

The AE profile in our study is similar to those described previously. Patients receiving monotherapy experienced more episodes of hyperkeratosis (34.7%) compared to those receiving combination therapy (2.3%), and pyrexia was the most frequent AE reported in the dabrafenib and trametinib group (27.2% of patients). No new findings were observed regarding the safety profiles of either regimen.

Currently, data on the use of dabrafenib as monotherapy or in combination with trametinib in a real-world setting are scarce.[17–20,22,23] The limitations inherent to the retrospective and observational nature of our study should be taken into account when interpreting our data; however, evaluating the efficacy and tolerability of dabrafenib as a single agent, as well as dabrafenib plus trametinib, in patients enrolled in compassionate use programs render our cohort highly representative of real-life scenarios. Although further studies involving series of patients with similar characteristics may be required to corroborate these results, our experience may also be considered useful for designing and initiating studies of these agents in other countries.

In summary, our results suggest that the use of dabrafenib alone or in combination with trametinib, in a compassionate program, is safe and effective in terms of toxicity, response, and survival rates. However, differences in patients' prognostic features ought to be considered.

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