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REVIEW ARTICLE

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Treatment of patients with advanced melanoma harboring the *BRAF* V600 mutation

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ABSTRACT

The advances in the treatment of melanoma patients with V600 mutations in the *BRAF* gene over the past few years result from the introduction of targeted drugs and modern immunotherapy. Unfortunately, at the moment there is a lack of data from a randomised clinical trial that determines the optimal sequence of anti-BRAF/anti-MEK drugs and immunotherapy in *BRAF* (+) patients. This paper discusses the most important clinical trials performed so far, the results of which may be helpful in the selection of systemic treatment in patients with advanced or metastatic melanoma harbouring *BRAF V600* mutation. Formal analysis indicates that molecularly targeted treatment is the method of choice in the first-line setting in patients with *BRAF* (+) melanoma because the value of anti-BRAF/anti-MEK drugs in this population was confirmed by consistent results of three phase 3 studies. Conversely, evidence for the effectiveness of immunotherapy in advanced *BRAF* (+) melanoma are much weaker. However, both methods significantly improved the prognosis, and in some patients with *BRAF* gene mutation they led to long-term survival. Currently, the research is ongoing, and the results may resolve this issue.

Key words: metastatic melanoma, *BRAF* mutation, BRAF inhibitors, immunotherapy

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Introduction

For many years, the results of treatment of patients with advanced melanoma were unsatisfactory. Median survival time was only six months, and only about 25% of patients survived a year despite the use of chemotherapy. The situation has been significantly changed in the last five years, since several new medicines were registered which markedly improved the prognosis. This progress also applies to melanoma patients with the *BRAF V600* mutation, known to be associated with shorter overall survival (OS); in this case it results from introduction of targeted drugs and modern immunotherapy [1, 2].

Targeted therapy anti-BRAF

The discovery of the importance of *BRAF V600*-activating mutations, occurring in about 50% of patients with advanced melanoma, as well as the associated activation of the MAPK pathway (RAS/RAF/MEK/ERK), allowed the development of small molecule inhibitors of BRAF serine-threonine kinase, dabrafenib, and vemurafenib [1, 3]. Despite the high antitumor activity measured by objective response rate (ORR), resistance developed relatively rapidly during the use of both drugs, which was, among other things, related to reactivation of the MAPK pathway. The occurrence of resistance limited the effectiveness of treatment, and median progression-free survival (PFS) did not exceed 6–7 months. Only the combination of BRAF inhibitor with an anti-MEK drug (cobimetinib or trametinib) resulted in further improvement of treatment results — an increase of ORR (by 14–20%), median PFS (about 2–5 months), and median OS (about 5–8 months) as well as a reduction in the incidence of anti-BRAF-induced skin tumours [1, 3–6].

All three studies evaluating the use of BRAF inhibitor in combination with MEK inhibitor in previously untreated *BRAF* (+) patients: coBRIM (comparing the use of cobimetinib and vemurafenib with vemurafenib) [4];

Table 1. Effects of combined anti-BRAF/anti-MEK therapy in experimental groups in phase 3 trials [3–6]

	coBRIM	COMBI-d	COMBI-v
Objective response rates (%)	70	69	64
Median PFS (months)	12.3	11	12.6
Median OS (months)	22.3	25.1	25.6

PFS — progression-free survival; OS — overall survival

COMBI-d (dabrafenib and trametinib with dabrafenib alone) [5]; and COMBI-v (dabrafenib and trametinib with vemurafenib) [6] confirmed the superiority of anti-BRAF and anti-MEK therapy over anti-BRAF monotherapy (Table 1). Slightly shorter median OS observed in the coBRIM study may be associated with a higher percentage (44% *vs.* 34–36%) of patients with initially elevated LDH, which is a strong unfavourable prognostic factor in advanced melanoma. Despite the lack of direct comparison of both combined therapies (dabrafenib with trametinib *versus* cobimetinib with vemurafenib), consistency of results and indirect analysis indicate comparable activity and effectiveness of both treatment regimens [3–6].

Immunotherapy

Currently, immunotherapy also has a basic role in the treatment of patients with advanced melanoma, by targeting immune checkpoints. Ipilimumab was the first antibody that, by binding CTLA-4 antigen (cytotoxic T cell antigen 4), enhanced the T-cell-dependent antitumour response and resulted in prolonged survival of melanoma patients. In a study comparing the use of ipilimumab in combination with dacarbazine with dacarbazine with placebo, in previously untreated patients with advanced melanoma, the median OS was 11.2 *vs.* 9.1 months, respectively, and three-year survival reached 20.8% *vs.* 12.2% [7].

Significantly lower toxicity and greater efficacy were observed after the use of drugs blocking PD-1 receptor (programmed death 1) and its ligand PD-L1. The pivotal studies regarding the use of nivolumab (anti-PD-1 monoclonal antibody) were CheckMate 037 [8, 9], CheckMate 066 [10], and CheckMate 067 [11, 12], whereas Keynote 006 was the key study for pembrolizumab [13, 14].

The CheckMate 037 study recruited patients with (22%) or without *BRAF* mutation, who had previously received ipilimumab (*BRAF* [+] patients — also anti-BRAF drug). Patients received nivolumab or chemotherapy with dacarbazine or carboplatin and paclitaxel (investigator's choice). There was no difference in OS (median — 15.7 *vs.* 14.4 months) and PFS (median — 3.1 *vs.* 3.7 months), which could result from minor differences in baseline characteristics of the study groups — slightly more patients (20% *vs.* 14%) in the experimental group had metastases in the central nervous system (CNS) and increased lactate dehydrogenase (LDH) level — 52% *vs.* 38%. Further treatments (anti-PD-1 therapy given on progression) also differed between the arms — 11% *vs*. 41%. However, the response rate and median duration of response were significantly higher in the group receiving nivolumab — 27% *vs.* 10% and 32 *vs.* 13 months, respectively [1, 8, 9].

Another two studies looked at the use of nivolumab in previously untreated patients with unresectable or disseminated melanoma. In the CheckMate 066 study dacarbazine was a comparator and the primary endpoint was OS. The study did not include patients with the *BRAF* mutation and, similarly to CheckMate 037, with symptomatic metastases in CNS. As in the previous study, the response rate in the group receiving nivolumab was higher than in the chemotherapy group (40% *vs*. 13.9%). In addition, the median PFS was significantly higher (5.1 *vs*. 2.2 months), and the percentage of patients who survived one year was significantly higher (72.9% *vs*. 42.1%, with 58% reduction in risk of death). At the time of publication of the study results, OS was not achieved in the nivolumab group, while it was 10.8 months in the control group [10].

The CheckMate 067 study included *BRAF* (+) patients (32% of the study population) and had PFS and OS as co-primary endpoints. In this study, previously untreated patients with unresectable melanoma at stage III or IV received nivolumab monotherapy, nivolumab in combination with ipilimumab, or ipilimumab monotherapy. The median PFS was 11.5 *vs.* 6.9 *vs*. 2.9 months, respectively. After a minimum of 36 months of observation, the median OS was not reached in patients receiving nivolumab in combination with ipilimumab; it was 37.6 months for nivolumab and 19.9 months for ipilimumab. The three-year survival rate was 58% for patients in the first group, 52% in the second group, and 34% in the ipilimumab arm [11, 12].

The Keynote 006 study compared pembrolizumab and ipilimumab in patients with inoperable or metastatic melanoma, who had not previous systemic treatment or received only one treatment line. *BRAF* mutations occurred in 35% of patients treated with pembrolizumab, half of whom received prior anti-BRAF/anti-MEK therapy. The co-primary endpoints were PFS and OS.

During the follow-up of 23 months, median OS was not reached in pembrolizumab-treated patients (for ipilimumab — 16 months), and the two-year survival rate in patients treated with pembrolizumab was 55% [13, 14].

In all studies objective response rates (31–44%) and median PFS (about 5–7 months in the groups receiving nivolumab and pembrolizumab monotherapy) were slightly lower as compared with anti-BRAF/anti-MEK therapy [1]. Some patients, however, had a long-term clinical benefit. In general, 52% of patients treated with nivolumab in the Checkmate 067 study survived three years, and 55% of patients treated with pembrolizumab in the Keynote 006 study survived 24 months [12, 14]. The time from treatment initiation to response was longer than for anti-BRAF/anti-MEK therapy. For nivolumab-treated patients it ranged in various studies between 1.2 and 12.5 months (median approx. 2.2–2.78 months) [9, 11]. The combination of nivolumab with ipilimumab resulted in a further improvement in PFS (median 11.5 months) and objective response rates (58%), approaching the results obtained with the use of anti-BRAF/anti-MEK therapy, although at the expense of significantly higher toxicity than anti-PD-1 monotherapy. Median time to response to combined treatment was comparable (2.8 months), and the duration of response ranged between 1.1 and 11.6 months [11].

In the Checkmate 037 study the response rate to nivolumab in *BRAF* (+) patients was numerically lower than in *BRAF* (–) patients (23% *vs.* 34%) [8]. Similarly, in the Checkmate 067 study the three-year PFS rate in patients treated with nivolumab was lower (22% *vs.* 36%), as was median PFS (5.6 *vs.* 7.9 months) in *BRAF* (+) patients compared to *BRAF* (–). In the case of combined nivolumab and ipilimumab the median PFS had a similar value (11.7 *vs.* 11.2 months, respectively), and overall survival rate after three years was slightly higher in the *BRAF* group (+) (68% *vs*. 53%), which might suggest that anti-PD-1 monotherapy in *BRAF* (+) patients is less effective than the combination of nivolumab and ipilimumab [12].

While in previously untreated patients with inoperable or metastatic melanoma and no *BRAF* mutation the treatment of choice is immunotherapy, in the case of patients with *BRAF V600* mutation, besides immunotherapy, we also have anti-BRAF/anti-MEK targeted treatment with effectiveness confirmed by the results of phase III clinical trials involving this population.

Sequential therapy

A very important question regards sequential use of anti-BRAF/anti-MEK drugs or immunotherapy and selection of patients in whom the initiation of a specific treatment would be of greater clinical benefit. Unfortunately, we do not know the answer to the question about the optimal treatment sequence in *BRAF* (+) patients. There are no data from randomised clinical trials that would directly compare targeted therapy and immunotherapy in previously untreated patients or determine the best sequence of therapies. The majority of studies with immunotherapy have involved a mixed population in which patients with *BRAF* mutations accounted for no more than 35% [13] or — as in the Checkmate 066 study — *BRAF* gene mutation was an exclusion criterion [10]. In addition, while studies on anti-BRAF/anti-MEK therapies have been conducted in a previously untreated population, studies with immunotherapy included patients receiving the first line of treatment or previously undergoing immunotherapy or anti-BRAF therapy. Sometimes, previous use of anti-BRAF/anti-MEK therapy was obligatory.

The above-mentioned circumstances mean that patient populations participating in clinical studies are diverse and it is difficult to draw conclusions about the superiority of one of the methods or the optimal treatment sequence based on the obtained results. Undoubtedly, the formal degree of reliability of scientific evidence supports the use of anti-BRAF/anti-MEK therapy.

Several retrospective analyses were published, mostly in small groups of patients (n = 34, 25, and 274), aiming to determine the optimal treatment sequence for *BRAF* (+) patients. It should be emphasised that a serious limitation of these analyses is the probable and difficult to control selection bias. Due to higher direct activity of anti-BRAF agents in patients with BRAF (+) disease patients who were qualified for immunotherapy instead of anti-BRAF treatment could have better prognosis resulting from less rapid progression and smaller tumour volume or less frequent critical internal organ involvement. The conclusions from these observations indicated that in the case of use of anti-BRAF treatment in the first-line setting a larger number of patients did not receive or were unable to complete the planned second-line therapy due to rapid disease progression. Nevertheless, one- and two-year survival rates assessed in one of these studies did not differ significantly and amounted to 80% *vs.* 89% and 67% *vs*. 51% (p = 0.97) for targeted therapy followed by immunotherapy and for the reverse sequence, respectively. However, these observations come from an era before anti-PD-1 and anti-MEK therapy [15–17].

The more recent retrospective study, evaluating immunotherapy with the use of anti-PD-1 drugs, suggests better results when immunotherapy is being used upfront. One of the conclusions was the observation that patients with a longer duration of response to anti-BRAF treatment (> 6 months) also had a greater benefit from anti-PD-1 treatment in the second-line, as

compared to patients with progression occurring during less than the first six months of treatment (34% *vs*. 15%, p = 0.04) [18].

One of the arguments supporting the superiority of immunotherapy in first-line treatment is information about long-term responses in some patients undergoing immunotherapy compared to fast-growing resistance to anti-BRAF/anti-MEK therapy (median PFS approx. 12 months). However, long-term responses are also observed in anti-BRAF/anti-MEK therapy. Recently published results of 36-month follow-up in the COMBI-d study showed that 19% of patients in the combined arm were being still treated at this time point [1, 3, 5]. In contrast to targeted treatment, immunotherapy is characterised in phase 3 clinical studies by lower objective response rates ranging between approx. 30% (monotherapy) and approx. 60% (combined use of nivolumab or pembrolizumab and ipilimumab) compared to about 70% for anti-BRAF/anti-MEK drugs. Median PFS achieved during immunotherapy (4–7 months for monotherapy and 11.5 months for the combined use of nivolumab and ipilimumab) also appears to be slightly lower than for anti-BRAF/anti-MEK therapy (11–12 months). However, both treatment strategies give the patients long-term survival and — with an indirect comparison — a similar median OS [1, 4–14].

Information that to some extent could help to draw conclusions about the right sequence of treatment would be a comparison of objective response rates obtained in second-line treatment. In the two observational studies mentioned above, it was found that previous immunotherapy had no effect on the response rate obtained with anti-BRAF therapy [16, 17]. Regarding use of immunotherapy after anti-BRAF treatment, in one retrospective study more responses were found compared to the immunotherapy used in the first-line setting [17]. However, in a combined analysis of results of treatment with nivolumab in *BRAF* (+) and *BRAF* (–) patients it was found that the earlier use of anti-BRAF drugs and ipilimumab did not affect the response rate, and the duration of response was similar in both groups [1, 19]. In turn, the results of Keynote 006 study with pembrolizumab suggest that immunotherapy results may be worse in patients previously receiving anti-BRAF/anti-MEK therapy; the response rate for immunotherapy in the *BRAF* (+) population was 41% in previously untreated patients compared to 22% in patients previously receiving anti-BRAF treatment [1, 13, 14]. Similar results were observed in a phase 2 study in patients with metastases in CNS, who had not undergone immunotherapy before. The response rate to combined treatment with nivolumab and ipilimumab was 50% in the previously untreated population, while in patients receiving anti-BRAF therapy it was only 16%. Undoubtedly, the data presented — partly discrepant — do not allow us to draw unambiguous and reliable conclusions [20].

Time to response to immunotherapy with one drug ranged in various studies between 1.2 months and even 12.5 months with a median of 8–12 weeks [9, 11, 19]. Besides this, the fact that only asymptomatic or oligosymptomatic patients with no CNS metastatic disease were qualified in some immunotherapy studies meant that anti-BRAF/anti-MEK therapy was often preferred in patients with severe symptoms, with elevated baseline LDH activity or metastases in critical organs due to the rapidly obtained objective response (median about six weeks for anti-BRAF monotherapy), sometimes even within a few days of starting treatment [4–6]. However, the intuitive belief in the legitimacy of using immunotherapy in the first-line setting in patients without significant symptoms, normal LDH level, and low volume of cancer lesions, while the use of anti-BRAF therapy in those with more disease lesions, more severe accompanying symptoms, and high LDH activity, seems not to have sufficient evidence. Firstly, in studies using anti-BRAF/anti-MEK therapy in subgroups of patients with initially normal LDH activity, very good results were obtained — 48–56% of patients lived for at least three years (in the subset also having metastases in less than three locations — even approximately two-thirds of patients) [1, 4–6]. Secondly, the results of the Checkmate 067 study indicated that a combination of nivolumab with ipilimumab is also effective in patients with elevated LDH activity and more advanced disease and may produce a therapeutic effect even about a month from the start of treatment. The three-year survival rate among patients with elevated LDH activity undergoing anti-BRAF treatment was 20–25%, and for immunotherapy with nivolumab with ipilimumab (when LDH > 2 × upper limit of normal) it reached 31% [11, 12].

Although expression of PD-L1, until recently, appeared to be a natural predictive marker of response to anti-PD-1/PD-L1 therapy, the benefits of treatment have also been observed in patients without PD-L1 expression, which makes this biomarker not useful in clinical practice for better patient selection. Likewise, no additional biomarkers could be established allowing more effective selection of the group of patients benefiting from anti-BRAF/anti-MEK therapy [1].

The frequency of adverse events grade 3–4 was significantly lower during single-agent immunotherapy (ipilimumab — 10–15%, nivolumab — 12%, pembrolizumab — 12%) than in patients receiving anti-BRAF/anti-MEK combination therapy (48–60%) [1, 3–14]. Although life-threatening complications were also observed during immunotherapy (e.g. interstitial pneumonitis), they were mostly reversible or manageable with glucocorticosteroids. However, combination immunotherapy (nivolumab with ipilimumab) was

characterised by a similar frequency of side effects to targeted therapy (59%) and a higher percentage of patients who were discontinued due to toxicity (39% *vs.* 11–16%) [11, 12].

Summary

Formal analysis of clinical trial results indicates that targeted therapy is a method of choice in the first-line treatment in patients with advanced *BRAF* (+) melanoma because the value of anti-BRAF/anti-MEK drugs in this population was confirmed by consistent results of different phase 3 studies. Immunotherapy has much less formal evidence of efficacy in this group of patients. Patients with *BRAF* mutations were a minority in immunotherapy studies, and the comparator was not an anti-BRAF/anti-MEK drug. However, both targeted therapy and immunotherapy significantly improved the prognosis, and in some patients harbouring *BRAF* mutations it led to long-term survival.

The issue of optimal choice of treatment for patients with inoperable or disseminated melanoma with *BRAF V600* mutation remains unresolved to some extent. There are currently ongoing studies that aim to indicate the optimal sequence of treatment in *BRAF* (+) patients: anti-BRAF/anti-MEK therapy, followed by immunotherapy or vice versa, as well as the combination of anti-PD1 and anti-BRAF/anti-MEK therapy. An example of such trials is a phase 3 study (NCT02224781) led by the US National Cancer Institute. Its primary endpoint is to assess whether, in previously untreated patients with unresectable stage III or IV melanoma and *BRAF* mutation, the use of anti-BRAF/anti-MEK treatment sequence followed by ipilimumab/nivolumab after disease progression, or vice versa, will lead to a higher two-year survival rate. In addition, evaluation of response rate, PFS, and treatment tolerance is planned [21]. Similar studies concern the sequential use of immunotherapy and targeted treatment using other, not yet registered, anti-BRAF/anti-MEK drugs (e.g. the phase 2 SECOMBIT trial) [22]. It is hoped that the results of the mentioned studies will clearly determine the optimal order of treatment for patients with unresectable melanoma in stage III or IV and mutation in the *BRAF* gene.

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