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TO THE EDITOR:

The CheckMate 067 trial in the article by Wolchok et al,[1] with three different frontline strategies in patients with untreated unresectable stage III or stage IV melanoma (ipilimumab in combination with nivolumab, nivolumab, and ipilimumab), recently reported the longest median overall survival (OS) in a phase III trial of 72.1 months in the combination arm of the trial.[1]

We believe, however, that the preferred first-line immunotherapy strategy remains unknown. The combination arm has a detrimental toxicity profile, as compared with anti–programmed death-1 monotherapy, and its superiority remains formally unproven.

This study uses treatment-free interval to claim superiority of the combination. With 6.5-year follow-up, the median treatment-free interval was 27.6 months (0.0-83.0) in the combination arm versus 2.3 months (0.2-81.6) with nivolumab and 1.9 months (0.1-81.9) with ipilimumab. Such differences seem to favor the combination arm.

However, being free from treatment does not equal more efficacy. If the treatment was stopped early because of toxicity, this interval can be at least partly explained by the early withdrawal, with a prolonged efficacy. In this trial, treatment-related adverse events led to discontinuation in 42% of patients in the combination arm, 14% in the nivolumab group, and 15% with ipilimumab.[1,2] The median duration of treatment with the combination treatment was shorter (3.6 months [0-80.1]) than with nivolumab (8.6 months [0-79.8]): this may have account partly in differences in treatment-free intervals.

Being without treatment is also not synonymous with better quality of life (QoL) than being under treatment if these periods are plagued with late toxic effects. Grade 3 or 4 toxicities rates are higher in the combination arm (59%) than nivolumab monotherapy (24%) and ipilimumab (28%). These toxicities often require immunosuppressive agents and may lead to long-lasting impairment.[3] QoL may have been worse in the combination arm: no imputation data analysis was conducted for missing QoL forms, which were more common in the combination arm.[4]

Medians may exaggerate differences when one curve plateaus just above the median and one just below. The median OS in the combination arm and in the nivolumab arm was 72.1 months versus 36.9 months, respectively, with a reported hazard ratio of 0.84 (0.67-1.04), with no statistical difference reported for descriptive analysis only. Indeed, the trial was not designed to compare the combination arm and the nivolumab arm but to compare these groups with ipilimumab. Survival curves of the combination arm and the nivolumab arm crossed in at least in four instances: This indicates that the proportional hazards assumption may be violated if a formal comparison were to be made.

Postprogression therapy may affect OS results.[5] In the CheckMate 067 trial, among patients in the nivolumab group who received any further systemic therapy, 40% of them did not receive ipilimumab. The first phase III trial with ipilimumab showed an OS advantage in pretreated patients in a trial published in 2010.[6] The enrollment into the CheckMate 067 trial started in 2013, when ipilimumab was standard in refractory patients. It has been shown that ipilimumab alone, and more recently in combination, has activity in anti–programmed death-1 refractory patients.[7] The CheckMate 067 trial was run globally, a common explanation for substandard postprogression treatment. However, observed results cannot be fully applied in countries with unfettered access to standard options.

The formal comparison between dual checkpoint inhibition and anti–PD(L)-1 monotherapy is an unmet need. Given the reasons that have been exposed, a nonformal comparison, even if tempting, is hampered by many limitations, including statistical issues and postprogression treatment. The detrimental toxic profile of the combination arm, potentially affecting QoL, strengthens our call. For these reasons, we believe that it is premature to conclude ipilimumab in combination with nivolumab is the standard of care.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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