

Long term survival with anti-PD-1 based immunotherapy, but how is it best given?

Checkpoint inhibitor immunotherapy has transformed the treatment of melanoma, and most likely cures some patients with metastatic disease (1). We still have much to learn about how best to use these drugs and how to mitigate their side effects. The optimal combination regimens, treatment duration, patient selection and the point in the disease at which immunotherapy can be deployed to best effect remain open questions.

The report by Hodi and colleagues, in *The Lancet Oncology* (2), of updated results from the Checkmate 067 study amply demonstrates why the Nobel committee recognised Drs James Allison and Tasuku Honjo's work opening up the field of immune checkpoint inhibition for cancer therapy (3). Half the patients assigned nivolumab were alive 4 years later in a disease setting where ten years ago median survival extended to only a few months (4).

It appears that the combination of nivolumab and ipilimumab offers better survival than nivolumab alone: median survival has not yet been reached for the former (95% CI 38.2-not reached) and stands at 36.9 months (95% CI 28.3-not reached) for the anti-PD-1 agent alone. However the study design excluded formal comparison of these two arms, a significant error that is compounded by the absence of potentially corroborative studies of any size. Neither can it be argued that this is only appreciable with the benefit of hindsight, as the relative outcomes of the two nivolumab-containing arms has exercised the community from the study's conception. All comparisons between these two treatment regimens must therefore be qualified, and sub-group analyses even more so. That being said the data across the trial are very consistent and the continued separation of survival curves provides a strong case for the superiority of doublet therapy.

The issue facing patients in choosing treatment is therefore one of tolerability. Three times as many patients discontinued combination therapy due to drug toxicity as stopped nivolumab (134 vs 44). It is therefore very reassuring that the authors report, in their *post hoc* analysis, equivalent outcomes for patients who stopped combination therapy early due to an adverse event. No data are provided on patient experience once treatment has been stopped for toxicity, other than the observation that most grade 3 or 4 select adverse events resolved within 6 weeks. This lack and the absence of information on quality of life make it difficult to assess the value of the greater time off treatment for patients assigned ipilimumab and nivolumab. Whilst the ideal is for patients to be free from melanoma progression and off treatment this is less valuable if symptoms are prevalent, be they from the cancer or as a result of immunotherapy. The authors' analysis is heavily biased, in that absent a somatic mutation in *BRAF*, patients assigned combination therapy lacked further lines of treatment on stopping their regimen whereas those on only one agent had the other immediately available. A more informative comparison might therefore have been to consider total time off treatment in the three study arms, recognising that time off treatment after switching between ipilimumab and nivolumab is as valuable as that obtained after only one line of treatment. It is also important to take into account the time spent managing toxicities arising from immunotherapy, which can often be more demanding for patients than being on immunotherapy itself.

Tolerability and late side effects will assume even greater importance as checkpoint inhibitors start being used as adjuvant treatment. Nivolumab, pembrolizumab and ipilimumab have all been reported to improve survival in high risk resected melanoma (5, 6, 7) and the Checkmate 915 trial comparing the Ipilimumab/Nivolumab combination with Nivolumab in this setting has completed accrual. Here, more emphasis may be placed on toxicity when weighing this against efficacy, especially whilst we lack the biomarkers to select patients for more intensive approaches and whilst the ability to salvage patients at the time of relapse is unknown.

For now Hodi and colleagues have provided further evidence that the combination of ipilimumab and nivolumab offers better outcomes than either agent alone for patients with metastatic disease fit enough to undergo treatment. No other criterion for choosing between combination therapy and single agent nivolumab has emerged, consistent with the lack of a formal comparison of these arms in the Checkmate 067 study.

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