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ORIGINAL RESEARCH

Durable Response to Vemurafenib and Cobimetinib for the Treatment of BRAF-Mutated Metastatic Melanoma in Routine Clinical Practice

Mª del Carmen Álamo[1]
Sebastian Ochenduszko[2]
Guillermo Crespo[3]
Mónica Corral[4]
Juana Oramas[5]
Pilar Sancho[6]
Javier Medina[7]
Fernando Garicano[8]
Pedro López[9]
Begoña Campos Balea[10]
Analia Rodríguez Garzotto[11]
Eva Muñoz-Couselo[12,13]

[1]Oncology Department, Hospital Universitario Virgen Macarena, Sevilla, Spain; [2]Oncology Department, Hospital Universitario Dr. Peset, Valencia, Spain; [3]Oncology Department, Hospital Universitario de Burgos, Burgos, Spain; [4]Oncology Department, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain; [5]Oncology Department, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain; [6]Oncology Department, Hospital Universitario Virgen del Rocío, Sevilla, Spain; [7]Oncology Department, Hospital Universitario Virgen de la Salud, Toledo, Spain; [8]Oncology Department, Hospital de Galdakao, Bizkaia, Spain; [9]Oncology Department, Complejo Hospitalario General de Jaén, Jaén, Spain; [10]Oncology Department, Hospital Lucus Augusti, Lugo, Spain; [11]Medical Department and Strategy, Roche S.A, Madrid, Spain; [12]Oncology Department, Hospital Universitario Vall d´Hebron, Barcelona, Spain; [13]VHIO Vall d'Hebron Institute on Oncology, Barcelona, Spain

Correspondence: Eva Muñoz-Couselo
Oncology Department, Hospital Universitario Vall d´Hebron, Passeig de la Vall d'Hebron, 119, Barcelona, 08035, Spain
Email emunoz@vhio.net

Background: The combination of *BRAF* and *MEK* inhibitors delays the onset of resistance and provides more sustained and dramatic responses in comparison with a *BRAF* inhibitor in monotherapy. The objective of the study was to evaluate the effectiveness of the combination therapy with vemurafenib/cobimetinib in terms of durability, and to describe differential characteristics in patients associated to durable responses in real-world settings.

Patients and Methods: Retrospective, observational, cross-sectional, multicenter study involving 41 patients with advanced melanoma harboring a $BRAF^{V600}$ mutation who initiated a combination therapy with vemurafenib/cobimetinib between May 2018 and March 2019. Participants were differentiated regarding the durability of the response: durable (complete response, CR, or a partial response, PR, for at least 12 months) and non-durable (stable disease, SD, progressive disease, PD, or CR/PR <12 months). Secondary endpoints included treatment adherence, labor productivity, anxiety/depression, and safety profile.

Results: During the combination therapy, 12 patients (29.3%) had a CR, 19 a PR (46.3%), 5 showed SD (12.2%), and 5 had PD. A total of 12 patients (29.3%) were considered as achieving a durable response and 29 (70.7%) as a non-durable one. Practically all socio-demographic and clinical characteristics were similar between patients. Body mass index was the only differential factor (with higher body mass index achieving a non-durable response). The treatment adherence was 100% in patients with durable response and 66.7% in those with non-durable.

Conclusion: The combination treatment with vemurafenib/cobimetinib results in an important impact on long-term survival, leading to a steady CR in one-third of the patients.

Keywords: vemurafenib, cobimetinib, BRAF, metastatic melanoma, durable response, clinical practice

Introduction

Melanoma represents a substantial and growing public health burden.[1] According to the World Health Organization, 287,723 new cases of melanoma were reported in 2018, with 60,712 deaths.[2] The worldwide incidence is 3.5 and 4.0 per 100,000 inhabitants among men and women, respectively. Most of cases (83%) are diagnosed at a localized stage, showing a 5-year survival of 99.0%.[3] However, when spread to regional lymph nodes (9% of newly diagnoses), 5-year survival decreases to 66.2%, and when metastasizes (4% of cases) it reduces to 27.3%. Between 40–60% of cutaneous melanomas harbor a mutation in *BRAF* gene, predominantly (≥97%) in the codon 600.[4] The most frequent mutation (90%) consists of the

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substitution of valine for glutamic acid (*BRAF* ^{V600E}), followed by the substitution for lysine (*BRAF* ^{V600K}, between 8–20% of patients), arginine (*BRAF* ^{V600R}, 1%), methionine (*BRAF* ^{V600M}, 0.3%), and aspartic acid (*BRAF* ^{V600D}, 0.1%). *BRAF* mutant melanomas are associated with more aggressive biological behaviors and reduced survival than wild-type ones.[5,6] The discovery of *BRAF* mutations led to the development of targeted therapies, including selective inhibitors of the *BRAF* ^{V600}-mutated kinase (vemurafenib, dabrafenib and encorafenib) and inhibitors of the downstream *MEK* kinase (trametinib, cobimetinib, and binimetinib).[4] Vemurafenib was the first approved *BRAF* inhibitor, based on results from the Phase III BRIM-3 trial which demonstrated significant improvement with vemurafenib in overall survival (OS, 13.6 months) and progression-free survival (PFS, 5.3 months) compared with dacarbazine (9.7 and 1.6 months, respectively) for metastatic *BRAF* mutant melanoma.[7] Despite the proven clinical benefit of *BRAF* inhibitors, only 5% of patients achieve a complete response (CR), and the disease frequently progresses approximately 6–7 months after initiating the treatment due to acquired resistance.[8] The reactivation of the mitogen-activated protein kinase pathway represents the main cause of resistance to *BRAF* inhibitors. This resistance affects directly to the rate and duration of tumor responses.[8] There is thus a clinical need to identify the most effective therapy for these patients. The combination therapy of a *BRAF* and *MEK* inhibitor (such as vemurafenib/cobimetinib) has been shown to improve substantially survival, and to provide more durable and greater tumor responses than *BRAF* monotherapy in patients with *BRAF*^{V600} mutant advanced melanoma.[7] The 5-year follow-up data of the double-blind, randomized, multicenter, phase III coBRIM trial, involving 495 patients with *BRAF*^{V600} mutant melanoma, has recently revealed a superior median PFS with vemurafenib/cobimetinib (12.6 months) and objective response rate (70%) than vemurafenib plus placebo (7.2 months and 50%, respectively).[9] Among patients receiving vemurafenib/cobimetinib, median OS and PFS were higher in patients with normal lactate dehydrogenase (LDH) at baseline (38.5 and 15.0 months, n=131) than with elevated LDH (14.8 and 8.6 months, n=112). Furthermore, coBRIM trial originally showed that the health-related quality of life of patients was maintained with vemurafenib/cobimetinib, in contrast to vemurafenib/placebo.[10] To date, there are no published studies specifically designed to address the effect of vemurafenib/cobimetinib in routine clinical practice, or to determine which patients can achieve long-term clinical effects. Therefore, the objective of the present study was to evaluate the effectiveness of the combination therapy in terms of durability, and to describe differential characteristics of patients associated with durable responses in real-world settings.

Patients and Methods

Study Design

Retrospective, observational, cross-sectional, multicenter study involving patients with advanced melanoma harboring a *BRAF*^{V600} mutation who initiated a combination therapy with vemurafenib/cobimetinib between May 2018 and March 2019. A total of 15 centers across Spain participated in the study. Exclusion criteria were: having received any prior treatment for melanoma in the metastatic setting; lack of medical records from the last 12 months (before study inclusion); participation in another clinical study; or having a mental disease or being unable to make decisions and follow instructions.

Endpoints and Study Variables

The primary endpoint included the percentage of patients with durable clinical response to the combination therapy with *BRAF* and *MEK* inhibitors, and the comparison of sociodemographic and clinical characteristics of patients with durable and non-durable responses. A patient was considered to achieve a durable clinical response when having a CR or a partial response (PR) for at least 12 months. In case of stable disease (SD), progressive disease (PD), or CR/PR for less than 12 months, the patient was considered to achieve a non-durable clinical response. Evaluated sociodemographic and clinical characteristics of patients were age, gender, race, body mass index (BMI), Eastern Cooperative Oncology Group performance status at diagnosis, primary tumor location, type of *BRAF* mutation, tumor stage at treatment initiation, and metastatic location at treatment initiation. Other effectiveness variables included: time to response, duration of the response, and time to progression. The time to response was defined as the time between the initiation of the combination treatment and the best response achieved. The duration of the response was defined as the time elapsed between the best response achieved and the progression or death, by any cause. The time to progression was defined as the time elapsed between the start of the treatment and progression. Tumor stage at treatment

initiation was determined with the 2009 version of the American Joint Committee on Cancer melanoma staging and classification.[11] Additionally, secondary endpoints included the determination of the treatment adherence, labor productivity, anxiety/depression, and the safety profile. Adherence to the treatment was determined by using the 6-item simplified medication adherence questionnaire (SMAQ) in patients with active treatment at the time of the study visit.[12] A negative result in the SMAQ Questionnaire represents adherence to the treatment, whereas a positive result stands for non-adherence. Labor productivity was determined with the work productivity and activity impairment questionnaire (WPAI-GH), in patients with active treatment at the time of the study.[13] Only the item of "activity impairment" (percent activity impairment due to health) was determined. Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS), in patients with active treatment at the time of the study visit.[14] The HADS describes 14 items and global (range score: 0–42) and dimensions score (anxiety and depression, range score: 0–21 each one). Scores of dimensions were categorized into: normal (score 0–7), borderline abnormal (score 8–10) and abnormal (score 11–21). The analysis of safety outcomes was based on the incidence and severity of adverse events (AEs), using the Common Terminology Criteria for Adverse Events v4.0, and summarizing according to the system organ class, with MedDRA 21.0.

Sample Size Determination and Statistical Analysis

The sample size was determined according to the primary objective, ie percentage of patients with a durable clinical response and the description of differential characteristics associated with the response. It was estimated that 53 patients could provide a precision of ±13.5% in the proportion of patient's characteristics; with a 0.95 of confidence level. Assuming 5% of patients with non-evaluable data, the estimated sample size was 55–56 patients. Continuous variables were expressed as mean, standard deviation (SD), median, or interquartile range (25th-75th percentile), whereas categorical ones as absolute and relative frequencies. Comparisons of sociodemographic and clinical characteristics of patients were performed using the Mann–Whitney *U*-test, in continuous variables, and chi-square or Fisher´s exact tests, in categorical ones, when appropriate. Statistical significance was established when $P \leq 0.05$. All statistical procedures were carried out with SAS 9.4.

Results

A total of 48 patients were initially recruited; however, only 41 were evaluable for the primary objective. During the combination therapy, 12 patients (out of 41, 29.3%) had a CR, 19 patients a PR (46.3%), 5 patients showed SD (12.2%), and 5 patients had PD (12.2%; Table 1). Median time to the best response was: 5.0 months (IQR, 2.9–7.2 months) for CR; 2.1 months (IQR, 1.8–3.4 months) for PR; and 2.2 months (IQR, 2.0–2.8 months) for SD. The median duration of the response was 7.3 months (IQR, 6.8–12.1 months) in patients with CR, and 4.8 months (IQR, 1.0–16.0 months) and 7.3 months (IQR, 7.0–7.4 months) for those with PR and SD, respectively. In patients with PD, the median time to progression was 3.5 months (IQR, 2.6–5.5 months).

According to the durability of the clinical response, 12 patients (29.3%) were considered as achieving a durable response, and 29 (70.7%) as a non-durable one. In the group of patients with non-durable response, 9 (31.0% of them) and 10 patients (34.5%) had a CR and PR lasting less than 12 months, respectively; 5 patients (17.2%) had SD, and 5 showed PD (17.2%). The median duration of the response in patients with a non-durable response was 5.4 months (IQR, 2.1–7.4 months). Sociodemographic and clinical characteristics in patients

Table 1 Best Response Achieved During the Combination Therapy in Total Patients

	Value
Best response achieved, n (%)	
Complete response	12 (29.3)
Partial response	19 (46.3)
Stable disease	5 (12.2)
Progressive disease	5 (12.2)
Time to response, median months (IQR)	
Complete response	5.0 (2.9–7.2)
Partial response	2.1 (1.8–3.4)
Stable disease	2.2 (2.0–2.8)
Duration of the response, median months (IQR)	
Complete response	7.3 (6.8–12.1)
Partial response	4.8 (1.0–16.0)
Stable disease	7.3 (7.0–7.4)
Time to progression, median months (IQR)	3.5 (2.6–5.5)

Abbreviation: IQR, interquartile range.

Table 2 Sociodemographic and Clinical Characteristics in Patients Considering the Durability of the Response

	Patients with Durable Clinical Response (N=12)	Patients with Non-Durable Clinical Response (N=29)	P value
Age, mean years (SD)	55.8 (16.5)	58.5 (13.1)	0.716
Gender, n (%)			0.087
Male	4 (33.3)	19 (65.5)	
Female	8 (66.7)	10 (34.5)	
Race, n (%)			1.000
Caucasian	12 (100.0)	28 (96.6)	
Black	0 (0.0)	1 (3.4)	
BMI, mean Kg/m^2 (SD)	24.4 (6.0)	29.2 (5.6)	0.028
ECOG PS at diagnosis, n (%)			1.000
0	11 (91.7%)	23 (79.3)	
1	1 (8.3)	4 (13.8)	
2	0 (0.0)	1 (3.4)	
3	0 (0.0)	1 (3.4)	
Primary tumor location, n (%)			0.059
Skin	11 (91.7)	22 (75.9)	
Cervix	1 (8.3)	0 (0.0)	
Data not available	0 (0.0)	7 (24.1)	
Type of *BRAF* mutation, n (%)			0.251
V600E	6 (50.0)	20 (69.0)	
Unspecific	6 (50.0)	9 (31.0)	
Tumor stage at treatment initiation, n (%)			1.000
IIIc unresectable	1 (8.3)	3 (10.3)	
IV	11 (91.7)	26 (89.7)	
Metastatic location at treatment initiation, n (%)			
Lung	6 (50.0)	15 (51.7)	1.000
Liver	3 (25.0)	7 (24.1)	1.000
Skin	2 (16.7)	8 (27.6)	0.694
Brain	0 (0.0)	2 (6.9)	1.000
Other	7 (58.3)	19 (65.5)	0.730

Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status.

considering the durability of the response are shown in Table 2. With the exception of BMI (mean, 24.4 Kg/m^2, SD, 6.0 with durable response versus 29.2 Kg/m^2, SD 5.6, with non-durable response; P=0.028), all sociodemographic and clinical characteristics of patients were similar among groups. The mean age of patients was 57.8 years (SD, 14.0 years). A slightly higher percentage of patients with durable response was female (66.7%), in contrast to the non-durable response (34.5%). The primary tumor was predominantly located in the skin (numerically higher in the group with durable response, 91.7%, versus non-durable, 75.9%). Main location of metastases were: lung (50.0% versus 51.7%), liver (25.0% versus 24.1%), and skin (16.7% versus 27.6%). Treatment characteristics in total patients considering the durability of the response are shown in Table 3. The adherence to the treatment was 100% in patients with durable response and 66.7% with non-durable one. Regarding labor productivity, no differences were found in activity impairment between patients with durable response (mean, 35.0; SD, 17.3) and non-durable response (mean, 23.3; SD, 40.4). One patient (out of 4, 25.0%) and 2 patients (out of 3, 66.7%) from the group with and without durable response, respectively, showed an abnormal response in the HADS anxiety scale. Considering depression, one patient from the group with non-durable response showed an abnormal response in the scale. No statistical differences were found between groups in anxiety and depression symptoms.

Regarding safety, 261 AEs (40.5% of total) were reported by patients with durable response, and 384 AEs (59.5%) by those with non-durable response. A total of 18 AEs (2.8%) were considered as serious (4 in group with durable response and 14 without it). Of AEs, 45.9% of cases were related with cobimetinib, 51.3% with vemurafenib, and 42.5% with both cobimetinib and vemurafenib (the relationship was not available in approximately 9% of AEs). Most frequent AEs related to the combined therapy considering the durability of the response are shown in Table 4. Most frequent AEs were: asthenia (58.3% of patients with durable clinical response versus 37.9% with non-durable one), diarrhea (41.7 versus 27.6%), arthralgia (50.0 versus 10.3%), erythema and rash (25.0 versus 17.2%, in each), and photosensitivity reaction (16.7 versus 17.2%). Severity was mild in 68.5% of AEs, and moderate in 19.4%. In 74.9% of cases no action was required. Of AEs, 83.4% were resolved.

Discussion

Great effort has been made to identify novel therapeutic agents that aim specific targets in melanoma.[15] *BRAF* inhibitors have demonstrated greater clinical efficacy than conventional chemotherapy for the treatment of *BRAF* mutant melanomas.[4,7] Nevertheless, they are also associated with limited objective responses and the development of resistance.[8] The combination of *BRAF* and

Table 3 Treatment Characteristics in Total Patients Considering the Durability of the Response

	Patients with Durable Clinical Response (N=12)	Patients with Non-Durable Clinical Response (N=29)	P value
Dose modification, n (%)	8 (66.7)	15 (51.7)	0.497
Reasons *			
Toxicity	12 (85.7)	24 (80.0)	1.000
Investigator decision	0 (0.0)	4 (12.3)	0.290
Clinical reasons	2 (14.3)	2 (6.7)	0.581
Time until dose modification, median months (IQR)	6.5 (2.5–11.8)	1.8 (0.5–5.3)	0.129
Adherence to treatment, n (%) **			
Adherent	4 (100.0)	2 (66.7)	0.429
Non-adherent	0 (0.0)	1 (33.3)	
Concurrent radiation therapy, n (%)			1.000
Yes	1 (8.3)	3 (10.3)	
No	11 (91.7)	26 (89.7)	
Oncologic surgery, n (%)			1.000
Yes	0 (0.0)	2 (6.9)	
No	12 (100.0)	27 (93.1)	

Notes: *The percentage in each group was calculated according to the total number of modifications (14 and 30 in patients with and without a long-term clinical response, respectively). **Adherence calculated over patients with active treatment at the moment of the study visit (4 and 3 in patients with and without a long-term clinical response, respectively).
Abbreviation: IQR, interquartile range.

MEK inhibitors has been proven to delay the onset of resistance and provide more sustained and dramatic responses in comparison with a *BRAF* inhibitor in monotherapy. Franken et al,[16] in a systematic literature review and network meta-analysis, identified the combination of vemurafenib/cobimetinib as one of the most favorable treatments for advanced melanoma in terms of PFS (hazard ratio, HR, 0.2). The majority of information on the efficacy of vemurafenib/cobimetinib derives from clinical trials.[9] To our knowledge, none of the studies have reported the efficacy of this combination of agents in real-world settings. Only an abstract by Guardo et al,[17] involving 14 patients with *BRAF* mutant metastatic melanoma, reported the experience with vemurafenib/cobimetinib from an Italian Center. The median follow-up was 23 weeks. A total of 3 patients achieved a CR, 8 a PR, 1 SD, and 2 PD. The objective response rate was 78.5% (11 cases). Most frequent AEs were: grade 1–2 rash (4 patients), grade 1 aspartate/alanine aminotransferase elevation (1 patient), grade 2 total bilirubin increase (1 patient), and grade 1 diarrhea (1 patient). Other real-world studies have evaluated the efficacy of *BRAF* and *MEK* inhibitors in monotherapy or in combination, but including predominantly patients receiving encorafenib/binimetinib and/or dabrafenib/trametinib; being thus non comparable with our results.[18–21] In our present study, 29.3% of patients achieved a durable response of at least 12 months. The onset of the response was 6.9 months in patients having a CR, and 3.3 months in those with a PR. Given the proven efficacy of therapies, it has become necessary to identify patients who may benefit from each type of agent.[22] In our study, practically all sociodemographic

Table 4 Most Frequent Adverse Events Related to the Combined Therapy in Patients Considering the Durability of the Response

n (%)	Patients with Durable Clinical Response (N=12)	Patients with Non-Durable Clinical Response (N=29)
Asthenia	7 (58.3)	11 (37.9)
Diarrhea	5 (41.7)	8 (27.6)
Arthralgia	6 (50.0)	3 (10.3)
Erythema	3 (25.0)	5 (17.2)
Rash	3 (25.0)	5 (17.2)
Photosensitivity reaction	2 (16.7)	5 (17.2)
Skin toxicity	3 (25.0)	3 (10.3)
Nausea	4 (33.3)	2 (6.9)
Pruritus	2 (16.7)	2 (6.9)
Anemia	2 (16.7)	2 (6.9)

and clinical characteristics were similar between patients with durable and non-durable clinical responses. The BMI was the only differential factor (patients with higher BMI achieving a non-durable response). Although obesity is a known risk factor for the development of cancer and poor prognosis,[23] and our observation would be in line with it, diverse studies have associated overweight and early obese states with improved survival; what has been called "the obesity paradox".[24] Indeed, McQuade et al,[25] in a retrospective, multicohort analysis with 2046 patients with metastatic melanoma who had received *BRAF* and *MEK* targeted therapy, immunotherapy, or chemotherapy, concluded that obesity was correlated with improved PFS (HR: 0.8; 95% confidence interval, 95% CI: 0.7–0.9) and OS (HR: 0.7; 95% CI: 0.6–1.0), in comparison with normal BMI. Yet, other studies have demonstrated opposite results.[26,27] Fang et al,[27] in a study involving 1186 patients with melanoma showed significant associations between higher BMI and poorer survival outcomes (HR for OS was 1.2; 95% CI: 1.1–1.3), after adjustment for sex, age, and stage. In our study, treatment adherence was also similar among patients with durable and non-durable clinical response. Therefore, durability of the response seems not to be associated with adherence to the treatment. Nevertheless, given the low number of patients with data on treatment adherence, no strong conclusions can be made in this regard.

On the other side, safety profile of the *BRAF*/*MEK* combination therapy has not been associated with an increase in the incidence of AEs, in comparison with agents in monotherapy.[28] In our study, even though the AEs caused by the combination treatment led to dose modification in 56.1% of cases, most of patients (85.7%) were adherent to the treatment. This fact was also reinforced by the fact that patients could experience anxiety (42.9% of total) or depression symptoms (14.3%). The main limitation of our study was its retrospective design, providing only available information. Another limitation was the low number of patients included in the study; however it derives directly from the availability of this subpopulation of patients in real-world settings. Furthermore, it cannot be strongly concluded that BMI is a factor associated with durable or non-durable responses, as the study was not specifically designed to identify factors associated with durable clinical responses. Besides these limitations, results are in agreement with observed previously in clinical trials.[9]

In conclusion, the combination treatment with vemurafenib/cobimetinib results in an important impact on long-term survival, leading to a steady CR in one third of the patients. Further prospective study, involving larger cohort of patients, are needed to corroborate these results.

Data Sharing Statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Ethical Approval and Consent Statement

Procedures were approved by the Ethics Committee of the Hospital Vall d'Hebron, and in concordance with the Declaration of Helsinki. Excepting deceased patients (whose informed consent was waived by the Hospital Vall d'Ebron), all subjects signed an informed consent to be included in the study. In any case, patient data confidentiality was guaranteed.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

BCB declares that has received consulting honoraria from Boehringer and Sanofi and is on the speaker's bureau of

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