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Association of selected (immune-related) adverse events and outcome in two adjuvant phase III trials, Checkmate-238 and EORTC1325/KEYNOTE-054

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We read with a great interest the paper of Mandala *et al*, recently published in your journal.[1] It was based on the CheckMate 238 randomized study, comparing 1-year adjuvant nivolumab to ipilimumab in resected stage IIIB/C and stage IV without evidence of disease melanoma patients. Indeed, we published a paper dealing with essentially the same topic.[2] The EORTC 1325/KN-054 randomized study compared 1-year adjuvant pembrolizumab to placebo in a similar patient population (resected high-risk stage IIIA-C melanoma). We would like to draw the attention of the readers to several important facts.

The two studies had the same design (double-blinded study), same treatment duration (1 year), and a similar patient population, although of a higher-risk prognosis in the CheckMate 238 study. The experimental arm comprised anti-PD-L1 inhibitors (nivolumab for the CheckMate 238 study and pembrolizumab for the EORTC 1325/KN054 study), but the control group was different: ipilimumab and placebo, respectively. This should not impact the prognostic impact of the occurrence of selected (immune-related) treatment-related adverse event (TRAE) on the subsequent efficacy outcome, recurrence-free survival (RFS), in patients treated with nivolumab or pembrolizumab.

The list of 'selected TRAE' (as named in the CheckMate 238 study) and of 'immune-related adverse events' (irAEs) (as named in the 1325/KN054 study), was vastly similar in the two studies: skin (vitiligo, severe skin reaction), gastrointestinal (GI) (severe diarrhea, colitis), endocrine (ie, hyperthyroidism, hypothyroidism, thyroiditis, hypophysitis, pneumonitis and diabetes mellitus), pulmonary (pneumonitis, sarcoidosis), hepatic (hepatitis), and renal. However, there were several AEs which were included only in the selected TRAE list only: skin (pruritus, rash erythema, eczema) which were most probably of grade 1 or 2, GI (diarrhea, of grade 1–2) and liver (increased aspartate aminotransferase, alanine aminotransferase). Of note, in the EORTC 1325/KN054 study, diarrhea of grade 1 or 2 was not considered as an irAE as its etiology could have several causes (GI infection, nocebo effect after the explanations of possible side-effects of immunotherapy, pre-existing diarrhea due to concomitant medication for a chronic disease, etc). Same for pruritus and rash, which could occur after any injection (eg, vaccine). These are not necessarily always proportional with an immune response. Increased liver enzymes can be due to several causes not related to an irAE (eg, alcohol consumption, non-alcoholic fatty liver disease). In the CheckMate 238 study, any-grade paresthesia (2.7%), peripheral neuropathy (0.4%), and axonal neuropathy (0.2%) were included as well. Therefore, one may expect differences between the study results regarding the incidence of irAE, and their dispersion of occurrence over time.

The incidence of irAE, first dose to 100 days following last dose, was higher in the nivolumab group (306/504=67.4%) (Table A2)[1] than in the pembrolizumab group (190/509=37.3%).[2] Most of the 30% difference could probably be explained by the incidence of diarrhea (24.8%), pruritus (23.5%), and rash (20.6%), reported as being the first TRAE, almost always of grade 1 or 2. These were far higher than the incidence of skin disorders (6.3%) and severe GI reactions (3.4%) which were reported in the EORTC 1325/KN-054 study.

In the CheckMate 238 study,[1] the occurrence of TRAEs was especially reported within the three first months from the start of nivolumab (217/504=48%), whereas the irAEs were reported over a more extended time period in the EORTC 1325/KN-054 study (20% of irAE within 3 months; figure 2A).[2] As the 71% (37.3%/67.4%) of the TRAEs occurred within the 3 months, the authors used a landmark analysis in order to assess the prognostic value of these TRAE on the subsequent RFS, in patients still alive and free of disease at 3 months from start of nivolumab. The Kaplan-Meier curve showed that patients who experienced an irAE had an RFS which was very similar to those without an irAE before 3 months. In the body text, the authors indicated: 'In a cox model analysis, the occurrence of a select TRAE reported between first study dose and 100 days after last study dose was not associated with RFS in patients treated with nivolumab (table 1). HR for RFS in patients without a select TRAE compared with patients with a select TRAE was 0.97 (95% CI: 0.70 to 1.34; p=0.858),'. However, in the cap of the, where these results were summarized, it was indicated: '*Cox model was used which included a time-varying indicator for select TRAEs'. The reader is confused. Does table 1 contain results of a landmark analysis or using a Cox model with time-dependent indicator for selected TRAEs? If the latter is the case, what is the reason for the discrepancy between the estimates reported in table 1 and those that can be deduced from table 2 (see the next paragraph)? In the EORTC 1325/KN054 study, we refrained to produce a landmark analysis: only 52% (20%/37.3%) of the irAE occurred within 3 months. Therefore, such kind of analysis would suffer from a dilution effect and be characterized by a low power: RFS events within 3 months could not be taken into consideration and a substantial number of patients (91=48% of 190) without irAE at 3 months developed later an irAE. Even in the CheckMate 238 study, this was still true, as 158 patients (out of 452 still in follow-up after 3 months) developed, later, a selected TRAE.

Despite the discrepancies indicated above, the results of the two studies were largely similar (see table 2 in the CheckMate 238 study[1] and table 3 in the EORTC 1325/KN054 study[2] when a Cox model with time-dependent covariates was used, which is a more powerful approach than landmark analysis). By computing the ratio of HR for the Experimental group after irAE vs the Control group to the HR for Experimental group without/before irAE versus the control group, one obtains, 0.68 (=0.65/0.96) in the CheckMate 238 study and 0.61 in the EORTC 1325/KN054 study. It means that in the nivolumab group, the risk of recurrence or death following the occurrence of an irAE was approximately 68% of the one for those who did not experience an irAE (yet). This is extremely similar to estimate in the pembrolizumab group after an irAE (61%). Despite this clear trend (but p=0.14), the authors strongly concluded: 'No association between RFS and select TRAEs was evident.' Interestingly, their results were also consistent when only skin irAE were considered (0.55/0.81=0.68), but they had the opposite direction when only GI AEs were considered (0.81/0.62=1.31). As indicated above, the occurrence of a grade 1 or 2 diarrhea may be due to many causes other than an irAE. The authors did not comment about this high variability in the results, which could be due to the inclusion of many grade 1 TRAEs (eg, diarrhea, pruritus, skin rash). For the nivolumab versus ipilimumab comparison, they did find a stronger treatment effect among those who had a TRAE which did not require an immunosuppressant treatment (HR=0.60), as compared with those who required an immunosuppressant treatment after a TRAE (0.87).[1] This was consistent with our findings (HR 0.34 and 0.50, respectively) for the pembrolizumab vs placebo comparison.[2]

Lastly, in the Results section, the authors described the association which was evaluated in the ipilimumab group: 'Moreover, as with nivolumab treatment, the presence or absence of select TRAEs reported between first study dose and 100 days after last study dose (time-varying covariate) was not associated with RFS in the ipilimumab group (HR 0.62; 95% CI 0.41 to 0.96; p=0.0301 (to account for multiple comparisons, p≤0.01).' In our opinion, this result should not be interpreted as suggesting a lack of an association. Of note, the observed HR=0.62, is essentially the same as our estimate HR=0.61 in the pembrolizumab arm,[2] and this despite a high rate of stopping treatment due to toxicity ('treatment discontinuations due to ….study drug toxicity with ipilimumab (208/331)').[1]

In the Discussion, the authors focused only on the nivolumab treatment group and concluded: 'This analysis revealed that …with nivolumab… an association between the development of early TRAEs with nivolumab and RFS was not evident when the data were analyzed by two different statistical techniques.' In our opinion, the last paragraph of the Discussion does not properly reflect the results either 'There was no association between treatment-related select AEs and RFS, …such immune-mediated events may not be predictive of efficacy.'

To conclude, the CheckMate 238 and EORTC 1325/KN054 studies both observed that the occurrence of irAEs was associated with a 30%–40% reduction in the of risk of recurrence or death among high-risk melanoma patients treated with adjuvant immune checkpoint inhibitors (ICIs). Focusing more on adverse events that have a greater chance to be immune-related in the CheckMate 238 study would likely improve the power of the analysis in that study. An assessment of serial immune auto-immune antibodies using classical (eg, antinuclear antibody) or newer techniques could better discriminate those who can benefit more from ICIs.[3 4]

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