Efficacy and toxicity of rechallenge with combination immune checkpoint blockade in metastatic melanoma: a case series

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Abstract

Background

The efficacy and potential toxicity of rechallenge with combination ipilimumab and nivolumab has not been described. Retreatment of patients with immune checkpoint inhibitors in the setting of prior significant toxicity lacks evidence-based guidance.

Methods

We present the first three, consecutive patients who received re-treatment with combination ipilimumab and nivolumab for metastatic melanoma managed at our institution.

Results

Rechallenge with combination ipilimumab and nivolumab in the setting of prior grade 3 toxicity with initial combination therapy is feasible, and responses are seen. We highlight the fact that grade 3 toxicity is likely to recur, but if so, can be manageable.

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Conclusions

Retreatment with ipi + nivo may be considered an option in carefully selected, well-informed patients. More research is required to delineate the benefits and risks with this approach.

Keywords

Advanced melanoma
Combination immune checkpoint therapy
Ipilimumab
Nivolumab
Immune-related toxicity

Abbreviations

ALT	Alanine aminotransferase
CT	Computed tomography
ECOG	Eastern Co-operative Group
FDG	2-Fluoro-2-deoxy-D-glucose
Ipi + nivo	Ipilimumab and nivolumab

irAE	Immune-related adverse event
MMF	Mycophenolate mofetil
MRI	Magnetic resonance imaging
PET-CT	Positron emission tomography-computed tomography
RECIST	Response evaluation criteria in solid tumours
ULN	Upper limit of normal

Introduction

Immune checkpoint blockade with ipilimumab, pembrolizumab and nivolumab improves overall survival in patients with metastatic melanoma [1, 2, 3]. The combination of ipilimumab and nivolumab (ipi + nivo) has the highest response rate and progression-free survival compared to monotherapy with these agents, but without mature overall survival data [4, 5]. However, combination treatment is associated with severe (grade 3/4) immune-related adverse events (irAEs) in 55% of treated patients, although the majority is reversible with appropriate treatment [4]. Retreatment of patients with immune checkpoint inhibitors in the setting of prior significant toxicity lacks evidence-based guidance. We present the case histories of three consecutive patients who were successfully rechallenged with combination ipi + nivo. All three patients developed grade 3 toxicity associated with their first combination immunotherapy treatment. To our knowledge, this is the first report of patients rechallenged with ipi + nivo.

Case presentations

Case 1

A 62-year-old lady presented in April 2013 with a breast mass found to be *BRAF*-mutant metastatic melanoma. A staging scan revealed subcutaneous and lung metastases. Her past medical history included two primary melanomas in 2007 and 2008, asthma requiring inhaled steroids and brain radiotherapy to a cavernoma around age 40. She was enrolled into the CheckMate-067 trial (NCT0184405) and was randomised to ipi + nivo in August 2013. Lactate dehydrogenase (LDH) was normal.

Three weeks following cycle 1 she was admitted to hospital with frontal headaches, nausea and vomiting and an elevated alanine aminotransferase (ALT) at 107 U/L (upper limit of normal (ULN): <40). As the headaches responded to analgesia, steroids were withheld. Lumbar puncture revealed a leukocytosis with elevated protein, but no evidence of infection. A provisional diagnosis of immune-related aseptic meningitis was made. ALT peaked at 216 on day 4 of the admission and then improved. A hepatitis screen was negative.

Cycle 2 was administered one week following discharge in early September 2013. Less than a week following treatment, her headaches recurred and she was re-admitted for observation, but discharged after 4 days. Her ALT remained elevated during this time (106 U/L at admission, 200 U/L at discharge). Again, steroids were withheld. Close monitoring subsequent to discharge revealed deteriorating liver function with an ALT peak of 536 one week later (cycle 2, day 21) prompting admission again and initiation of prednisolone 60 mg daily. A rapid improvement ensued. The first staging computed tomography (CT) scan was performed in October 2013 and confirmed a partial response by RECIST 1.1. Prednisolone was weaned over a month. ALT remained within the normal range for 6 months and restaging revealed further response.

In April 2014 routine biochemistry assessments revealed a flare of immune-related hepatitis with an ALT of 380 U/L prompting admission for intravenous methylprednisolone 1 mg/kg. Upon reduction in the ALT 5 days later, treatment was changed to prednisolone 30 mg and weaned over 4 weeks. Liver function remained normal for several months and 6 weekly CT scans confirmed the ongoing partial response.

A re-staging CT scan in November 2014 was suggestive of right hilar nodal progression, confirmed with positron-emission tomography (PET)-CT. With hindsight, slight progression was evident on the CT scan in May 2014, shortly after recommencement of prednisolone. Given it was a single-site relapse in the context of medium-term disease stability, radiotherapy was administered to this region.

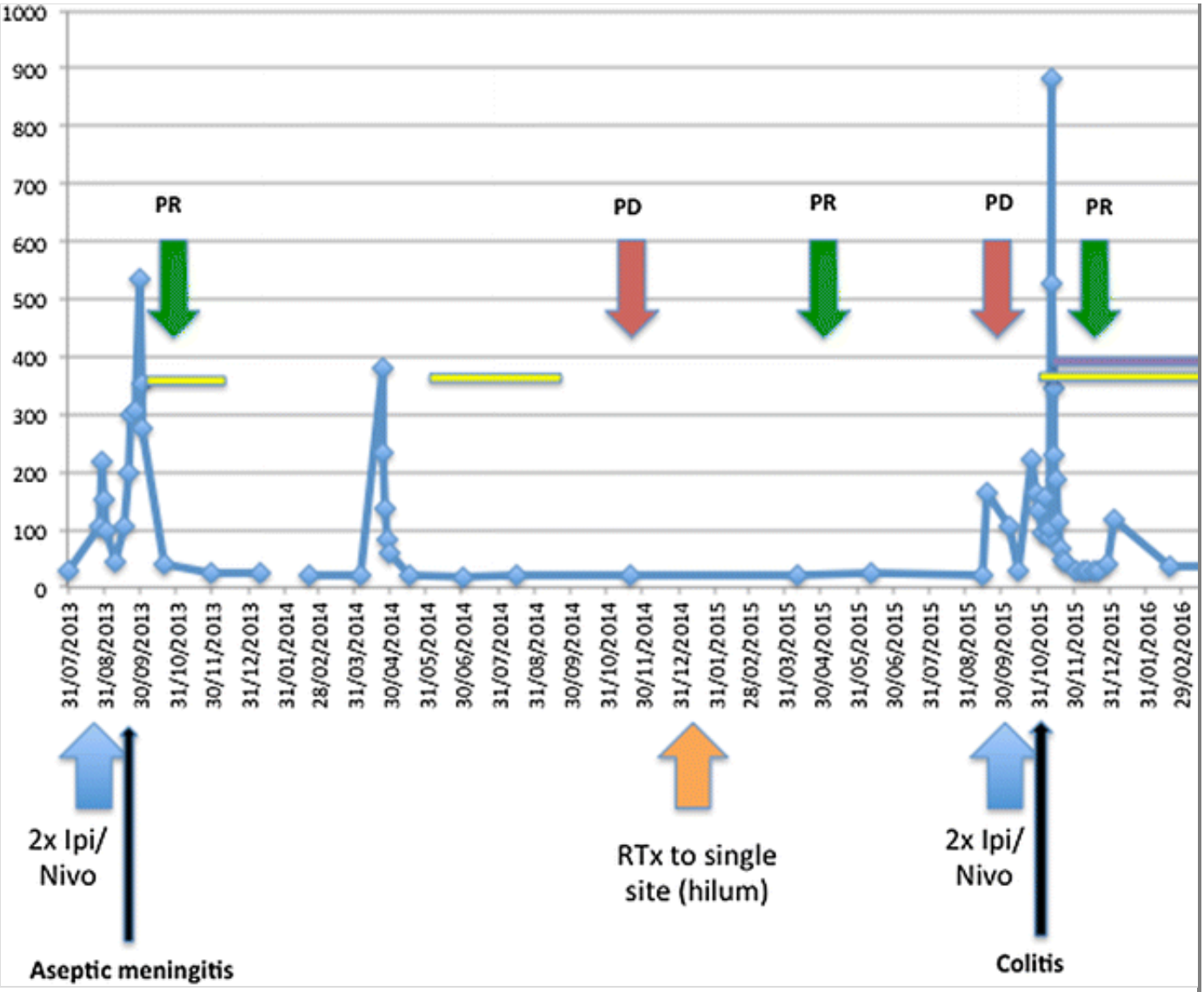
Progressive disease was again noted in September 2015, this time in parenchymal lung lesions. A decision was made to rechallenge the patient with ipi + nivo. ECOG performance status was 0, and her LDH was normal at this

time. After cycle 2, she developed grade 3 colitis requiring admission and treatment with IV methylprednisolone 1 mg/kg. A sigmoidoscopy showed no evidence of macroscopic colitis, but evidence of microscopic inflammation on biopsy. Concurrent with the diarrhoea, her ALT began to rise again, peaking at 220 U/L before spontaneously falling prior to steroid initiation. Repeat viral hepatitis serology was negative. A re-staging CT performed in early November 2015 revealed a mixed response to treatment, with new mediastinal lymphadenopathy but regression of pulmonary nodules.

On day 10 of the admission, methylprednisolone was changed to oral prednisolone 75 mg. ALT at this time was 102 U/L. Two days later it increased to 883 U/L and both IV methylprednisolone at 2 mg/kg and mycophenolate mofetil (MMF) 500 mg bd were commenced. The ALT began to fall immediately, returning to normal (30 U/L) 3 weeks later. During this time, corticosteroids and mycophenolate were weaned. A further CT scan performed 2 months after cycle 2 of ipi + nivo showed reduction in the mediastinal nodal mass and barely discernible pulmonary nodules. She remained on MMF for 6 months and still continues on low-dose prednisolone (5 mg) (8 months total steroid duration). Her ALT has remained mostly within the normal range. She has not progressed on routine imaging surveillance. The timeline of the multiple hepatitis episodes in relation to ipi + nivo treatment and other toxicities is depicted in Fig. 1.

Fig. 1

Chronology in Case 1 of recurrent hepatitis in context of combination ipilimumab/nivolumab treatment, response, other immune-related toxicity and use of immunomodulatory medication. *ALT* Alanine aminotransferase, *PR* partial response, *PD* progressive disease, *ULN* upper limit of normal, *RTx* radiotherapy, *MMF* mycophenolate mofetil



Case 2

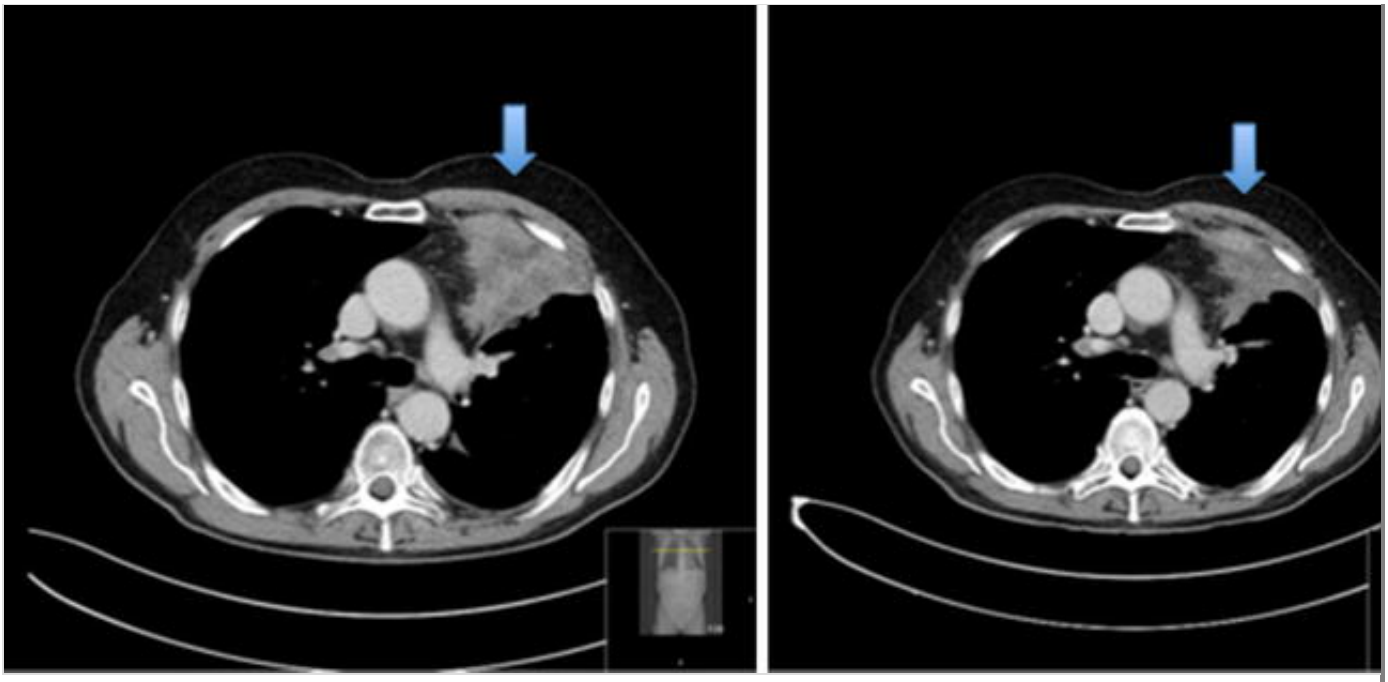
A 68-year-old gentleman presented with *BRAF*-mutant metastatic melanoma in July 2015. He had a large pulmonary mass with a pleural effusion, and ECOG performance status was 2. He had no past medical history of note. LDH was normal. First-line treatment with ipi + nivo was administered. Two weeks after his first cycle, he presented with back pain, leg weakness and paraesthesia. MRI spine and brain were unremarkable. Over the following 24 h, his neurological status deteriorated with further weakness and IV methylprednisolone 2 mg/kg was initiated. Consultant neurology input was sought, and a diagnosis of lumbar plexopathy was made. Concurrent with the neurological toxicity a grade 3 hepatitis was noted, with a peak ALT of 426U/L (ULN < 40U/L). Improvement occurred in both his neurological status and liver function with methylprednisolone, and this was eventually converted to oral prednisolone

100 mg and a slow wean was instituted. Further treatment was withheld. Both adverse events resolved completely.

A restaging CT scan performed 8 weeks after cycle 1 ipi + nivo showed a partial response in the lung lesion. Unfortunately, a scan 4 weeks later demonstrated progressive disease and treatment with dabrafenib and trametinib was commenced. After 7 months of disease control on therapy, his disease progressed again in the lung. A decision was made to rechallenge him with ipi + nivo, under the cover of prednisolone 30 mg daily to mitigate severe toxicity. ECOG performance status was 1 at this point, and LDH was elevated (279U/l; ULN 192U/l). He tolerated the first 3 cycles of treatment well and prednisolone was weaned to 10 mg. LDH normalised after one cycle of therapy. Ten days after cycle 3, he developed Grade 3 diarrhoea and was admitted for IV methylprednisolone 2 mg/kg. Due to inadequate control of symptoms, infliximab was initiated 24 h later. A re-staging CT scan again demonstrated response in the lungs (see Fig. 2). His diarrhoea improved 24 h after infliximab, and he was changed to prednisolone 70 mg on a weaning schedule. Three weeks later he required re-admission for recurrent immune-related diarrhoea and was managed with IV methylprednisolone 2 mg/kg and further infliximab. He improved rapidly and was discharged on 120 mg prednisolone. Repeat imaging 6 weeks from the prior CT demonstrated a slight increase in tumour size, but overall the disease is considered stable. Maintenance nivolumab has been commenced despite steroid dependent-diarrhoea (prednisolone maintained at 30 mg).

Fig. 2

Efficacy of rechallenge combination ipilimumab and nivolumab in Case 2—CT scan at baseline (*left*) and after 2 cycles (*right*)



Case 3

A 39-year-old lady was diagnosed in September 2013 with relapsed *BRAF*-mutant melanoma following presentation with back pain, one year from completion of adjuvant bevacizumab for Stage III melanoma (on the AVAST-M trial, Eudra-CT number 2006-005505-64). Cross-sectional imaging demonstrated tumours in the liver, porta hepatis and superior retroperitoneum, and LDH was elevated (386U/l; ULN 192U/l). Her past medical history was unremarkable. ECOG performance status was 0. She was enrolled in the CheckMate-067 trial and was randomised to receive combination ipi + nivo, followed by nivolumab maintenance. Cycle 1 was administered in late October 2013. The first 18 months of treatment were complicated only by grade 1 rash with pruritus. In addition, she had a partial response by RECIST 1.1 seen on her first two re-staging CTs, followed by a sustained partial response.

Three weeks following cycle 12 (in maintenance nivolumab phase), the patient developed grade 2 diarrhoea and grade 2 nausea. Oral prednisolone (30 mg) was prescribed as an outpatient and down-titrated over four weeks. Domperidone proved efficacious for nausea. The diarrhoea reduced to grade 1 after 4 days of prednisolone and had normalised by 14 days. Stool cultures were negative for infection, and blood tests were unremarkable. Ten days after completing the course of oral prednisolone, the diarrhoea recurred (grade 3) and she was admitted for intravenous methylprednisolone (1 mg/kg) and nivolumab was

ceased. The methylprednisolone dose was doubled on the second day due to a lack of improvement. Flexible sigmoidoscopy revealed no macroscopic nor microscopic abnormality. She was discharged with oral prednisolone (60 mg) 3 days later, and this was weaned successfully over 6 weeks.

The restaging CT at 35 months unfortunately demonstrated enlarging portocaval lymphadenopathy. Given the excellent initial response observed with ipi + nivo and complete resolution of diarrhoea, our patient was rechallenged with ipi + nivo in February 2016. LDH was normal, and ECOG performance status remained 0. A CT scan after 4 cycles revealed a reduction in size of all measurable disease, consistent with a partial response. No toxicities were observed during the rechallenge. At the patient's request, maintenance nivolumab was deferred. A follow-up CT 5 months after initiation of treatment was stable. Another CT 4 weeks later confirmed ongoing disease control.

Discussion

Although retreatment of patients with ipilimumab after an initial period of disease control may be effective without excessive toxicity [6], to our knowledge this is not yet described for the combination of ipi + nivo. We report the details of three patients successfully rechallenged with ipi + nivo, resulting in disease response. In two of our patients, this occurred over 2 years from the initial treatment and in one, 12 months from first cycle of ipi + nivo. In each situation, grade 3 toxicities were seen with initial therapy, two during the induction phase resulting in early discontinuation, the other in the maintenance nivolumab phase.

In Cases 1 and 2, rechallenge was associated with significant immune-related toxicities: grade 3 diarrhoea and grade 4 hepatitis in one patient and grade 3 diarrhoea in the other (despite ongoing prednisolone). For Case 1, the recurrent hepatitis manifested as a significant biochemical change only and was never associated with symptoms, synthetic dysfunction or coagulopathy. Prolonged immunomodulation with both prednisolone and mycophenolate was required, however. The diarrhoea necessitated hospital admission, though it improved with steroid treatment and endoscopically did not meet criteria for colitis. The diarrhoea in Case 2 required initiation of infliximab due to inadequate improvement with corticosteroids alone. In Case 3, no recurrence of diarrhoea

was noted with combination rechallenge, nor any other toxicities of note. This scenario differed from the other two in that the original toxicity did not occur during combination therapy, but later in the maintenance phase.

Case 1 in particular reaffirms the potential for durable responses with combination ipi + nivo despite toxicity. From a large retrospective series, there is no suggestion that patients treated with ipilimumab who developed toxicity have their outcomes compromised by immune modulation [7]. Accordingly, in the Checkmate-067 trial, of the 120 patients (36%) who discontinued combination treatment early due to toxicity, 81 (68%) experienced a complete or partial response [4]. The median duration of response in this group who discontinued early was 13 months, comparable with the overall population (12 months) [8]. We also acknowledge that there were a number of favourable prognostic factors present in all our patients upon rechallenge—normal LDH in Cases 1 and 3, M1b disease in Cases 1 and 2, ECOG performance status of 0 or 1 in all cases.

Occurrence of multiple concurrent toxicities is more common with the combination of ipi + nivo than with either agent as monotherapy [8]. In the reported subgroup analyses from the CheckMate-067 trial, 2 irAEs occurred in 25% (vs 5 and 8% with nivolumab and ipilimumab monotherapies respectively), 3 in 5% (vs 1 and 1%) and >3 in 2% (vs 0 and 0%) of those treated with ipi + nivo. Interestingly, in Case 1, our patient appeared to have a predisposition to recurrent hepatitis, but developed a second, different irAE in conjunction with this after each treatment episode. Notably, she developed hepatitis for the second time 7 months from her first combination treatment. This is indicative of prolonged immune activation which may have also accounted for her durable initial response. Prolonged steroids have been warranted this occasion to control the hepatitis—over 8 months—in contrast to the median time to resolution of 4–8 weeks as previously reported in ipi + nivo studies [4, 9].

Rechallenge immune checkpoint blockade with combination ipi + nivo may be efficacious, although there is potential for substantial toxicity. These cases demonstrate that toxicity is likely to recur early in people who originally developed adverse events during their induction phase. We also demonstrate that toxicity remains manageable, although is potentially prolonged. The risk/benefit ratio of rechallenge must be considered on an individual basis and

informed discussions of potential risk with patients remain important in this setting. More research is required to determine the optimal schedule for rechallenge and to quantify the risks involved.

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Compliance with ethical standards

Conflict of interest James Larkin is a non-remunerated consultant for Novartis, Pfizer, Bristol Myers Squibb (BMS), Merck Sharp & Dohme (MSD), Roche/Genentech, Glasko Smith Kline (GSK) and Eisai and receives institutional research support from Pfizer, BMS, Novartis and MSD. James Larkin and Martin Gore are supported by the National Institute for Health Research Royal Marsden Hospital and Institute of Cancer Research Biomedical Research Centre (NIHR RMH/ICR BRC). Samra Turajlic is a Cancer Research UK (CRUK) Clinician Scientist and is funded by CRUK (Grant Ref. C50947/A18176) and the NIHR RMH/ICR BRC (Grant Ref. A109). The remaining authors have declared no conflicts of interest.

Informed consent We are very grateful to our patients who gave consent for their clinical details to be included in this paper.

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