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Katarzyna Kozak, Tomasz Świtaj, Hanna Koseła-Paterczyk, Paulina Jagodzińska-Mucha, Paweł Rogala, Paweł Teterycz, Piotr Rutkowski

Department of Soft Tissue/Bone, Sarcoma and Melanoma, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Summary of experience of melanoma patients treated with BRAF/MEK inhibitors according to Polish National Drug Reimbursement Program Guidelines

Address for correspondence:
Lek. Katarzyna Kozak
Klinika Nowotworów Tkanek Miękkich, Kości i Czerniaków
Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie — Państwowy Instytut Badawczy
ul. Roentgena 5, 02–781 Warszawa
Phone: 22 546 20 31
e-mail: wiater.katarzyna@gmail.com

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ABSTRACT

Introduction. Combined inhibition of BRAF and MEK improved progression-free survival and overall survival in patients with *BRAFV600*-mutation-positive metastatic melanoma. We conducted a retrospective study on real-life patients with BRAF-mutant melanoma treated with BRAF/MEK inhibitors.

Patients and methods. Patients with untreated, unresectable stage IIIC/IV melanoma positive for the *BRAFV600* mutation were treated with dabrafenib/trametinib or vemurafenib/cobimetinib. All patients received BRAF/MEK inhibitors as first-line therapy according to Polish National Drug Reimbursement Program Guidelines. Median follow-up time was 41 months. For the survival analysis, the Kaplan-Meier estimator was used with log-rank tests for univariate comparisons.

Results. A total of 95 patients were included (48 women and 47 men; median age: 55 years). 80 patients received dabrafenib/trametinib and 15 received vemurafenib/cobimetinib. Overall, 12 patients continued therapy after the cutoff date. The objective response rate was 71%, including six patients (6%) with a complete response and 62 patients (65%) with a partial response. Median progression-free survival was 10 months and median overall survival was 15 months. High LDH level, ECOG > 0, stage M1c–M1d and three or more metastatic organ sites negatively impacted PFS and OS. Higher adverse event rate was reported in patients receiving vemurafenib/cobimetinib (87%) as compared to patients treated with dabrafenib/trametinib (64%). Overall, grade 3–4 toxicity was reported in 20% of patients. The most frequent adverse events in the dabrafenib/trametinib group were pyrexia, fatigue, nausea and arthralgia. In the vemurafenib/cobimetinib group, the most frequent adverse events were skin toxicity (rash, photosensitivity), arthralgia, myalgia and diarrhea.

Conclusions. Despite the high response rate to BRAF and MEK inhibitor therapy, the overall survival is lower in clinical practice than observed in clinical trials. This difference may be explained by a more heterogeneous patient population seen in routine clinical practice, with more advanced disease and comorbidities.

Key words: *BRAF* mutation, metastatic melanoma, targeted therapy

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Introduction

Standard treatment in patients with metastatic melanoma with the *BRAF V600* mutation is BRAF/MEK inhibitors or immunotherapy based on anti-PD1 antibodies. The *BRAF* V600 mutation (v-raf murine sarcoma viral oncogene homolog B1) is present in about 50% of melanoma patients. Currently, three combinations of BRAF/MEK inhibitors are registered in Europe (dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib). The first two combinations are available in Poland within the Drug Reimbursement Program of the Ministry of Health and can be applied in any line of treatment in patients with advanced mela-

noma who have a *BRAF V600* mutation. A second treatment option independent of the *BRAF* mutation status are anti-PD1 antibodies as monotherapy or in combination with an anti-CTLA4 antibody. Currently, in Poland, these antibodies can be used exclusively in monotherapy. Nivolumab and pembrolizumab are available as 1st or 2nd line treatment whereas ipilimumab in the 2nd line of treatment. As both molecularly targeted drugs and immunotherapy prolong the time of progression-free and overall survival it has not been established which treatment should be used in the 1st line, moreover in the light of retrospective analyses both groups of drugs have higher effectiveness when they are used as 1st line treatments. Currently, randomized clinical trials aimed at establishing the optimal mode of treatment are ongoing. Both combined treatment (BRAF/MEK inhibitors plus immunotherapy), as well as different options of sequential treatment, are being investigated. The aim of the present work is the evaluation of the results of treatment with BRAF/MEK inhibitors of patients with advanced melanoma in the scope of everyday clinical practice. Responses to anti-PD1 therapy used in the second line of treatment after failure of treatment with BRAF/MEK inhibitors are also evaluated.

Material and methods

95 patients were included who were on the drug program with BRAF/MEK inhibitors between October 2014 and May 2017. In 27 patients the MEK was added during treatment with a BRAF inhibitor. At that time the drug program allowed targeted treatment of patients with nonresectable or metastatic melanoma positive for the *BRAF* mutation with a good performance status according to the Eastern Cooperative Oncology Group (ECOG 0 or 1). Patients with metastases to the brain could be included in the drug program if the metastases were asymptomatic. The patients were treated to disease progression or unacceptable toxicity. According to the program of evaluation of the response to treatment, this was determined based on the results of imaging tests performed every 8–10 weeks according to Response Evaluation Criteria In Solid Tumours (RECIST 1.1). Data concerning tolerance of treatment were presented according to the fourth version of the scale of treatment toxicity — CTCAE (Common Terminology Criteria for Adverse Events). Overall survival (OS) was calculated from the date of starting targeted treatment to the date of death or the date of the last observation in surviving patients (censored observations). The date for calculating progression-free survival (PFS) was determined similarly. The final date (complete observations) for PFS was the date of disease progression. In patients in whom disease progression had not occurred so far the final date was taken to be the date of the last observation of the patient (censored observations). The Kaplan-Meier method was used to analyze survival. The comparisons of curves in individual patient subgroups (monofactorial analysis) were performed using the log-rank test. Statistical analysis was performed using MedCalc Software (version 19.1.3). The median follow-up time was 41 months (range 2–50).

Results

Most patients (84%) received dabrafenib at a dose of 300 mg/day with trametinib at a dose of 2 mg/day. The remaining patients were treated with vemurafenib (1920 mg/day) in combination with cobimetinib (60 mg/day). All patients received BRAF/MEK inhibitors in 1st line treatment. The median age at the start of targeted therapy was 55 years (range 25–84). The distribution of sex in the investigated group was uniform: 48 women and 47 men. Most patients had an ECOG performance status of 1 (68%). Lactate dehydrogenase (LDH) levels were higher than normal in 41% of patients. Metastases to the central nervous system (CNS) before initiating targeted therapy were present in 37%, and metastases to > 2 organs were found in 43% of patients. The characteristics of patients are presented in Table 1.

The percentage of responses to treatment was 71%. A complete response to treatment was observed in 6% patients, and a partial one in 65% of patients. Median progression-free survival was 10 months, and median overall survival was 15 months (Tab. 2). No differences in median PFS and OS were observed between patients receiving two different combinations. Univariate analyses indicated that factors associated with poorer progression-free survival were ECOG 1, high LDH level and metastases localized in > 2 organs (Tab. 3). Figure 1 and 2 present curves of PFS and OS as a function of LDH concentration and M1. Median PFS in the group of patients with low progression of the disease (number of metastatic organ sites ≤ 2) was 17 months, whereas in the group of patients with the number of metastatic organ sites > 2 it was only 6 months. Median OS for both groups were 29 and 8 months, respectively. The best survival was observed in patients with LDH level within the normal range and ≤ 2 metastatic organ sites. Median PFS and OS in this group of patients were 20 and 34 months, respectively. The shortest survivals were observed in patients with metastases to multiple organs (> 2) and LDH levels > upper limit of normal (ULN). Median PFS and OS in this group of patients were only 5 and 6 months, respectively (Figure 3).

At the time of data analysis, 69 (73%) patients had died due to melanoma progression. Treatment with

Table 1. Patient characteristics

	Number of patients N = 95	
	n	%
Age (median)	55	
Sex		
Women	48	50.5
Men	47	49.5
Performance status according to ECOG		
0	30	31.6
1	65	68.4
Degree of progression at the start of targeted therapy		
M1a	14	14.7
M1b	8	8.4
M1c	38	40
M1d	35	36.8
Lactate dehydrogenase (LDH) level		
≤ ULN	56	58.9
> 1 – ≤ 2 × ULN	29	30.5
> 2 × ULN	10	10.5
Metastases to the central nervous system (CNS)	35	36.8
Number of metastatic organ sites		
≤ 2	54	56.8
> 2	41	43.2
2nd line treatment	41	43.2
Anti-PD1	38	40
Anti-CTLA4	1	1.1
Clinical trial	2	2.1

ULN — the upper limit of normal

Table 2. Results of treatment of patients with a positive *BRAF* mutation with nonresectable/metastatic melanoma with BRAF and MEK inhibitors

	BRAFi + MEKi N = 95
The best response to treatment	
Complete response (CR)	6 (6%)
Partial response (PR)	62 (65%)
Stable disease (SD)	21 (22%)
Progressive disease (PD)	6 (6%)
Objective response to treatment	
Complete response + partial response (CR + PR)	70 (74%)
Progression-free survival (PFS)	
Median (months)	10
Overall survival (OS)	
Median (months)	15

BRAF/MEK inhibitors was continued in 12 patients, 6 patients were receiving anti-PD1 therapy. The remaining patients were receiving subsequent lines of treatment (chemotherapy, repeated treatment with BRAF/MEKi). In total after finishing treatment with BRAF/MEK inhibitors, 38 patients (40%) had received anti-PD1 therapy. The percentage of responses to treatment in this group of patients was 21%. In most patients, disease progression was observed during the first evaluation of response to the treatment.

Adverse events during therapy with BRAF/MEK inhibitors were observed in most patients. They occurred more frequently in patients treated with vemurafenib and cobimetinib (87% patients) than with dabrafenib and trametinib (64% patients). Adverse events at level 3–4 were observed in 20% patients. Dose reduction was necessary in 16% of patients treated with dabrafenib and trametinib and 20% of patients treated with vemurafenib and cobimetinib. Treatment was stopped in two patients because of toxicity (general fatigue, nephrotoxicity). Among the most common adverse effects observed in the group of patients treated with dabrafenib and trametinib were: pyrexia/chills, fatigue, nausea and arthrhalgia. In the case of vemurafenib and cobimetinib skin complications predominated (rash and photosensitivity), myalgia, arthralgia and diarrhea.

Discussion

The use of BRAF/MEK inhibitors in patients with metastatic melanoma and positive for the *BRAF* mutations yields a high percentage of positive responses to treatment also in everyday clinical practice. The objective responses to treatment observed here (71% of patients) are in agreement with the results of large randomized, Phase III clinical trials for both combinations. In the COMBI-d (NCT01584648) and COMBI-v (NCT01597908) trials objective responses to treatment with dabrafenib and trametinib were observed in 68% [1] and 64% [2] patients, respectively, and in the coBRIM (NCT01689519) trial the percentage of responses to treatment with vemurafenib and cobimetinib was 68% [3]. Median PFS and OS in the above-mentioned clinical trials were 11–13 months and 22–26 months, respectively. Despite, the high percentage of responses to therapy observed in patients subjected to the present analysis, median PFS and OS were, however, shorter than those observed in the above-mentioned phase III clinical trials. Median PFS was 10 months, whereas the median OS was 15 months. This is related to the specific effectiveness of BRAF/MEK inhibitors, which allow a high percentage of treatment responses regardless of the stage of the disease, this also is true

Table 3. Results of treatment of patients with nonresectable/metastatic melanoma with BRAF and MEK inhibitors depending on clinical factors

Clinical factor	Number of patients N = 95	Progression-free survival (PFS) Median (months)		Overall survival (OS) Median (months)	
Performance status according to ECOG					
0	30	16	p = 0.0235	32	p = 0.0076
1	65	9		13	
Degree of progression at the start of targeted therapy					
M1a	14	30	p = 0.0668	Not attained	p = 0.0078
M1b	8	7		20	
M1c	38	8		13	
M1d	35	8		13	
Lactate dehydrogenase concentration (LDH)					
≤ ULN	56	14	p = 0.0109	24	p = 0.0009
> 1 – ≤ 2 × ULN	29	6		10	
> 2 × ULN	10	5		6	
Metastases to the central nervous system (CNS)					
Yes	35	8	p = 0.0846	13	p = 0.0298
No	60	11		20	
Number of metastatic organ sites					
≤ 2	54	17	p < 0.0001	29	p < 0.0001
> 2	41	6		8	
Number of metastatic organ sites and lactate dehydrogenase level (LDH)					
≤ 2 and ≤ ULN	57	20	p < 0.0001	34	p < 0.0001
> 2 and > ULN	20	5		6	

ULN — the upper limit of normal

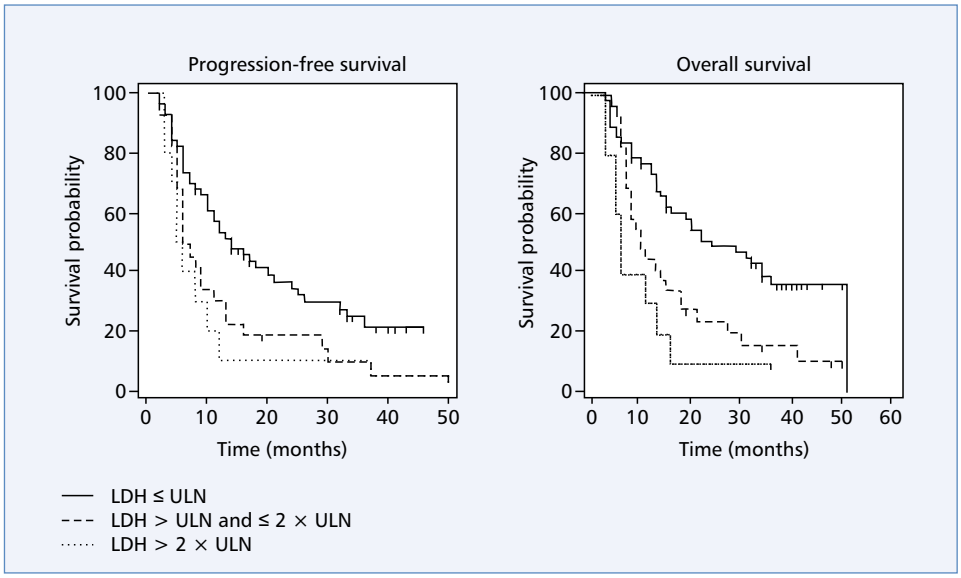

Figure 1. Progression-free survival and overall survival as a function of lactate dehydrogenase (LDH) activity. ULN — upper limit of norma

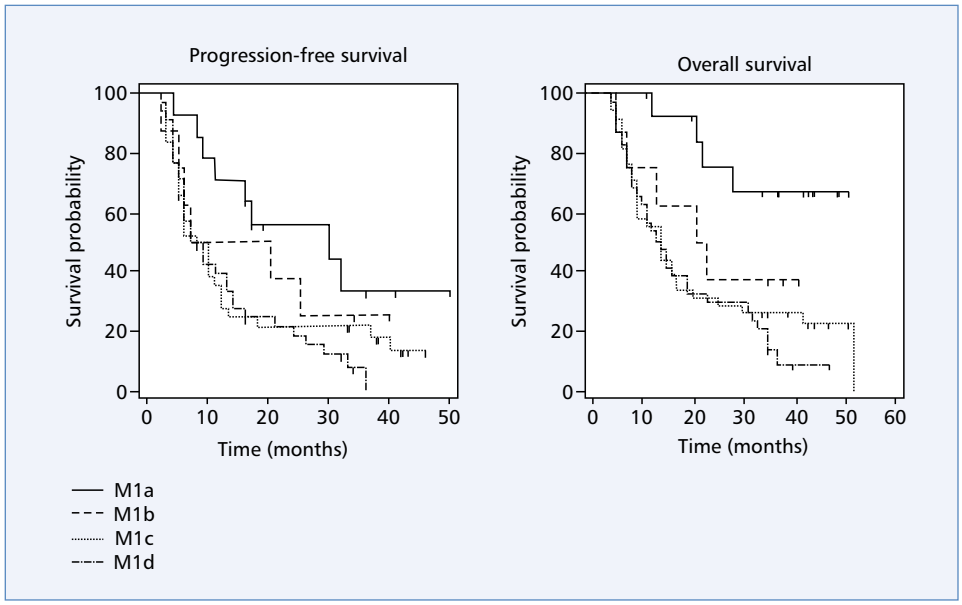

Figure 2. Progression-free survival and overall survival as a function of M1

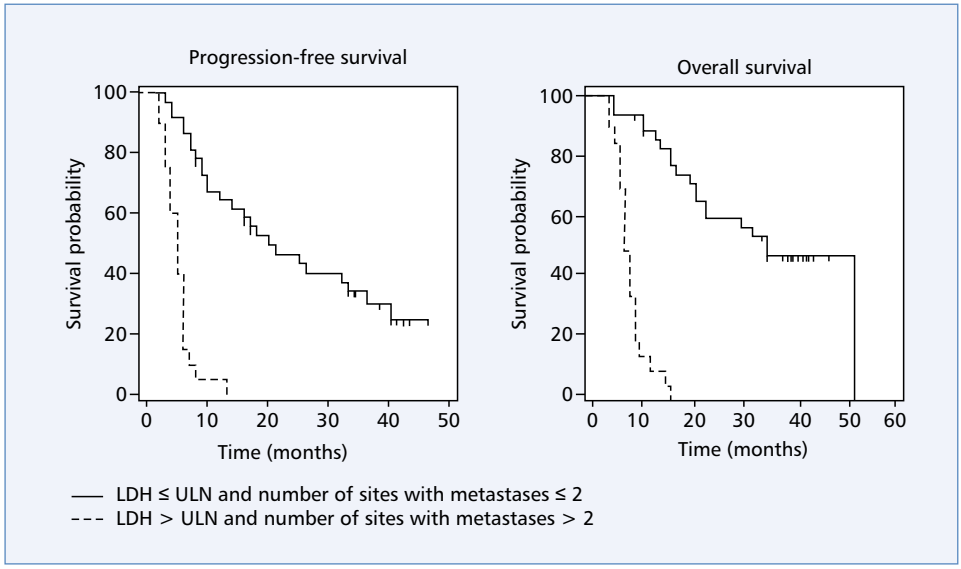

Figure 3. Progression-free survival and overall survival as a function of lactate dehydrogenase (LDH) level and the number of metastatic organ sites. ULN — upper limit of normal

for patients with multiple metastases within the central nervous system (CNS) and multiple metastatic organ sites. The problem in targeted therapy is still the resistance to the applied treatment. How fast it develops depends on how advanced the disease is before initiating BRAF/MEK inhibitor therapy. In everyday clinical practice, which is reflected very well in the analyzed patient population, much more commonly than in clinical trials this group encompasses patients with many metastases to the brain, a high LDH level (especially > 2 × ULN) or metastases to multiple organs. In the analyzed patient population the shortest medians of overall survival were observed in patients with brain metastases (13 months), LDH levels > 2 × ULN (6 months) and in patients with metastases to multiple organs (8 months). An especially short survival was observed in patients with elevated LDH accompanied by metastases to multiple organs. Median PFS and OS in this group of patients were just 5 and 6 months, respectively. It is worth pointing out that the presented patient population was treated with inhibitors as 1st line treatment. This was initially due to the lack of access to immunotherapy based on

anti-PD1 antibodies and a different initial program of drugs with anti-PD1. Due to the present access to immunotherapy based on anti-PD-1 antibodies currently in most patients treated in the Department of Soft Tissue/Bone, Sarcoma and Melanoma immunotherapy is used as 1st line treatment which is in agreement with the tendency worldwide. This is related to the possibility of obtaining responses lasting several years which are maintained even if immunomodulatory therapy is stopped. Therefore in asymptomatic patients with good performance status and not very rapid disease dynamics treatment is more commonly started as immunotherapy. It should, however, be stated that this group also has long-term responses during therapy with BRAF/MEK inhibitors. An analysis summing up the long term effects of treating patients with dabrafenib and trametinib in the scope of COMBi-d and Combi-v trials indicates a high percentage of overall survival in patients with advantageous prognostic factors. The percentages of 5-year progression-free survival and overall survival in patients with normal LDH levels were 25% and 43%, respectively. In the group of patients with normal LDH levels and fewer than 3 metastatic organ sites, the percentage of 5-year overall survivals was as high as 55% [4]. The results of treatment with dabrafenib and trametinib in patients with particularly unfavourable prognostic factors, that is LDH levels two times higher than the upper limit of normal are quite different. Schadendorf et al. in an earlier analysis of the results of the COMBI-d and COMBI-v trials noted in this group of patients median PFS of only 5.5 months and percentages of progression-free 2 and 3-year survivals of 2% and 0, respectively [5]. Based on the results of the CheckMate 067 trial, it seems that the best option in this group of patients is a combination of nivolumab with ipilimumab, which yielded a percentage of overall 3-year survivals of 28% [6].

In this analysis, the response to treatment with anti-PD1 antibodies as 2nd line treatment after unsuccessful therapy with BRAF/MEKi was also evaluated. The percentage of responses to anti-PD1 therapy was 21%, which is confirmed by numerous retrospective analyses published so far [7–9]. Unfortunately in some patients treated with BRAF/MEK inhibitors rapid progression of the disease is observed after the drugs are discontinued. In most patients subjected to this analysis, immunotherapy was stopped already during the first 3 months of treatment because of the progression of the disease. One of the basic reasons for the progression of the disease during targeted treatment is metastasis of the disease to the CNS or progression of already existing metastases to the brain. This localization of metastases is associated with a lower percentage of responses to anti-PD1 antibodies. Taking the results of phase II of the ABC (Anti-PD1 Brain Collaboration) and CheckMate 204 trials the only effective option for immunotherapy in patients with metastases to the brain is a combination of anti-CTLA4 and anti-PD1 antibodies. Intracranial responses to treatment with nivolumab and ipilimumab in the scope of the above-mentioned clinical trials were observed in 46–52% patients [10, 11]. Such treatment is not, however, included in current drug programs for patients with advanced melanoma.

The availability of BRAF/MEK inhibitors in the scope of treatment programs since several years has made their safety profile familiar to oncologists. In patients undergoing the present analysis, the percentage of complications was lower than that reported in clinical trials, which is probably due to the retrospective character of this work. In COMBI-d and COMBI-v trials during treatment with dabrafenib and trametinib, the most common were pyrexia (51–53%), nausea (30–35%), diarrhea (24–32%) and chills (30–31%) [1, 2]. In the coBRIM trial, the most common adverse effects of vemurafenib and cobimetinib were: diarrhea (56%), nausea (40%), skin rashes (32%) and arthralgia (32%) [3]. No strong irreversible complications were observed in the population subjected to the present analysis. In the case of the combination of vemurafenib with cobimetinib the basic adverse effect was skin toxicity, which is relatively easy to avoid by modifying the dose. It should be kept in mind that patients have to be properly educated in order to avoid burning of the skin due to vemurafenib phototoxicity. Protection against UVA light should be constant, regardless of the time of the day or season. During the whole period of treatment, the patients should use broad-spectrum UVA + UVB filters. For the dabrafenib and trametinib combination, the basic problem is pyrexia which occurs in even one half of the patients. In 2015 Menzies et al. published a detailed analysis of the course of pyrexia in patients during treatment with dabrafenib and trametinib. The median time to appearance of the first episode was 19 days, the median time of its duration was 9 days. Successive episodes appeared after 3–4 weeks after the previous one but were shorter (median 4–5 days) [12]. Dose modification in the case of this adverse effect often does not bring the expected result. The only effective measures are interruptions of treatment and proper education of the patients. Interrupting treatment with dabrafenib already upon the appearance of prodromal symptoms makes the pyrexia episodes shorter and less intense. In the case of persistent recurring pyrexia making it difficult to maintain continuous treatment oral prednisone at a dose of 10–25 mg/day should be considered [13].

This analysis confirms the efficacy of BRAF/MEK inhibitors used in everyday clinical practice. BRAF/MEK inhibitors yield responses even in patients with a high degree of disease progression which has a significant impact on improving their quality of life. However,

because of resistance which appears especially early in symptomatic patients further research in overcoming the resistance in order to sustain the initial response to treatment are necessary. The improvement in treatment may be caused by new combinations of drugs with immunomodulating activity and targeted to particular molecules or more intensive immunotherapy.

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