

The treatment landscape in advanced melanoma is changing dramatically with the approval of new drugs. Vemurafenib was the first approved targeted agent for the treatment of *BRAF*-mutant advanced melanoma. However, treatment with a *BRAF* inhibitor is linked with acquired resistance occurring in half of the patients after approximately six months. Combination of MEK and *BRAF* inhibitor therapy results in extension of the time to resistance, translating into longer overall survival of treated patients. Similar clinical benefits are observed with therapy using antibodies against immune-checkpoint inhibitors in the same patient population. Due to the fact that results of randomised studies comparing these two treatment strategies back to back have not been presented yet, the best first and second line treatment option in patients with *BRAF*-mutant melanoma is unknown. Currently, phase 3 studies are also evaluating the efficacy of targeted therapy combined with immunotherapy in patients with *BRAF*-mutant and *BRAF* wild-type advanced melanoma. Identifying a biomarker for the selection of patients benefiting most from the treatment will be crucial for further survival improvement in patients with advanced melanoma.

**Key words:** *BRAF* inhibitors, MEK inhibitors, melanoma.

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# *BRAF* and MEK inhibitors in the era of immunotherapy in melanoma patients

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## Introduction

The treatment landscape of advanced melanoma is changing together with the marketing authorisation of new medicinal products. Seven new drugs and three combinations of these drugs have been approved in the treatment of melanoma since the year 2010. Currently, in patients with *BRAF* wild-type (wt) advanced melanoma, anti-PD1 (programmed cell death factor 1) therapy with nivolumab or pembrolizumab is the standard of care. The combination of nivolumab and ipilimumab (anti-CTLA4 antibody) is also an option in patients with advanced non-resectable melanoma, but the treatment toxicity is very significant. In patients with *BRAF* mutation the above immunotherapy strategies can also be applied. High clinical efficacy is also observed in advanced melanoma patients with *BRAF* mutants using *BRAF* plus MEK inhibitors. Currently phase 3 studies are comparing the efficacy of immunotherapy and targeted therapy in patients with *BRAF* mutation.

## Genetic subtypes of melanoma

Activating mutation of the serine-threonine kinase *BRAF* gene is the most frequent genetic alteration in melanomas. *BRAF* mutation is observed in about 50% of skin melanoma and in 10–20% of mucosal melanoma cases [1–4]. Mutation in *BRAF* gene activates *BRAF* protein, which increases proliferation and survival of melanoma cells [5]. Most frequently (in about 90% of cases) valine is substituted with glutamate in the 600 codon (V600E), less frequently with lysine (V600K) or arginine (V600R) [1, 2].

The second most frequent genetic alteration is *RAS* mutation, observed in 25% of melanomas. The most commonly seen is *NRAS* mutation [2, 4, 6]. Mutations in the *RAS* gene keep *RAS* protein in the active state, which activates *RAF* and subsequently *MEK* and *ERK*, leading to activation of the *MAPK* signalling pathway. *RAS* can also activate other pathways such as the *PI3K* (phosphatidylinositol-3 kinase) pathway [7]. *BRAF* and *NRAS* are mutually exclusive.

Another frequently observed aberration (14%) is the mutation in the *NF1* (neurofibroma factor 1) gene. *NF1* regulates *RAS* through GTP-ase activating protein. Due to the mutation in the *NF1* gene, *NF1* protein loses regulative properties leading to continuous activation of *RAS* [8]. The *NF1* mutation is observed in 46% of *BRAF*-mutant and *NRAS* wild-type melanoma cases [3].

The triple-wild-type melanomas do not carry any of the mentioned mutations (*BRAF*, *NRAS*, *NF1*). This subgroup is linked instead with *GNAQ* (observed frequently in uveal melanoma) or *KIT* mutations [2].

## BRAF inhibitors

Currently two BRAF inhibitors are approved in Europe and US for the treatment of patients with *BRAF*-mutant advanced melanoma – vemurafenib and dabrafenib. Encorafenib is the next highly explored BRAF inhibitor. These drugs are orally bioavailable, ATP-competitive, small-molecule inhibitors of BRAF kinase.

In a randomised phase 3 study (BRIM-3) patients receiving vemurafenib demonstrated a higher response rate compared to those treated with dacarbazine (DTIC) – 57% vs. 9%. The median progression-free survival (PFS) in the study group treated with vemurafenib was significantly longer – 6.9 vs. 1.6 months (HR 0.38;  $p < 0.0001$ ). Patients treated with vemurafenib also presented longer median overall survival (OS) compared to the control group – 13.6 vs. 9.7 months (HR 0.70;  $p = 0.0008$ ) [9, 10].

The most frequently observed adverse events (AEs) in patients treated with vemurafenib are arthralgia (56%), fatigue (46%), rash (41%), and photosensitivity (41%). The highest frequency of grade 3 and 4 toxicity is cutaneous squamous cell carcinoma (SCC) (19%), keratoacanthoma (10%), rash (9%) and elevated aminotransferases (11%) [11].

Dabrafenib was approved in advanced melanoma following the results of a randomised phase 3 study (BREAK-3) in patients with *BRAF* mutation. This trial demonstrated similar results to the BRIM-3 study. The response rate in patients treated in the dabrafenib group was higher compared to the DTIC group – 50% vs 6%. The median PFS in patients receiving dabrafenib was 6.9 months and 2.7 months in patients treated with DTIC (HR 0.37;  $p < 0.0001$ ). The median OS at the last study update was 18.2 months in the dabrafenib group and 15.6 months in the DTIC group (HR 0.76) [12, 13].

Treatment with dabrafenib was associated with hyperkeratosis (36%), rash (30%), alopecia (27%), skin papilloma (22%), palmar-plantar hyperkeratosis (19%), arthralgia (19%), fatigue (18%), and headache (18%). The most frequently observed grade 3 and 4 adverse events were cutaneous SCC (7%) and pyrexia (3%) [12, 13].

It is difficult to compare the toxicity of vemurafenib and dabrafenib. However, in patients treated with vemurafenib higher frequency of photosensitivity (dabrafenib – 2%) and SCC/keratoacanthoma was observed. In patients receiving dabrafenib pyrexia is more frequently documented.

## MEK inhibitors

MEK inhibitors are bioavailable, non-ATP competitive, allosteric binding inhibitors of MEK. Cobimetinib is a MEK1 inhibitor, while trametinib and binimetinib inhibit both MEK1 and MEK2.

In a phase 3 study trametinib demonstrated increased median PFS compared to DTIC (4.8 vs. 1.5 months, HR 0.45,  $p < 0.001$ ) in patients with advanced *BRAF*-mutant melanoma. Also the 6-month OS was higher in patients receiving trametinib (81% vs. 67%,  $p = 0.01$ ) [14].

In a phase 2 study binimetinib was evaluated in patients with advanced melanoma harbouring *BRAF* or *NRAS* mutation. The response rate was 20% in both groups with similar median PFS (3.6 months – *BRAF*-mutant, 3.7 months

– *NRAS*-mutant) [15]. Binimetinib was also evaluated in a phase 3 study (NEMO) in patients with *NRAS* mutation. The median PFS in patients treated with binimetinib was 2.8 months compared to 1.5 months in the group treated with DTIC (HR 0.62;  $p < 0.001$ ) [16]. MEK inhibitors present a different toxicity profile than BRAF inhibitors. The most frequently observed AE is rash, observed in 57% of patients. MEK inhibitors cause papulopustular rash, while BRAF inhibitors cause hyperkeratotic maculopapular rash. Other frequently observed MEK inhibitor related AEs include diarrhoea (43%) and peripheral oedema (26%). The most frequently noted grade 3 and 4 AEs are hypertension (12%), rash (8%) and fatigue (4%). Other AEs also noted included nausea, alopecia, constipation, vomiting, reduction of left ventricular ejection fraction (LVEF) and ocular toxicity (blurred vision, reversible chorioretinopathy) [17, 18].

## BRAF plus MEK inhibitors

Treatment with BRAF inhibitors is associated with acquired resistance after an earlier response. Half of the patients developed progression of the disease after approximately 6 months of treatment. It has been shown that addition of MEK inhibitor to BRAF inhibitor therapy may break the treatment resistance in preclinical studies [19].

In a randomised phase 3 study (COMBI-d) the combination of dabrafenib with trametinib showed a higher response rate compared to dabrafenib alone in patients with advanced *BRAF*-mutant melanoma – 69% vs. 53% ( $p = 0.0014$ ). The median PFS was also longer in patients receiving the combination therapy (11.0 vs. 8.8 months; HR = 0.67;  $p = 0.0004$ ). The median OS in patients treated with dabrafenib combined with trametinib was 25.1 compared to 18.7 months in patients receiving dabrafenib monotherapy (HR = 0.71;  $p = 0.0107$ ) [20]. In a longer follow-up 3-year survival in patients treated with the combination was observed in 44% of patients. [21]

Similar results were observed in another phase 3 study (COMBI-v) where dabrafenib combined with trametinib was compared with vemurafenib, showing a higher response rate in patients receiving two drugs – 64% vs. 51% ( $p < 0.001$ ). The median PFS was longer in the group treated with dabrafenib plus trametinib compared to the vemurafenib group (11.4 vs. 7.3 months; HR 0.56;  $p < 0.001$ ) [22]. At the European Society of Medical Oncology (ESMO) 2016 congress updated survival results from this study were presented. In patients receiving dabrafenib plus trametinib the median OS was 26.1 months, while in the group treated with vemurafenib it was 17.8 months (HR = 0.68), with 3-year OS in 45% and 31% of patients respectively [23]. The evaluated quality of life was significantly better in the combination group [24].

In a phase 3 study (coBRIM) the efficacy of vemurafenib combined with cobimetinib (MEK inhibitor) was compared with vemurafenib alone. Patients treated with the combination of BRAF and MEK inhibitor demonstrated a higher response rate than in the BRAF inhibitor monotherapy group – 68% vs. 45% ( $p < 0.001$ ). The median PFS was longer in patients receiving the combination – 9.9 vs. 6.2 months (HR = 0.51;  $p < 0.001$ ). The median OS in patients

treated with the combination of vemurafenib and cobimetinib was 22.3 months, while in the group receiving vemurafenib alone it was 17.4 months (HR = 0.70;  $p = 0.005$ ) [25]. At the Society for Melanoma Research (SMR) 2016 congress updated survival results from this study showed 3-year OS in 37.4% of patients treated with the combination and 31.1% receiving vemurafenib alone. These differences in survival between the COMBI-v and coBRIM study might be associated with higher frequency of patients with elevated serum LDH in the coBRIM study (46% vs. 34%) [26]. Elevated LDH is a poor prognostic factor regardless of the treatment used [21, 26–28].

In a phase 1b study (BRIM7) in 63 treatment naïve patients receiving vemurafenib combined with cobimetinib the median OS was 31.2 months, while 3- and 4-year survival was 39.2% and 35.9% respectively [26].

Another interesting molecule is encorafenib, a BRAF inhibitor with higher affinity to BRAF and extended binding time. Encorafenib was evaluated in combination with binimetinib (MEK inhibitor) in a phase 3 study and demonstrated longer median PFS (14.9 months) compared to vemurafenib alone (7.3 months) with HR of 0.54 ( $p < 0.001$ ). In the third group of patients receiving encorafenib monotherapy the median PFS was 9.6 months with HR of 0.75. However, the difference as compared to encorafenib plus binimetinib was not statistically significant ( $p = 0.051$ ) [29].

### Elevated lactate dehydrogenase

It has been shown that melanoma patients with elevated serum LDH treated with immune checkpoint inhibitors present a poor prognosis [27, 28].

In the COMBI-d study 25% of patients with elevated and 52% with normal LDH level treated with dabrafenib plus trametinib survived 3 years. The best 3-year survival time (62%) was noted in patients with normal LDH and less than 3 metastatic sites. Patients presenting elevated LDH and treated with vemurafenib in the control arm also presented a worse outcome compared to those with normal LDH. Patients with elevated LDH treated with vemurafenib and cobimetinib in the coBRIM study also had a worse prognosis (3-year survival: 22.8%) compared to patients with normal LDH (3-year survival: 47.8%) [26].

### Combination of targeted therapy with immune checkpoint inhibitors

Various preclinical studies showed increased efficacy of targeted therapy combined with immune checkpoint inhibitors as compared to monotherapy with these drugs [30]. An early phase clinical study evaluating the combination of vemurafenib with ipilimumab revealed unexpected toxicity in patients with advanced melanoma. The observed hepatotoxicity occurred within the first 2 to 5 weeks of treatment in 6 out of 10 patients and required discontinuation of the study [31]. In another study dabrafenib +/- trametinib was combined with ipilimumab, but due to increased incidence of colitis with perforation of the colon the accrual of patients was subsequently terminated [32].

The high toxicity of BRAF/MEK inhibitors combined with ipilimumab and the parallel development of antibodies targeting PD1 and PDL-1 lead to the alternative strategy of exploring the combination of anti-PD1/PD-L1 with targeted therapy.

A phase 1 study evaluating the combination of anti-PD-L1 (MEDI4736) with dabrafenib and/or trametinib in *BRAF*-mutant and *BRAF* wild-type melanoma patients was carried out. In the 26 patients with *BRAF* mutation receiving the combination of MEDI4736, dabrafenib and trametinib the response rate (RR) was 69% and the disease control rate (DCR = CR+PR+SD) was 79%. In 20 patients with *BRAF* wild-type melanoma treated with trametinib and MEDI4736 the RR was 21% and DCR was 80%. In the last *BRAF* wild-type group the 19 patients were receiving trametinib monotherapy with subsequent administration of trametinib and MEDI4736, followed by MEDI4736 monotherapy (RR = 21%; DCR = 80%). However, the treatment-related AE depended on the study group. Any grade AEs were observed in 85–100%, and grade 3 and 4 AEs were noted in 17–40% of patients [33].

At the SMR 2016 Congress results from a phase 1b study evaluating the combination of atezolizumab (anti-PD-L1) with vemurafenib and cobimetinib were presented. Only 29 *BRAF*-mutant advanced melanoma patients were evaluated. The RR was 83% (CR – 10%, PR – 72%) with stable disease (SD) observed in 10%. Only 3% of patients developed progression of the disease. The treatment benefit was, however, associated with high toxicity. All grades of treatment-related AEs were seen in all patients, while grades 3 and 4 AEs were noted in 40% of patients [34]. Currently the phase 3 study is ongoing [35]. Results of a phase 1b study in patients with *BRAF* wild-type melanoma receiving the combination of atezolizumab together with trametinib demonstrated an RR of 50%, with high toxicity. However in this cohort only 10 patients were evaluated [36]. A phase 3 study in this group of patients is planned shortly.

An interesting phase 3 study evaluating the efficacy of combination of PDR001 (anti-PD1) with dabrafenib and trametinib compared to dabrafenib and trametinib alone is starting accrual in the near future [37]. A phase 2 study evaluating the combination of pembrolizumab with dabrafenib and trametinib in patients with *BRAF*-mutant advanced melanoma is about to be completed. In another cohort *BRAF* wild-type melanoma patients are receiving pembrolizumab combined with trametinib (concurrent or intermittent dosing) [38].

### Conclusions

The combination of BRAF and MEK inhibitors shows very high activity in advanced melanoma patients with the *BRAF* mutation. Currently, there is a lack of phase 3 study results comparing the efficacy of targeted therapy and immune checkpoint inhibitors in patients harbouring the *BRAF* mutation; therefore the treatment decision for the physicians in this patient population is very difficult. The combination of targeted therapy with immune checkpoint inhibitors shows promising results in early phase

trials, but requires validation in ongoing phase 3 studies [34, 36, 39, 40]. Novel treatment strategies in preclinical melanoma studies are promising. The combination of cancer vaccines with anti-PD1 antibodies shows a synergistic effect [41]. Moreover, agents targeting cancer metabolism enhance the activity of anti-PD1 therapy. Another important discovery is that the patient gut microbiome may enhance anti-PD1 treatment. The promising early results of combinatorial treatment strategies bring hope for further progress in the management of patients with advanced melanoma. The most expected are the results of the adjuvant treatment trials of advanced melanoma patients with resected metastases both of targeted strategies and various immunotherapeutic approaches.

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