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Treatment of BRAF+ melanoma in light of current drug programs

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ABSTRACT

The past decade has seen significant advances in the understanding of molecular pathogenesis of cutaneous melanoma. Currently, mutations of *BRAF* oncogene have been a well established and powerful predictive role as validated target in recently developed molecular targeted therapy for melanoma. It has been proven in a number of studies that the effective treatment for this group of patients consists of the combination of a BRAF inhibitor and MEK inhibitor, two such combinations are currently registered and reimbursed in Poland — vemurafenib and cobimetinib, dabrafenib and trametinib. Median progression-free survival (PFS) exceeds one year for BRAF and MEK combined therapy, and overall survival (OS) reaches approximately 2 years. Currently, the first line therapeutic option for BRAF-mutated advanced melanoma include also immunotherapy with anti-PD-1 antibodies (combination of PD-1/CTLA-4 blockers can be an option in a specific group of patients, although not reimbursed in Poland).

Key words: melanoma, BRAF, BRAF inhibitor, MEK inhibitor

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Introduction

Melanoma is a cancer that in Poland has the most dynamic growth in the number of cases — in the years 1982–2012 the number of new cases increased almost three-fold. Standardised mortality rates reach approximately 2.33/100,000 in men and 1.53/100,000 in women, which corresponds to approximately 7600 and 6350 deaths, respectively, from melanoma in recent years, and the number of new cases in 2014 exceeded 1600 in women and was about 1500 in men [1–3].

It is now known that certain melanoma subtypes are associated with specific mutations. *BRAF* mutations (v-raf murine sarcoma viral oncogene homolog B1) and *NRAS* [neuroblastoma RAS viral (v-ras) oncogene homolog] occur in 40–60% and 10–20% of skin melanomas, respectively. In most cases, the occurrence of these mutations is mutually exclusive. RAS/RAF/MEK/ERK over-expression and transmitting signals to growth factor receptors has been shown to play a major role in regulating cell proliferation, tumour invasion, and survival in the cells of the majority of melanomas [4–9]. This is most often due to the presence of mutations that activate the individual components of this pathway, in more than half of melanomas — the *BRAF* gene [5, 6]. The most common *BRAF* mutation — p.V600E (74–90%) — is a point mutation of the sense-change type caused by the substitution of valine (V) by glutamic acid (E) at position 600 of exon 15 (1799) [5, 10–13]. Substitution of V600E results in a 500-fold increase in BRAF kinase activity compared to normal (wild-type) BRAF [12]. It is mainly found in non-chronic sun damage (NCSD) [7] and in younger age as well as in a high percentage of benign skin pigmentation, but not in ocular melanoma and only in 10% of melanomas occurring on mucous membranes and areas exposed to direct sunlight (CSD, chronic sun damaged).

The less frequent mutation p.V600K (16–29%) is characterised by valine substitution (V) by lysine (K) [15–17]. *BRAF* V600E results in constitutive activation of the ERK signalling pathway, resulting in stimulation of cell proliferation and tumour mass gain. *BRAF* V600E also has implications for tumour neoangiogenesis by stimulating vascular endothelial growth factor (VEGF) [18]. Without a doubt, mutant *BRAF* is important in the process of melanoma, but the presence of the same mutation *BRAF* V600E is not sufficient for the transformation of melanocytes in the direction of malignancy

[19, 20]. It is worth noting that the *BRAF* mutation is found in most benign pigmented moles (80%) [21, 22], which in rare cases undergo malignant transformation. In the development of melanoma, additional molecular disorders are necessary [22, 23]. Accurate knowledge of the role of *BRAF* mutation in the pathogenesis of melanoma had a strong impact on the development of further drug research targeted on a molecular level; the first effective molecularly targeted drug in patients with advanced melanoma with the presence of *BRAF* mutation was vemurafenib. Currently, inhibitors of BRAF are used routinely in combination with inhibitors of MEK, now these drugs are tested in the adjuvant treatment and in combination or sequentially with immunotherapy.

In patients with metastatic (primary or secondary) skin melanomas, it is mandatory to check the presence of *BRAF* mutation in fixed material [it may be also justified in cases with high risk of relapse (stage IIIB, IIIC, and IIID)]. The assessment of the mutations in *KIT* and *NRAS* genes is optional. No additional biopsies are needed to verify the presence of molecular abnormalities within the metastatic lesions [2, 24].

A breakthrough in the treatment of systemic melanoma has taken place within the last five years, which is associated both with the development of molecular targeted therapies and immunotherapy [1, 2, 24, 25]. New therapies introduced into everyday clinical practice applied in cases of unresectable/metastatic melanoma skin have little to do with clinical practice five years ago. In the last five years in Europe vemurafenib, dabrafenib, trametinib, cobimetinib, ipilimumab, nivolumab, pembrolizumab, and Talimogene Laherparepvec (T-VEC) were registered [1, 2, 24, 25]. Currently, seven new therapies are available in Poland — vemurafenib with cobimetinib, dabrafenib with trametinib, ipilimumab, pembrolizumab, and nivolumab. Unfortunately, their full reimbursement indications continue to differ from those used in Western Europe and the United States.

Currently, the basis of systemic treatment is combination therapy with molecular-targeted drugs and immunotherapy. Moreover, the latest data also provide hope for progress in the adjuvant treatment of patients at high risk of relapse.

Molecularly targeted therapy

Phase II–III studies demonstrated median survival in patients with metastatic melanoma treated with vemurafenib or dabrafenib of 13–18 months (similar in approximately 180 patients treated in our country with vemurafenib as routine clinical practice), which is significantly higher than previously observed in this group of patients [1].

Results of the coBRIM study, in which vemurafenib or vemurafenib with cobimetinib was used, confirmed that BRAF and MEK combination therapy in *BRAF*-positive metastatic melanoma patients was superior to monotherapy with no increase in toxicity: progression-free survival was 7.20 *vs.* 12.3 months (HR 95% CI: 0.58), CR (complete response) was 10.5% and 15.8%, respectively. The median overall survival (OS) was 22.3 months for the combination treatment as compared to 17.4 months for monotherapy ($p = 0.005$) [26]. Long-term results from the Phase 1b BRIM7 on the use of combination therapy with vemurafenib and cobimetinib in those treated (V-PD) or untreated (naive BRAFi) previously with vemurafenib showed median PFS in the group BRAFi-naive of 13.8 months and median OS of 31.2 months (three-year OS was 37%) [27].

Recent study results (COMBI-d and COMBI-v) showed that median overall survival (OS) with the combination of these drugs has increased to approx. 25 months (approximately two years), while three years ago the OS for metastatic patients was six months. The combined use of dabrafenib and trametinib resulted in the two-year overall survival of 51%, with the use of only a single drug being about 10% lower. The median time to progression of disease in patients treated with dabrafenib and trametinib was 11 months and was significantly higher than that for dabrafenib alone (8.8 months). Objective responses (partial and total responses) were 70% *vs.* 50%, respectively. Updated results of the COMBI-d were: the percentage of three-year OS was 44% in patients treated with dabrafenib and trametinib and 32% in the monotherapy group with dabrafenib. Three-year progression-free survival (PFS) was, respectively, 22% and 12% [28–30]. The best results were obtained in patients with normal levels of LDH and with no more than three metastatic sites. Another combination of BRAF (encorafenib, ENCO) and MEK (binimetinib, BINI) inhibitors was also evaluated in the Ib/II phase III study in patients with advanced melanoma with *BRAFV600* mutation. The percentage of confirmed responses was 72–78%. The median progression-free survival in patients with elevated lactate dehydrogenase (LDH) was 6.8 months, and in the group with normal LDH — 20 months. Tolerability of treatment was good, and similar results were obtained in Phase III study [31].

A new option for targeted treatment is to return to the combination of BRAF and MEK inhibitors after prior discontinuation due to progression. A phase II study demonstrated that in eight out of 25 patients (32%) partial remission of the disease was obtained by re-initiation of therapy with dabrafenib and trametinib, and stable disease in another 40%; median PFS on the so-called rechallenge was 4.9 months. During the 2017 ASCO congress 116 patients were analysed with

Table 1. Registered molecularly targeted drugs for the treatment of patients with advanced melanoma with the presence of *BRAF* mutations used in the context of drug programs in Poland

Name of the drug	Registration/ /Clinical trials	Efficacy	Adverse events/remarks
Vemurafenib (BRAF inhibitor) alone or in combination with cobimetinib (MEK inhibitor)	Registered in Europe and the USA in patients with a mutation in the *BRAF* gene	Median OS: 17 months (22.3 months for combined treatment) Median PFS: 5.3–7.2 months (12.3 months for combination therapy with cobimetinib); ORR — 48% Median time to obtain response: 1.4 months	Typical side effects include: arthralgia, rash, fatigue, photosensitivity, and development of squamous cell carcinoma or keratoacanthoma (skin-related adverse events are significantly less frequent when combined with cobimetinib). Quick response. Demonstrated activity in patients with brain metastases
Dabrafenib (BRAF inhibitor) in monotherapy or in combination with trametinib (MEK inhibitor)	Registered in Europe and the USA in patients with a mutation in the *BRAF* gene	Median OS: 18.2 months (25.1–25.6 months in combination with trametinib) 2-year OS (in combination treatment: 51–52%, 3-year: 44% Median PFS: 5.1–8.8 months in monotherapy (11–11.4 months in combination), 2-year PFS for combined treatment 30%, 3-year 22%. Percentage of responses: 54% in monotherapy or 64–69% in combination therapy	Typical side effects include: skin toxicity, fever, arthralgia, fatigue; reduction of skin toxicity with combination therapy (but with the occurrence of adverse events associated with MEK inhibitors). Quick response. Demonstrated activity in patients with untreated brain metastases
Trametinib (MEK inhibitor)	Registered in the USA (in combination with dabrafenib) and in Europe (monotherapy) in patients with a demonstrated mutation in the *BRAF* gene	Median PFS: 4.8 months; 6-month survival rate: 81%	Common side effects: rash, diarrhoea, peripheral oedema. Monotherapy has lower activity than BRAF inhibitors. Currently used in combination with dabrafenib. Activity in melanoma patients with the presence of NRAS mutations has also been demonstrated

OS — overall survival; PFS — progression-free survival; ORR — objective response rate

advanced melanoma, who were treated with a BRAF inhibitor and after the break in the therapy (due to progression) again received treatment with BRAF +/– MEK inhibitor. The median duration of treatment with BRAFi +/– MEKi inhibitor the first time was 9.4 months and then 7.7 months upon return to targeted molecular therapy. On return to treatment with BRAFi +/– MEKi, the response rate was 43%: total response (CR) 3%, partial response (PR) 39%, disease stabilisation 24%, disease progression (PD) 30%, and 4% no data. The median overall survival from onset of re-treatment was 9.8 months [32, 33].

A summary of the results of use of molecular targeted therapy in patients with advanced melanoma with the presence of *BRAF* mutations is shown in Table 1.

Preliminary results of the analysis of the Polish drug programs in the treatment of advanced melanoma with the presence of *BRAF* mutation using vemurafenib with cobimetinib or dabrafenib with trametinib presented at the Warsaw Skin Cancer Conference in 2017 showed an annual survival rate of 70%, which is comparable to the results obtained from clinical trials. There was no difference in OS between the combination of vemurafenib and cobimetinib and dabrafenib with trametinib [34].

Use of molecularly targeted therapy BRAF inhibitors of MEK and as adjuvant treatment after resection of lymph nodes improves disease-free survival and overall survival, but their definitive place in an adjuvant setting involves assessment of the full results of the clinical trials [35].

Immunotherapy

Non-specific immunotherapy (mainly with anti-CTLA4 monoclonal antibodies — ipilimumab and anti-PD-1 — nivolumab and pembrolizumab) also led to a significant improvement in the treatment of patients

Table 2. Comparison of treatment with BRAF +/– MEK inhibitors and immunotherapy with checkpoint inhibitors

Feature	Targeted treatment	Immunotherapy with anti-PD-1
Dosage schedule	Continuous daily orally	IV every 2–3 weeks
Safety (AE)	Grade 3/4 events in 35–52% of patients receiving BRAF + MEK inhibitor Dose reduction in about 1/4 of patients and cessation of therapy due to intolerance in 9–13%	Grade 3/4 AE incidence in 8–16% and discontinuation of therapy due to AE in 2–9%
Objective responses	ORR 64–67%	ORR in about 40% with anti-PD-1; ORR 43–62% with the anti-PD-1/anti-CTLA-4 combination (38–52% with *BRAF*+)
Survival	Median OS 25 months and a 2-year OS of 51%; unknown durability of response (especially after discontinuation of therapy)	Median OS 17–31 months; 2-year OS 57–60%; long-lasting responses; persistence of response after discontinuation of therapy; 2-year OS for anti-PD-1/anti-CTLA-4 64–79%

with metastatic melanoma. There are no definitive data on the sequence of the use of immunotherapy and molecular-targeted treatment in patients with *BRAF*-positive melanomas, although the activity of BRAF inhibitors is preserved after immunotherapy, as is the efficacy of immunotherapy (anti-PD-1) after treatment with inhibitors.

At the moment, the weight of the treatment of advanced melanoma using immunotherapy has moved towards the treatment of anti-PD-1 (nivolumab or pembrolizumab) acting on the control points of the immune system (as receptor PD-1 and its ligand PD-L1) and stimulating T-lymphocyte function mainly by blocking negative signalling molecules for their activation, or by implementing combination therapy with anti-CTLA-4 and anti-PD-1 antibodies (taking into account the greater toxicity and cost of this drug combination). These drugs have demonstrated in a clinical setting, either in monotherapy or in combination with ipilimumab, long-term clinical benefit in some patients with advanced melanomas and significant response rates (up to 50%), with annual survival of 70–80% and less toxicity than ipilimumab [36–38].

Summary

In the case of *BRAF* mutation in a patient with metastatic melanoma, the molecularly targeted therapy of choice is the combination of MEK inhibitor and BRAF in the first — or second-line therapy, or immunotherapy (Tab. 2, Fig. 1).

In summary, anti-PD-1 antibodies and combined treatment with BRAF and MEK inhibitors are endorsed both by Polish, European (ESMO), and American (NCCN) recommendations as a standard therapeutic option with proven efficacy in the treatment of advanced melanomas [1, 2, 24, 25]. For both pembrolizumab/nivolumab and combination therapy of the BRAF and MEK inhibitor, in the group of patients with metastatic melanoma with the presence of the *BRAF* mutation, the median OS from clinical trials is currently about two years (about four times longer than five years ago). It is not definitively known whether to start treatment in this group with immunotherapy or molecular-targeted drugs, hence the need to leave the decision for the treatment team. As part of existing drug programs in Poland, there is now the possibility of choosing the first line of therapy in patients with *BRAF* mutation — treatment for immunotherapy or treatment with BRAF + MEK inhibitors may be started and alternative therapy may be used if possible progression. Because BRAF inhibitors (+ MEK inhibitors) in patients with advanced *BRAF* mutations cause rapid response and tumour control in the majority of patients, with limited response time associated with the activation of resistance mechanisms, these drugs should always be considered as the choice of treatment in patients with symptoms of the disease and/or high tumour mass.

Figure 1 shows the current therapeutic regimen for patients with advanced melanoma with the presence of *BRAF* mutation.

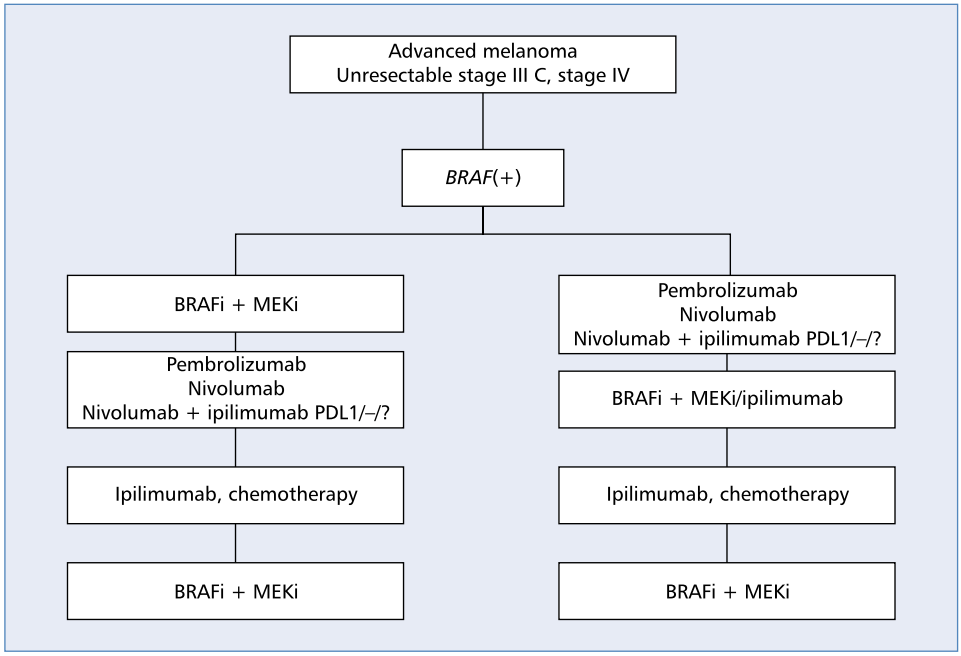

Figure 1. Scheme of therapeutic treatment in patients with advanced melanoma with *BRAF* mutation

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