Editorial Commentary

Is AJCC 8th Edition useful in qualifying melanoma patients to adjuvant therapy?

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The treatment landscape in patients with melanoma after radical resection of metastases has changed dramatically with the approval of anti-PD1 (nivolumab, pembrolizumab) and BRAF (dabrafenib) plus MEK (trametinib) inhibitors. These drugs were evaluated in phase 3 studies showing longer recurrence-free survival (RFS) comparing to the control arm, where patients received placebo (1,2). Only in the study testing nivolumab patients in the control arm were treated with active drug, ipilimumab (3). To date the overall survival (OS) data are only available from the dabrafenib plus trametinib trial, showing advantage over placebo (2). The approval prescriptions are very broad and there are few things to keep in mind while qualifying patients to these adjuvant therapies. All these drugs are approved in stage III melanoma (dabrafenib plus trametinib only in *BRAF*-mutant melanoma) and nivolumab additionally in patients after resection of stage IV melanoma. Moreover, the study evaluating pembrolizumab and dabrefenib plus trametinib included patients with stage IIIA-IIIC, while nivolumab trial patients with stage IIIB and IIIC. In these studies patients with micrometastases <1 mm were excluded. The KEYNOTE-054 trial evaluating pembrolizumab did not enroll patients with in transit metastases, while CheckMate 238 (nivolumab) and COMBI-AD (dabrafenib plus trametinib) did, however results from these cohorts were not presented separately. In all those phase 3 studies patients were enrolled based on AJCC (American Joint Committee on Cancer) 7th Edition staging system (1-3).

In the paper published by Eggermont AMM *et al.* the authors reported the outcome in patients treated with pembrolizumab in the KEYNOTE-54 trial according to the AJCC 8th Edition in comparison to the AJCC 7th Edition staging system (4). Many people were critical of the new AJCC staging system incorporating changes regarding stage III, which can create significant confusion in clinical practice. The concerns also related the lack of comparison possibility between present and future adjuvant trials results using AJCC 7th and AJCC 8th Edition (5). Nevertheless, the new AJCC staging system brought important improvement in the assessment of patients prognosis which may help in clinical decisions. The authors showed that with a 1.25-year median follow-up, the AJCC 7th and AJCC 8th Edition staging system had a strong prognostic value in terms of RFS. The benefit of pembrolizumab comparing to placebo was seen across all stage III subgroups according to AJCC 7th and 8th Edition, showing strong prognostic, but not predictive value for RFS. The analysis showed that in patients with stage IIIA according to AJCC 8th Edition, the 1-year RFS in the pembrolizumab and placebo group is 92.7% and 92.5%, respectively. While 1.5-year RFS in the pembrolizumab and placebo group is 92.7% and 84.8%, respectively with a HR (hazard ratio) 0.76. The estimated HR in stage IIIA indicated lesser benefit from pembrolizumab than patients with higher disease stage

(IIIB, HR 0.59; IIIC, HR 0.48; IIID, HR 0.69). However, these observations need confirmation in a longer follow-up. In conclusion, by using the new AJCC 8th Edition staging system the results of KEYNOTE-54 trial are not changed showing benefit from pembrolizumab across all stage III patients. However, at this moment it is important to note, that in patients not receiving new adjuvant systemic treatments, presenting stage IIIA per AJCC 7th Edition include a higher risk group than patients with stage IIIA per AJCC 8th Edition. The new staging system included Breslow thickness into stage III disease—the 5-year melanoma specific survival according to earlier staging system is 78%, AJCC 8th Edition is 93% (6). These patients with stage IIIA according to AJCC 8th Edition present low risk of recurrence and the toxicity of adjuvant therapy may overweigh the benefit and should be discussed with the patient. Results of the Eggermont AMM *et al.* also might be helpful when comparing the drug efficacy in future adjuvant trials using AJCC-8 staging system.

When discussing the introduction of new AJCC 8th Edition and its utility in clinical practice it is worth emphasizing that in the study evaluating nivolumab, only patients with stage IIIB and IIIC were eligible (stage IIIA where excluded) according to AJCC 7th Edition. Some cases that are stage IIIB/IIIC per the AJCC 7th Edition are reclassified as stage IIIA per the AJCC 8th Edition, and vice versa. These issues have to be included when qualifying patients to adjuvant therapy. The knowledge on recurrence probability is crucial to balance between the risks and potential benefits of given adjuvant treatment.

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Footnote

Conflicts of Interest: JM—advisory board Bristol-Myers Squibb, MSD; speakers' bureau – Bristol-Myers Squibb, GlaxoSmithKline, Roche, MSD, Novartis, Pierre Fabre; travel reimbursement: Bristol-Myers Squibb, GlaxoSmithKline, Roche, MSD, Novartis, Pierre Fabre. AM—is a shareholder of BioContract Sp. z o.o. (contract vaccine manufacturing company); speakers' bureau – Bristol-Myers Squibb; Roche; travel reimbursements: Roche, Bristol-Myers Squibb.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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