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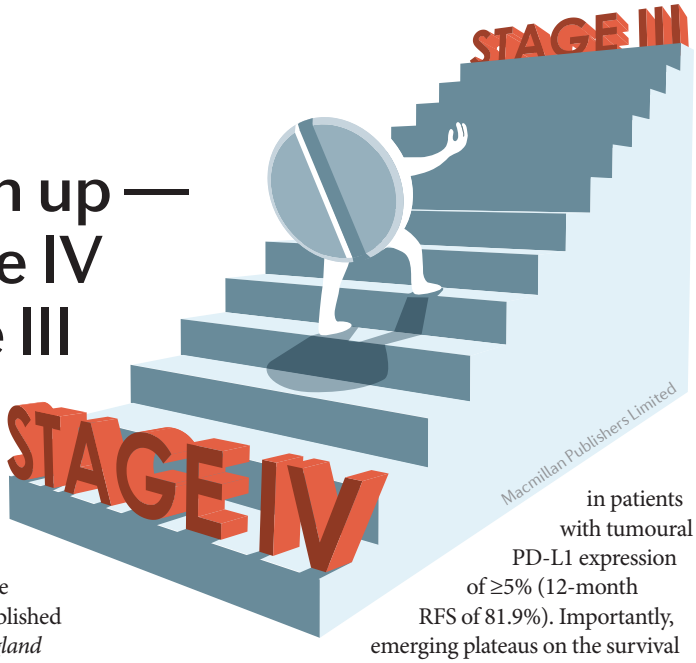
DRUG THERAPY

Moving on up — from stage IV into stage III



Effective and well-tolerated adjuvant therapies are a major unmet need for patients with various high-risk stage III cancers. Three practice-changing studies reported for the first time at the ESMO 2017 Congress, and published simultaneously in the *New England Journal of Medicine*, focused on moving therapies that are effective for unresectable metastatic disease into the 'adjuvant' setting, after curative-intent treatment.

Only ~40% of patients with resectable stage III–IV melanoma are cured by surgery alone; the cure rate might be increased with adjuvant therapy. In 2015, adjuvant immunotherapy with the anti-CTLA-4 antibody ipilimumab was approved by the FDA based on improved relapse-free survival (RFS) outcomes compared with placebo; however, observation remains the standard of care after resection of melanoma at many centres, owing to the high risk of adverse events associated with ipilimumab. Nivolumab, an anti-PD-1 antibody, has a favourable safety profile and good efficacy in patients with unresectable metastatic melanoma, supporting testing of this agent in the adjuvant setting.

In the CheckMate 238 trial, 906 patients with stage IIIB/C or IV melanoma were randomly assigned to receive adjuvant nivolumab or ipilimumab. The 12-month and 18-month RFS with nivolumab was 70.5% and 66.4%, respectively, versus 60.8% and 52.7% with ipilimumab, whereas the rate of grade 3 or 4 adverse events was 14.4% versus 45.9%. The activity of nivolumab was particularly promising in patients with tumoural PD-L1 expression of ≥5% (12-month RFS of 81.9%). Importantly, emerging plateaus on the survival curves raise hopes that nivolumab will improve cure rates.

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"This represents the first report of an effective adjuvant therapy for patients with high-risk melanoma compared with an active control arm, in which the therapy was actually well tolerated," states lead author Jeffrey Weber. "For patients with resected stage III–IV, *BRAF*-wild-type melanoma, nivolumab is a new treatment option that, if approved by FDA, will become widely used," he concludes.

In addition to nivolumab, patients with *BRAF*-mutated melanoma have a promising alternative adjuvant treatment option: combined BRAF and MEK inhibition (which also has excellent activity in patients with unresectable disease). COMBI-AD is the first trial of BRAF and MEK inhibition (with dabrafenib and trametinib, respectively) in patients with resected, stage IIIA–IIIC, $BRAF^{V600E/K}$-mutant melanoma (n = 870). After a median follow-up duration of 2.8 years, the estimated 3-year RFS was 58% with dabrafenib plus trametinib versus 39% with placebo, a risk reduction of 53%; the combination also improved distant-metastasis-free survival and overall survival (risk reductions of 49% and 43%, respectively).

Alexander Menzies, who was involved in COMBI-AD, comments on the implications of this trial: "these are amazing results, superior to those of most other adjuvant treatments for cancer, and will change clinical practice for patients with stage III melanoma." He opines that "dabrafenib plus trametinib should now be seen as standard care for those with $BRAF^{V600E/K}$-mutant melanoma — no longer can we consider interferon, ipilimumab, or observation appropriate."

Finally, results from the PACIFIC trial demonstrate that progress is also being made in improving patient outcomes after definitive therapy for stage III non-small-cell lung cancer (NSCLC). PACIFIC investigator Scott Antonia explains: "unresectable stage III NSCLC is usually treated with combined radiation and chemotherapy, resulting in cure for only ~15% of patients. In our study, patients were given anti-PD-L1 therapy with durvalumab after receiving chemoradiotherapy (n = 473), and this consolidation treatment resulted in a statistically and medically important increase in progression-free survival (PFS), compared with the placebo group (n = 236)." The median PFS was 16.8 months versus 5.6 months, and a possible plateau on the PFS curve at >40%, compared with ~20% with placebo, is intriguing. Antonia stresses, however, that the study remains blinded for overall survival, the most important outcome measure. Nevertheless, durvalumab was well tolerated, and Antonia concludes that "regulatory agencies and organizations that produce treatment guidelines will now consider recommending this treatment as a standard of care."

David Killock

ORIGINAL ARTICLES Weber, J. *et al.* Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1709030 (2017) | Long, G. V. *et al.* Adjuvant dabrafenib plus trametinib in stage III *BRAF*-mutated melanoma. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1708539 (2017) | Antonia, S. J. *et al.* Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1709937 (2017)