Review article

BRAF/MEK inhibitors in the systemic treatment of advanced skin melanoma

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ABSTRACT

A major progress has been made in the systemic treatment of advanced melanoma over the last few years. Targeted therapy has proven highly active, which is reflected in the response rate as well as progression-free survival and overall survival times. The paper aims to summarize the current knowledge on the available *BRAF* and *MEK* inhibitors.

Key words: melanoma, targeted therapy, *BRAF* inhibitors, *MEK* inhibitors

INTRODUCTION

Melanoma constitutes ca. 2% of all malignancies in Poland. The incidence and mortality rates have been on the increase for many years now, with 1195 cases diagnosed (and 621 deaths reported) in male patients in 2010, and 1350 cases diagnosed (and 570 deaths reported) in female patients in the same year [1]. 5-year survival of the patients diagnosed in the years 2003–2005 was around 71% for females and around 56% for male patients [2]. In the case of metastatic disease prognosis is poor, with median overall survival (OS) amounting to 6.2 months just a while ago, and only 3–4% of the patients crossing the 5-year survival threshold [3]. Over the past 6 years, however, a rapid progress has been made in the systemic treatment of advanced skin melanoma. Novel immunotherapeutic drugs as well as molecular targeted drugs have been developed and included in clinical practice. As a result, the prognosis of patients suffering from advanced melanoma is presently much better. The new drugs, different from regular chemotherapy in terms of their mechanisms of action are available only in the specialist oncology centres, equipped with sufficient clinical experience and therapeutic resources. The paper aims to summarize the current knowledge on the *BRAF* and *MEK* inhibitors used in the treatment of advanced skin melanoma.

THEORETICAL BASIS OF *BRAF*/*MEK* INHIBITION

The RAS/RAF/MEK/ERK kinase pathway is one of the pathways transmitting signals from growth factor receptors in the cell membrane to the DNA in the nucleus of the cell. In melanoma cells, the pathway is often over-activated, mostly due to the mutations activating the individual kinases [4]. The principal mechanism that leads to the overactivity of the entire pathway involves *BRAF* kinase mutations, observed in 40–70% of the melanoma patients [4, 5]. Point mutations, V600E or V600K (substituting valine with glutamic acid or lysine, respectively) are the most common ones. They lead to a 500-fold increase in *BRAF* kinase activity, and to constitutive activation of the further kinases [4]. The presence of *BRAF* mutation appears to worsen the prognosis of advanced melanoma patients, if adequate treatment is not initiated. Long et al. reported a median OS of 5.7 months for *BRAF* mutation patients who had not been treated with inhibitors. In the group of patients without the mutation, median OS was 8.5 months. For the *BRAF* mutations patients treated with inhibitors, median OS was not reached [6]. Discovery of that molecular target, i.e. the mutant *BRAF* kinase, made it possible to develop molecular targeted drugs, the highly active *BRAF* inhibitors vemurafenib and dabrafenib. Unfortunately, following several months of the anti-*BRAF* treatment, most patients develop resistance to such therapy, which results in disease progression. Therefore, another step forward was the development of drugs targeting another kinase of the RAS/RAF/MEK/ERK pathway, i.e. the *MEK* inhibitors: trametinib and cobimetinib. The safety of efficacy of the above mentioned drugs will be discussed in the sections that follow.

BRAF INHIBITORS: VEMURAFENIB AND DABRAFENIB

Vemurafenib is a selective inhibitor of mutated *BRAF* kinase isoform, registered for the treatment of adult patients suffering from non-resectable or metastatic melanoma showing signs of the *BRAF* V600 mutation. The drug is available in the form of 240 mg tablets, and the recommended dosing regimen is 960 mg (4 tablets) b.i.d., with the option of reducing the dose to manage adverse events, if necessary [7]. In a phase III clinical trial (BRIM-3) [8], vemurafenib and dacarbazine were compared in terms of their efficacy in 675 treatment-naïve metastatic melanoma patients with a *BRAF* mutation. Primary endpoints of the study included:

- OS
- progression free survival (PFS).

Secondary endpoints included:

- response rate (RR)
- duration of the response
- treatment safety.

Vemurafenib demonstrated a significant activity and a 6-month OS of 84% (vs. 64% in the dacarbazine arm). There was a 63% reduction in the risk of death, and a 74% reduction in the risk of death or disease progression as compared with dacarbazine ($p < 0.001$ for both comparisons). RR was 48% for vemurafenib and 5% for dacarbazine. The most common adverse events included: rash, fatigue, hair loss, secondary skin neoplasms (keratoacanthoma or basal-cell carcinoma), photophobia, nausea and diarrhoea. 38% of the study subjects required vemurafenib dose reduction due to the occurring adverse events. Importantly, vemurafenib demonstrated activity in patients with CNS metastases; OS of 5.3 months was reported in that population of patients in the MO25653 study [9].

Dabrafenib is another *BRAF* inhibitor. The drug was registered for the treatment of adult patients suffering from non-resectable or metastatic melanoma with signs of the BRAF V600 mutation as well as adults patients suffering from advanced non-small-cell lung cancer with a *BRAF* mutation. Dabrafenib is available in the form of 50 mg and 75 mg tablets, and the recommended dosage is 150 mg twice daily [10]. In the case of melanoma, the efficacy of dab-

rafenib monotherapy was assessed in 3 clinical studies: BRF113683 (BREAK-3), BRF113929 (BREAK-MB) and BRF113710 (BREAK-2). In the BREAK-2 phase II trial [11], its efficacy was assessed in patients with stage IV melanoma with a *BRAF* mutation, who had previously not been treated or progressed after the first line of treatment. In the group with *BRAF* V600E mutation, RR amounted to 59%, with a median response duration of 5.2 months. The BREAK-3 study [12] compared dabrafenib and dacarbazine in terms of their efficacy in treatment-naive patients with *BRAF* V600E mutation. PFS was the primary endpoint of the study, with median PFS totalling 5.1 vs. 2.7 months ($p < 0.001$) in the dabrafenib and dacarbazine arms, respectively. In the BREAK-MB phase II trial [13], the efficacy of dabrafenib was assessed in a population of patients with CNS metastases. In the subgroup of patients with *BRAF* V600E mutation, without prior local treatment, brain RR was 39%, with a median intracerebral duration of response of 4.6 months, and a median OS of 7.6 months. Results of the above mentioned study testify to the efficacy and safety of dabrafenib treatment in patients with CNS metastases. The adverse events reported are similar to those associated with vemurafenib. Additionally, fever frequently sets in during the therapy.

COMBINED TREATMENT WITH *BRAF* AND *MEK* INHIBITORS

The safety and efficacy of combined treatment with dabrafenib (150 mg twice daily) and the *MEK* inhibitor trametinib (2 mg once daily) was assessed in 2 randomized clinical trials.

In the COMBI-d study [14, 15], combined treatment (211 subjects) was compared with dabrafenib and placebo (212 subjects) in treatment-naïve melanoma patients with *BRAF* V600E/K mutation, suffering from (non-resectable) stage IIIc and stage IV cancer. Combined treatment turned out to be more efficacious than monotherapy in terms of PFS: 11 months (95% CI: 8.0–13.9) vs. 8.8 months (95% CI: 5.9–9.3); hazard ratio (HR): 0.67 ($p = 0.0004$); and OS: 25.1 (95% CI: 19.2–not reached) vs. 18.7 months (95% CI: 15.2–23.7). Survival benefit was reported for all subgroups, irrespective of the type of *BRAF* mutation and the baseline concentration of lactate dehydrogenase. Combined therapy was also linked to a different profile of adverse events. Fewer secondary skin neoplasms were observed in the study, whereas the incidence of fever was higher than in the case of dabrafenib monotherapy. The double *BRAF/MEK* inhibition was also found to improve the patients' quality of life as assessed with the EORTC-QLQ C30 questionnaire [16].

In the COMBI-v study [17], combined treatment with dabrafenib and trametinib was compared with vemurafenib monotherapy. Results were similar to those reported in the COMBI-d trial, with a clear therapeutic superiority of combined treatment over vemurafenib monotherapy in terms of the reported PFS: 11.4 vs. 7.3 months ($HR = 0.56$; $p < 0.001$), RR: 64% vs. 51% ($p < 0.001$), and median OS: not reached vs. 17.2 months ($HR = 0,69$; $p = 0.005$). Cases of squamous cell carcinoma and *keratoacanthoma* were only reported for 1% of the combined treatment patients as compared with 18% of those receiving vemurafenib monotherapy.

The safety and efficacy of vemurafenib (960 mg b.i.d.) combined with another *MEK* inhibitor, cobimetinib (60 mg once daily for the first 21 days of each 28-day cycle), was assessed in the co-BRIM phase III clinical study (247 patients on vemurafenib plus cobimetinib vs. 248 patients on vemurafenib plus placebo) [18–20]. Combined treatment turned out to be more efficacious in terms of PFS: 12.3 vs. 7.3 months ($HR = 0.58$), RR: 70% vs. 50%, and OS: 22.3 vs. 17,4 months ($HR = 0.70$; 95% CI: 0.55–0.90; $p = 0.005$). The incidence of grade 3 and 4 adverse events, assessed in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), was slightly higher in the study arm receiving both medications (65% vs. 59%), with the following events occurring at a higher frequency: central serous retinopathy, diarrhoea, nausea and vomiting, photophobia, and elevated activity of aminotransferases and creatinine in lab test results. On the other hand, a significant decrease in the incidence of secondary squamous cell carcinoma was observed in the combined treatment arm (2% vs. 11%).

The safety and efficacy data pertaining to the currently available *BRAF/MEK* inhibitors is presented in Table 1.

TABLE 1.
Safety and efficacy of molecular targeted drugs [14–20].

Parameter	Dabrafenib + trametinib	Vemurafenib + cobimetinib
mOS (months)	25.1	22.3
mPFS (months)	11–11.4	12.3
Fever, all grades according to CTCAE	52–53%	26%
Fever, CTCAE grade 3	4–7%	2%
Skin rash	22–23%	39%
Squamous cell carcinoma/ *keratoacanthoma*	1–2%	3%
Serous retinopathy	< 1%	13%
Reduction in the left ventricular ejection fraction	3–8%	12%

CTCAE – Common Terminology Criteria for Adverse Events; mOS – median overall survival; mPFS – median progression free survival.

Despite the high efficacy of targeted therapy, most patients develop resistance to it with time. Due to the still limited therapeutic options in advanced melanoma, the possibility of going back to the previously administered therapy (so-called re-challenge) appears to be interesting. The efficacy of that strategy was assessed in a Belgian phase II trial [21]. The study involved 25 melanoma patients with a *BRAF* mutation, who had progressed on a prior anti-*BRAF* therapy (with or without a *MEK* inhibitor). Treatment with standard doses of dabrafenib and trametinib was initiated at least 12 weeks after the previous therapy. Partial response (PR), according to the RECIST 1.1 criteria, was achieved in 8 (32%) patients, and stable disease (SD) in 10 (40%) of them. The treatment was tolerated well by the subjects, with no grade 4 adverse events reported. The value of the re-challenge strategy was later confirmed in another study, whose results were presented at this year's meeting of the American Society of Clinical Oncology (ASCO 2017) [22]. 116 patients who had been re-challenged with targeted therapy, were analysed for PFS, RR and OS after an average of 7.7 months of retreatment. CNS metastases were confirmed in 51 (44%) of the patients. The following outcomes were reported: RR was 43% (complete response 3%, PR 39%, SD 24%), median OS from retreatment was 9.8 months, and median PFS was 5.0 months. The above presented results indicate a possible therapeutic benefit stemming from the re-challenge strategy in selected cases.

CONCLUSIONS

Next to modern immunotherapy, targeted therapy plays an important part in the systemic treatment of advanced skin melanoma. Out of that class of drugs, the following are presently available in Poland under the therapeutic programme of the Ministry of Health: vemurafenib, dabrafenib, trametinib and cobimetinib. Some of the indisputable advantages of targeted therapy include:

- a high rate of objective response to treatment (up to 70%)
- a quick therapeutic effect
- confirmed activity in cases of CNS metastases.

Undoubtedly, the disadvantage of the therapy is the fact that it is restricted to patients with a confirmed *BRAF* mutation. Results of the clinical trials discussed in the present paper clearly indicate the superiority of combined *BRAF* and *MEK* inhibition over *BRAF* monotherapy. Thus, when qualifying patients for targeted therapy, one should consider one of the possible combinations: dabrafenib plus trametinib or vemurafenib plus cobimetinib. Both drug combinations show similar activity, with some differences in terms of the dosing regimen as well as the profile and incidence of adverse events. When taking decisions on the selection of a particular therapeutic option in advanced melanoma with a *BRAF* mutation, one should take into consideration the patient's general condition as well as the availability of the treatment chosen within the framework of the currently binding national drug reimbursement programme. Molecular targeted therapy appears to be particularly valuable in those patients, whose symptoms need to be managed fairly quickly. According to the authors of this paper, decisions on the treatment sequence (including the possibility of immunotherapy) should be taken by experienced clinicians on a case by case basis. We expect to learn more from the ongoing studies on the efficacy of targeted therapy as adjunctive treatment and in combination with immunotherapy. Results of those studies may lead to changes in the current melanoma management guidelines.

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