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ASO PERSPECTIVES

Adjuvant Systemic Therapy for High-Risk Melanoma

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Even after complete resection of their locoregional disease, many patients with melanoma are at risk for relapse and death. Recent advances in systemic adjuvant therapies have demonstrated clear benefit for patients with high-risk locoregional melanoma or resectable metastatic melanoma. Several randomized clinical trials have shown that patients with resected stage III melanoma treated with BRAF/MEK inhibition or immune checkpoint blockade benefit from approximately 50% reduction in the risk of recurrence, defining the current standard of care (COMBI-AD,[1,2] CheckMate 238,[3,4] and EORTC1325/KEYNOTE-054[5,6]).

The challenge of adjuvant therapy is in determining what is an acceptable risk–benefit ratio for an individual patient. The recently published CheckMate 915 evaluated combination adjuvant nivolumab plus ipilimumab versus nivolumab alone in patients with resected stage IIIB–D or IV melanoma. In this randomized phase III trial of over 1800 patients, administration of nivolumab 240 mg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks was compared with nivolumab 480 mg every 4 weeks alone. The dosing of each drug was designed to optimize benefit and risk profiles based on prior studies.[7] RFS in the two groups was equivalent [hazard ratio (HR) 0.92], while the ipi/nivo group demonstrated significantly increased frequency of adverse outcomes. This greater toxicity of the combination is consistent with previously published reports. Biomarker analysis did not identify any marker that would allow individuals to be substratified into a population predicted to gain additional benefit from either treatment paradigm. Thus, BRAF/MEK inhibition or single-agent PD1 remains the standard of care for adjuvant treatment in patients with stage IIIB–D and stage IV resectable melanoma.

Sentinel lymph node biopsy (SLNB) has emerged as a key tool in melanoma risk stratification. Randomized trials defined the role of regional nodal surgery in the care of patients with stage I–III melanoma: MSLT-I demonstrated that the addition of SLNB to wide local excision of primary melanoma did not improve MSS, while DeCOG-SLT and MSLT-II demonstrated that routine completion lymph node dissection in the setting of a positive SLNB did not improve MSS or overall survival.[8–11] SLNB did, however, predict recurrence-free survival. This led to the shift in the clinical use of SLNB primarily as a prognostic tool, with the added potential benefit of providing locoregional disease control.

The inclusion of sentinel lymph node biopsy (SLNB) data allowed the AJCC 8th edition of Melanoma Staging to better stratify the melanoma specific survival (MSS) of patients with stage I–III melanoma.[12] Under these criteria, patients with T stage > T2b and any evidence of regional metastases, four or more positive nodes detected via sentinel lymph node biopsy, clinically detected nodal metastases, or in-transit, satellite, or microsatellite disease fall into stage IIIB–D, with 10-year MSS ranging from 77% (stage IIIB) to 24% (stage IIID). However, the data from which these AJCC stage groups were derived largely reflect a time period before effective adjuvant treatment with immune checkpoint inhibitors and targeted therapies became standard of care for resected stage III melanoma patients. KEYNOTE-716 then demonstrated that even patients with high-risk resected stage II melanoma (IIB and IIC, high-risk primaries without evidence of lymph node metastases) could benefit from adjuvant pembrolizumab with significant improvement in recurrence- and distant metastasis-free survival.[13,14] These data suggest that many

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patients with high-risk primary tumors without evidence of metastatic disease (locoregional or distant) likely have systemic disease at the time of presentation.

With these expanded data supporting the use of adjuvant systemic therapies in stage IIB and higher melanoma, determining whether an individual patient should accept the nonnegligible risks of upfront adjuvant treatment remains the art and science of melanoma oncology. Detailed prognostic information should inform the decision made on a case-by-case basis. As demonstrated in CheckMate 915, even single-agent anti-PD1 adjuvant therapy carries a grade 3–4 adverse event rate of over 10%. For some patients, careful surveillance instead of adjuvant therapy—with salvage surgery or systemic therapy as needed—likely results in equivalent MSS outcomes as adjuvant therapy, with the added benefit of reserving the risks of treatment for those patients with demonstrated disease recurrence. Until we are able to reliably identify which patients will recur, the decision to treat with adjuvant systemic therapies should continue to rest on a careful consideration of the benefit it might provide in the context of an individual's ability to tolerate the possible adverse effects. And until we can use molecular tests for accurate risk stratification, we should continue to utilize SLNB for accurate staging. This relatively low-risk procedure provides patients, in combination with their primary tumor characteristics, our current best assessment of their risk for recurrence and death from melanoma.

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