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Reply to 'Comment on 'Efficacy and toxicity of treatment with the anti-CTLA-4 antibody ipilimumab in patients with metastatic melanoma after prior anti-PD-1 therapy''

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Sir,

We have read with great interest the correspondence from Imafuku *et al*. The authors provide further evidence that sequential treatment of anti-PD-1 blockade followed by the application of the anti-CTLA-4 antibody ipilimumab is associated with an increased rate of severe immune-related toxicity (Danlos *et al*, 2015; Khoja *et al*, 2015; Aya *et al*, 2016; Bowyer *et al*, 2016; Furudate *et al*, 2016). This contrasts with the reverse treatment sequence where no increased frequency of immune-related adverse events has been observed (Weber *et al*, 2015; Ribas *et al*, 2016). The observations of Imafuku *et al* suggest that the timing between the administration of the last dose of an anti-PD-1 antibody and the first dose of ipilimumab is a critical factor with all patients who experienced high-grade immune-related toxicity, having received their first dose of ipilimumab within 1 month after the last administration of an anti-PD-1 antibody. In our patient cohort, the median time interval between therapies has been 32 days in patients who developed severe autoimmune toxicity *vs* 46 days in patients without toxicity, a difference that was statistically not significant. It should also be remembered that a high receptor occupancy is achieved after only a single dose of an anti-PD-1 antibody that persists for several months so that the turnover of PD-1 expressing immune cell populations may also be important in determining the immunological outcome next to the half-life of the antibody itself (Brahmer *et al*, 2010). The sequence in which PD-1 and CTLA-4 molecules are engaged on effector T cells also leads to vastly different gene expression profiles and one may propose to distinct immunological outcomes providing a potential explanation why differences in immune-related toxicity can be observed depending on the treatment sequence of checkpoint regulators (Das *et al*, 2015).

Imafuku *et al* did not present any efficacy data, but it should be emphasised that treatment with ipilimumab after anti-PD-1 failure has significant clinical activity with an objective response rate of 10–15%, which is in keeping with the treatment experience of ipilimumab in anti-PD-1 therapy naive patients. This has recently been confirmed in a larger data set of patients who received ipilimumab after progression on pembrolizumab in the Keynote-006 clinical trial (Long *et al*, 2016).

Overall, these data highlight that ipilimumab is a treatment option after progression on anti-PD-1 therapy and patients should be closely monitored for immune-related adverse events, particularly, if anti-CTLA-4 therapy is initiated shortly after the last application of an anti-PD-1 agent. An ongoing randomised clinical trial (NCT02731729) will provide prospective data regarding the efficacy and toxicity of single-agent ipilimumab therapy, or combination therapy of ipilimumab and nivolumab in patients who progress on anti-PD-1 therapy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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