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IMMUNOTHERAPY

More gain, less pain

Head and neck cancer can evade the immune system by a number of mechanisms, including expression of PD-L1 and PD-L2. Positive data from phase I trials demonstrating responses to anti-PD-1 therapy of patients with a range of solid tumours triggered interest in investigating the anti-PD-1 agent nivolumab in patients with head and neck cancer. Maura Gillison, lead author of CheckMate 141, the open-label randomized phase III trial of nivolumab in patients with squamous-cell carcinoma of the head and neck (SCCHN), elaborates: "I have long been intrigued by the common presence of high-titre serum antibodies to HPV E6 and E7 proteins present among patients with HPV-positive head and neck cancer, which indicates immune tolerance." Viral-associated cancers provide unique tumour-specific antigens, which make them suitable candidates for immunotherapeutic approaches. Gillison and co-authors reported impressive results at ESMO 2016 and in the *New England Journal of Medicine*.

In CheckMate 141, 361 patients with recurrent SCCHN, with disease progression within 6 months following platinum chemotherapy, were randomly assigned in a 2:1 ratio to receive nivolumab or single-agent standard therapy consisting of either methotrexate, docetaxel or cetuximab. The response rate for nivolumab was 13.3% compared with 5.8% for standard therapy. Of note, complete responses were observed, and 1-year survival rates were nearly doubled with nivolumab compared with standard therapy (36.0% versus 16.6%). "This is the first drug to improve survival of patients with platinum-refractory head and neck cancer, and fulfils a tremendous unmet clinical need," explains Gillison.

Treatment-related adverse events of grade 3 or 4 occurred in 13.1% of patients treated with nivolumab, considerably less than the 35.1% of those who received standard therapy. Importantly, pain, physical, role, and social functioning, and quality of life were maintained or improved with immunotherapy, but worsened for patients receiving standard therapy. "Nivolumab achieved the clinical equivalent of a 'trifecta' showing not only prolonged survival, but reduced toxicity, and stabilization of quality of life," Gillison opines.

It is hoped that with a longer follow-up duration, survival will be maintained, indicating sustained clinical benefit for some patients; however, many patients on the trial experienced rapid disease progression and died. Therefore, predictive biomarkers of clinical benefit and therapeutic resistance are urgently needed to help guide selection of combination immunotherapy approaches to further improve upon these promising results.

Clinical trials in the first-line setting are ongoing. As Gillison summarizes, "these ongoing studies are sufficiently large to facilitate further investigation into potential predictive biomarkers of clinical benefit. Several clinical trials of immunotherapy combinations built on a platform of anti-PD-1 therapy in patients with platinum-refractory head and neck cancer are providing intriguing signals. Most importantly, we are rapidly moving these drug classes into the frontline treatment of locoregionally advanced head and neck cancer, with a goal of curing more patients."

Lisa Hutchinson

ORIGINAL ARTICLE Ferris, R. I. *et al.* Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1602252 (2016)