IMMUNOTHERAPY

Reality check for nivolumab in advanced-stage melanoma

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Nivolumab, a monoclonal antibody targeting PD-1, is an immunotherapeutic agent commonly used as a systemic therapy for patients with advanced-stage melanoma. The importance of a well-planned treatment regimen to the outcomes of patients receiving this agent has been highlighted in two new studies.

In the randomized, open-label, phase III CheckMate 037 trial, patients with advanced-stage melanoma with disease progression after receiving treatment with the anti-CTLA-4 antibody ipilimumab were randomly assigned to receive either nivolumab ($n = 272$) or investigator's choice of chemotherapy (ICC; dacarbazine or carboplatin plus paclitaxel; $n = 133$). Importantly, 99% of patients in the nivolumab arm started treatment, compared with 77% in the ICC arm. James Larkin, the lead investigator of this study, comments “we cannot do much about the dropout rate in an open-label trial. Among the patients treated in our centre [Royal Marsden Hospital, London, UK] there was a lot of excitement about participating in a trial of immunotherapy; those who found out they would receive chemotherapy were less likely to complete the treatment”.

In comparison with patients receiving ICC, patients in the nivolumab group had a greater overall response rate (27% versus 10%), and a longer median duration of response (32 months versus 13 months). No significant differences in overall survival (16 months versus 14 months) or median progression-free survival (PFS; 3.1 months versus 3.7 months) were observed. The disparity in dropout rates, together with different baseline levels of poor prognosis markers (favouring patients in the ICC group), and a high likelihood of crossover to other treatments outside the trial, might have contributed to these survival outcomes. Nevertheless, Larkin comments “we recruited a good number of patients for this study. Our results illustrate

the difficulties associated with unblinded trials”.

Patients receiving anticancer immunotherapies can have, as Georgina Long explains, “different patterns of tumour response, such as lesion growth or appearance of new lesions before they experience response”. Long and colleagues conducted a retrospective analysis, the largest of its kind, of the clinical features associated with nivolumab beyond disease progression in patients with advanced-stage melanoma treated in the CheckMate 066 and 067 studies.

A total of 519 patients received nivolumab in both studies: 306 (58%) experienced disease progression. Nivolumab treatment was prolonged for 85 patients (treatment beyond progression (TBP) group), but not for 221 patients in the non-TBP group. At the time of analysis, the median overall survival duration had not been reached for patients in the TBP group, and was 10.6 months for those in the non-TBP group.

In addition, Long describes, “nearly a third of patients in the TBP group (who were deriving clinical benefit, in the opinion of the treating clinician) had a response (a target lesion reduction >30%) after the documented first progression. Furthermore, among all patients treated beyond progression, an association was observed between better prognostic features at baseline and a >30% reduction after progression”. The next steps, Long concludes, would be to “examine biomarkers that help us select patients who, in fact, might respond to therapy after disease progression”.

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ORIGINAL ARTICLES Larkin, J. et al. Overall survival in patients with advanced melanoma who received nivolumab versus investigator's choice chemotherapy in CheckMate 037: a randomized, controlled, open-label phase III trial. *J. Clin. Oncol.* <https://doi.org/10.1200/JCO.2016.71.8023> (2017) | Long, G. V. et al. Nivolumab for patients with advanced melanoma treated beyond progression: analysis of 2 phase 3 clinical trials. *JAMA Oncol.* <http://dx.doi.org/10.1001/jamaoncol.2017.1588> (2017)