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Commentary to

Targeted therapy for advanced cutaneous melanoma

The review article "Targeted therapy for advanced cutaneous melanoma" prepared by an expert team from Italy presents in detail current possibilities of therapy for patients with advanced melanoma with the use of molecular targeted agents. During the last decade, the unprecedented development in melanoma treatment is mainly related to the introduction of two different therapeutic strategies: nonspecific immunotherapy using monoclonal antibodies anti-CTLA4 or anti-PD1 (immune checkpoint inhibitors) and targeted therapy with serine-threonine kinases inhibitors. These advances in targeted therapy are related mainly to blockade of the signal pathway of mitogen-activated protein kinases (MAPK), which is overactivated due to mutation in the *BRAF* gene in approximately 50% of melanoma patients [1]. The use of BRAF inhibitor in *BRAF*-mutated melanoma patients allowed for objective responses in about half of patients, which was related to improvement in progression-free survival and overall survival. Further development of targeted therapies led to the introduction of the second inhibitor of the MAPK pathway — MEK inhibitor. This dual blockade was more effective in maintaining a similar safety profile. The development of immunotherapy, especially implementation in clinical practice a combination of nivolumab and ipilimumab, resulted in a scenario in which BRAF/MEK inhibitors are usually used after immunotherapy failure [2]. It is associated with the mechanism of action of immunotherapy enabling, in many patients, long-term disease remissions. Nowadays, research focuses on combined therapies, i.e. combination of kinase inhibitors with immunotherapy and sequential therapy for optimal management of patients with *BRAF*-mutated advanced melanoma because therapy with BRAF inhibitors in monotherapy or in combination with MEK inhibitors increases expression of cancer antigens, lymphocyte T CD8+ infiltrates, and PD-L-1 expression [3].

The results of recent studies (COMBI-d, COMBI-v, coBRIM, and COLUMBUS) showed that in patients with metastatic melanomas with *BRAF* mutation, the use of a combination of BRAF and MEK inhibitors (dabrafenib and trametinib or vemurafenib with cobimetinib or encorafenib with binimetinib) yields better results than monotherapy with no increase in toxicity [4–6]. The median overall survival time on the combination of both drugs was improved to about 23–33 months and a median progression-free survival to 12–14 months. Better survival is achieved in patients with normal LDH activity and serum concentration and less than three organs involved in metastases. All these two combinations are currently accessible in Poland in the Drug Program B.59 in any line of therapy in patients with advanced melanoma with confirmed presence of $BRAF^{V600}$ mutation, change of one combination into another in case of intolerance, and reintroduction of therapy with kinase inhibitors in subsequent lines of therapy. The above-mentioned drugs have a beneficial influence also in patients with stable and/or asymptomatic metastases to the brain.

A new option of the molecularly targeted therapy is to rechallenge the combined therapy with BRAF and MEK inhibitors after this therapy has been stopped due to disease progression. A phase-II study revealed that restarting therapy with dabrafenib and trametinib resulted in partial remission in eight of 25 patients (32%) and stabilization of the disease in another 40% of patients. The median disease progression-free time after

Received: 25.02.2022 Accepted: 25.02.2022 Early publication date: 03.03.2022

Oncology in Clinical Practice, DOI: 10.5603/OCP.2022.0010, Copyright © 2022 Via Medica, ISSN 2450–1654, e-ISSN 2450–6478

reintroduction reached 4.9 months [7]. The similar are results of analysis of data of 116 patients with advanced melanoma, who had received therapy with BRAF inhibitor, progressed, and received another therapeutic modality, and then were restarted on combined therapy with BRAF ± MEK inhibitor. The median time of treatment duration was 9.4 and 7.7 months for the primary and reused molecularly targeted therapy, respectively. After restarting the use of BRAF ± MEK inhibitors the response rate was 43%: complete response rate 3%, partial response rate 39%, stabilization of the disease 24%, and progression of the disease 30% (no data 4%). The median overall survival time from the restart of the therapy reached 9.8 months [8, 9].

There is no final data on the optimal sequence of immunotherapy and targeted therapy in patients with *BRAF* mutation. The activity of BRAF inhibitor is maintained after immunotherapy and of immunotherapy (anti-PD-L1) after treatment with BRAF inhibitors BRAF inhibitors [10]. The results of SECOMBIT and DREAMseq trials indicate that the combination of nivolumab and ipilimumab gives the best outcomes if used as the first-line option in patients with advanced *BRAF*-positive melanoma. There is no definitive data on what the preferred therapy is in the case of inoperable or metastatic relapse after previous adjuvant therapy [11]. It is important to mention, that BRAF + MEK inhibitors are a valuable option in adjuvant therapy in stage-III melanoma [12]. BRAF + MEK inhibitors give fast responses in *BRAF*-mutated advanced melanomas and disease control with a limited duration of responses, which is related to the activation of resistance mechanisms. Due to these characteristics therapy should be considered as a treatment of choice in patients with symptomatic disease and/or high tumor mass, but, in the majority of cases, the treatment of choice is immunotherapy (preferably a combination of anti-PD-1 and anti-CTLA-4) [13, 14].

Conflict of interest

P. Rutkowski has received honoraria for lectures and Advisory Boards from Novartis, MSD, BMS, Roche, Pierre Fabre, Pfizer, Sanofi, Merck, Blueprint Medicines, Philogen.

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