

Efficacy of the combination of ipilimumab and nivolumab following progression on pembrolizumab in advanced melanoma with poor risk features

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To the Editor,

The approved combination of ipilimumab and nivolumab (ipi + nivo) demonstrates potent clinical activity, including in patients with poor prognostic factors such as an elevated lactate dehydrogenase (LDH) [1]. In the subgroup with elevated LDH, the response rate is superior with the combination but its durability in this cohort is not established [2]. Neither the efficacy of ipi + nivo in treating brain metastases nor clinical outcomes of patients treated with ipi + nivo after primary progression on anti-PD-1 therapy have been described. The extent to which high-dose steroids may reduce treatment efficacy is unclear—there is evidence that the response rate to anti-PD-1 agents in patients on corticosteroids or other immunomodulatory medications is worse; however, clinical benefit is not precluded [3].

In a recently published case series in this journal, Kirchberger et al. investigated the combination of low-dose ipilimumab (1 mg/kg) and pembrolizumab (2 mg/kg) in nine patients, who progressed after sequential single-agent pembrolizumab and ipilimumab. Out of nine, six patients had brain metastases but whether they were symptomatic is not described. No treatment-related adverse events occurred. Three out of nine patients achieved stable disease as their best response with progression-free survival rates of 4, 6 and 14 months, respectively. No partial responses were seen [4]. However, the combination of ipilimumab plus pembrolizumab is currently not licenced for use in metastatic melanoma.

We describe the case of a 27-year-old male with metastatic BRAF-mutant melanoma involving the brain and leptomeninges, in addition to visceral sites, who was treated with ipi + nivo following primary progression on pembrolizumab after four cycles. Before pembrolizumab, he received 10 months of dabrafenib and then progressed. He received whole-brain radiotherapy after the first cycle of pembrolizumab due to the symptomatic progression of central nervous system disease. At the initiation of ipi + nivo, his LDH was 312 (upper limit of normal (ULN) 192 U/L) and dexamethasone 4 mg twice a day (bd) was maintained due to ongoing symptomatic brain oedema. On days 6 and 9 of cycle 1 ipi + nivo, two neurological deteriorations occurred, consistent with flares of intracerebral oedema. These were managed with

re-escalation of dexamethasone to 8 mg bd and cycle 2 was delayed by a week to enable dexamethasone to be weaned back to 4 mg bd.

On cycle 2 day 1, the alanine aminotransferase (ALT) was elevated at 122 U/L (ULN <40 U/L). Treatment was administered with close monitoring of liver function. Due to a further rise in ALT to 186 U/L, dexamethasone was re-escalated to 8 mg bd. A presumptive diagnosis of immune-related transaminitis was made and other aetiologies were excluded. Given the steroid-refractory nature of the hepatitis, mycophenolate mofetil was initiated early and the ALT began to slowly fall over the next few weeks.

Restaging imaging 8 weeks from cycle 1 demonstrated a mixed response with pseudoprogression in the liver but a notable reduction in the tonsils and cervical lymph nodes. The intracranial metastases were stable. The liver lesions were stable on subsequent imaging. After 6 months, without any further treatment, the patient had a maintained extracranial and intracranial response on scans and the ALT had normalised. Steroids have been reduced to prednisolone 5 mg and mycophenolate mofetil has been ceased. Imaging at 7 months, however, shows progression in his right ureter and in his brain.

This case demonstrating disease control for 7 months highlights that durable benefit may be seen after treatment with ipi + nivo, even in patients with poor prognostic factors such as disease refractory to anti-PD-1 blockade, an elevated baseline LDH, active brain and leptomeningeal metastases and a need for prolonged immunosuppression. We hope that this report may also be of use to clinicians when considering combination treatment after anti-PD-1 monotherapy.

References

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