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Response to: Association of selected (immune-related) adverse events and outcome in two adjuvant phase III trials, Checkmate-238 and EORTC1325/KEYNOTE-054 by Eggermont *et al*

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We wish to thank Eggermont *et al*[1] for their thoughtful communication regarding our recently published article, 'Adjuvant nivolumab for stage III/IV melanoma: evaluation of safety outcomes and association with recurrence-free survival'[2] The authors appear to suggest that the differing conclusions of that article, that there was no significant association between outcome of relapse-free survival and immune-related toxicity, and their recent work based on the EORTC1325/Keynote-054 study indicating the opposite, was due to the differing definitions of toxicity in the two studies. It is certainly true that there were differences in the definition of immune-related toxicity in the two studies, and we would argue that the differences made the Checkmate 238 data more clinically relevant and support the conclusions of our study. Eggermont *et al* indicate, for example, that grade 1–2 diarrhea should be excluded from the definition of an immune-related adverse event (irAE), since it could be due to placebo, infection, or other pre-existing causes. They also suggest that grades 1–2 pruritus and rash should be excluded from the definition of an irAE, since they could also be due to other causes. While that may be true, in fact there were two factors that support the inclusion of these side effects in Checkmate 238. The first is that in actual clinical practice, the vast majority of episodes of diarrhea of grade 2 or more in patients receiving checkpoint inhibitors are drug related and invariably respond to steroids or other immune suppression. Most guidelines for the workup of diarrhea on checkpoint inhibitors require an infectious workup to rule out infection, particularly *Clostridioides difficile*, making the argument about infectious causes of diarrhea unpersuasive. The second is that all toxicities noted in Checkmate 238 required attribution by the investigator. This would tend to rule out other causes of immune toxicities, since that would result in an attribution of 'not related'.

We certainly agree with Eggermont *et al* that the large difference in immune-related toxicities noted until day 100 between the two studies were based on the differences in definition. However, we believe that the more inclusive definition of toxicity in Checkmate 238 make our data more rigorously derived and the conclusions related to any association between toxicity and outcome more reliable. The authors of the Mandala *et al* article, several of whom have extensive experience in treating patients with checkpoint inhibitors, would agree that the more inclusive definition of an irAE provides greater clinical relevance and real-world context to the results of Checkmate 238. Eggermont *et al* suggest that a less inclusive definition of irAEs would confer greater power to the data from Checkmate 238. We disagree and feel that the data would be less reliable, not more. Eggermont *et al* do not provide evidence to support their hypothesis that earlier-grade diarrhea and skin side effects are less important or less immunologically relevant than the higher-grade and more restrictive definition of gastrointestinal and skin toxicity from Keynote-054. By being overly selective in the choice of side effects of checkpoint inhibition to include in one's analysis, one may indeed come to a different conclusion from that of Mandala *et al*, but we stand by the lack of association between immune-related side effects and relapse-free survival observed in the nivolumab data from Checkmate 238 and feel confident in its clinical relevance.

We would also like to address any confusion surrounding tables 1 and 2 of the Checkmate 238 study,[3] as suggested by Eggermont *et al*. Table 1 contains results of a Cox model of the nivolumab treatment effect, including a time-varying indicator for select treatment-related adverse events (TRAEs; restricting analysis to patients in the nivolumab arm alone). Table 2 contains the treatment effect (nivolumab vs ipilimumab) for the categories 'without/before select AEs' and 'after select AEs' obtained from a Cox model that included a treatment indicator, a time-varying indicator for select TRAEs, and the interaction term between the variables. The estimates from table 3 in the EORTC 1325/KEYNOTE-054 study are slightly different and seem to present the HR for 'without/before select AEs' and 'after select AEs' obtained from a Cox model that included a treatment indicator and the interaction term between the treatment indicator and a time-varying indicator for select TRAEs. Indeed, from that type of analysis, one could estimate the pembrolizumab treatment effect for any irAE to be approximately 0.60 (ie, 0.37/0.62). For Checkmate 238, the nivolumab treatment effect for any select TRAE is approximately 0.97.

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