EDITORIAL

For reprint orders, please contact: reprints@futuremedicine.com

Melanoma Management

Anti-PD-1 monotherapy versus anti-PD1 plus anti-CTLA4 in advanced melanoma: how do we decide?

"…both combination therapy and single-agent anti-PD-1 therapy significantly improves survival, and both represent reasonable 'standard-of-care' therapies."

Lewis Au[1], Aine O'Reilly[1] & James Larkin*[,1]

First draft submitted: 9 June 2017; Accepted for publication: 26 June 2017; Published online: 2 August 2017

KEYWORDS
• anti-CTLA4 • anti-PD-1 • combination therapy • immunotherapy • metastatic melanoma

The introduction of immune checkpoint inhibitors has revolutionized the treatment of metastatic melanoma. Ipilimumab monotherapy first showed a survival advantage compared with a gp100 vaccine or chemotherapy [1,2]. Further improvements in survival outcomes were seen for pembrolizumab over ipilimumab alone in a large Phase III trial (KEYNOTE-006) [3] with recent updates showing ongoing superior overall survival (OS) after follow-up of 33.9 months [4]. Phase III study of combination nivolumab plus ipilimumab versus both drugs alone (CheckMate 067) after a minimum follow-up of 28 months showed a median overall survival of 20 months for those in the ipilimumab arm, but median overall survival had not been reached in the combination or nivolumab only arms [5]. While the CheckMate 067 study was not powered for comparison between the combination and the nivolumab arm, OS, progression-free survival and response rates favor nivolumab plus ipilimumab numerically. The OS rates were 64 versus 59% (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.69–1.12), progression-free survival were 43 versus 37% (HR 0.76, 95% CI 0.62–0.94), respectively at 2 years, and overall response rates were 58.9% for combination treatment compared with nivolumab alone at 44.6% in the 2017 updated analysis.

As such, both combination therapy and single-agent anti-PD-1 therapy significantly improves survival, and both represent reasonable 'standard-of-care' therapies. Clinical trial data suggest that combination therapy does increase efficacy; but how are we advising our patients on the most appropriate immunotherapy regimen for advanced melanoma?

Expected toxicity tolerance

The clinical decision for intervention starts with a risk versus benefit analysis. In general terms, 'ideal candidacy' for an upfront doublet approach would be the robust patient who would tolerate the higher toxicity rates of combination

[1]The Royal Marsden Hospital, Fulham Road, London, SW3 6JJ, UK
*Author for correspondence: Tel.: +44 20 7811 8576; Fax: +44 20 7811 8103; james.larkin@rmh.nhs.uk

Future Medicine part of fsg

therapy, and with that, potentially prolonged immunosuppressive treatment for immune-related toxicities. Grade 3/4 toxicity rates for nivolumab plus ipilimumab are approximately 55% [6–8]. In comparison, anti-PD-1 monotherapy is generally very well tolerated, with grade 3/4 toxicity rates of approximately 10% [3]. Treatment discontinuation rates were 36.4 versus 7.7% for combination versus nivolumab alone, respectively in CheckMate 067. Overall, patients who have a poor expected tolerance to the increased toxicity of combination treatment would be by default more suitable for anti-PD1 therapy alone. In the real-world setting, distance and access to centers with expertise in managing immune related toxicities, as well as patient reliability to report toxicities, and social support should all play a part in the evaluation of potential toxicity management.

"The clinical question that remains is how we select those whose long-term survival hinges on upfront combination therapy rather than anti-PD-1 alone."

Patient selection for treatment

Currently, there is a lack of robust biomarkers to guide patient selection for combination therapy upfront versus anti-PD-1 alone. By default, those treated with upfront anti-PD-1 alone have the potential option of sequential monotherapies with second-line anti-CTLA-4 treatment. While salvage ipilimumab can induce responses comparable to use in first-line setting for those who have failed prior anti-PD-1 therapy [9], elevated serum lactate dehydrogenase (LDH) has been shown to be an incremental and independent negative prognostic marker for therapy response rate to ipilimumab monotherapy in a retrospective analysis of 134 patients [10], where 80% of patients were treated in the second or beyond line setting. In comparison, the clinical benefit for upfront combination therapy was favorable across subgroups including elevated LDH in a preplanned analysis in CheckMate 067 [5]. For this group, upfront combination therapy may be more efficacious rather than sequential treatment. Further to the question of optimal sequencing, a multicenter, retrospective series where 37 patients were salvaged with combination therapy following failure of anti-PD1 treatment reported a response rate of 21% and a 1-year survival rate of 55% [11], notably inferior to the reported efficacy for combination treatment (58.9% response rate, 73 and 64% 1-year and 2-year survival rates, respectively) in the first-line setting in CheckMate 067. It is noteworthy that internationally, combination therapy has gained regulatory approval in Australia via the Therapeutic Goods Administration for use in stage IV melanoma patients specifically with elevated LDH in the first-line setting.

Adding weight to the need for biomarkers in patient selection are the long-term survival data of responders treated with pembrolizumab alone in the first-line setting [4]. Robert *et al.* reported that in KEYNOTE-006 – after median follow-up of almost 3 years – for 104 of the total 556 patients (19%) who demonstrated a clinical response to pembrolizumab and completed treatment for 2 years, 91% of patients are progression free after a further median follow-up of 9.7 months. Currently we await the long-term survival data for the durability of response for those treated with doublet therapy but results would be expected to at least reflect those in KEYNOTE-006. The clinical question that remains is how we select those whose long-term survival hinges on upfront combination therapy rather than anti-PD-1 alone.

Patient characteristics to consider

Those with clinical characteristics not conventionally explored in clinical trials such as patients with altered or immune deficiencies warrant further consideration in the therapeutic decision.

• Autoimmunity

The presence of active autoimmune diseases (AD) and the use of immune checkpoint inhibitors continue to be an area of clinical debate. The current published experience comes mostly from retrospective series for single-agent anti-PD-1 or ipilimumab treatment, and the patient outcomes in combination therapy are largely unknown. 52 patients with pre-existing AD who have been treated with anti-PD1 immunotherapy have been reported in a case series by Menzies *et al.* [12]. The cohort consisted of mostly rheumatological (n = 27, 13 with rheumatoid arthritis) conditions, along with dermatological (n = 8), endocrine (n = 4), respiratory (n = 2) and hematological (n = 2) disorders. 29% had clinically active disease at baseline. Of the 52 patients, 20 (38%) experienced exacerbation of their underlying autoimmune disorder, leading to a 4% therapy discontinuation rate. Those with clinically active AD at baseline seemed more likely to experience a flare (9 of 15 patients) compared with those with AD which were inactive at the start of treatment (11 of 37 patients). Overall, autoimmune flare did not appear to impact treatment efficacy with a comparable rate of response with anti-PD-1 clinical trials data. Treatment with ipilimumab

monotherapy in the context of autoimmunity has also been reported in a retrospective series of 30 patients where 13 patients had an exacerbation requiring immunosuppressants [13]. This was manageable, and again this did not appear to impact therapeutic outcomes.

While active autoimmune disease does not appear to be an absolute contraindication with single-agent checkpoint blockade, there are currently no data to guide the use of combination therapy.

• Organ transplant/HIV/hepatitis

At present, there are limited case reports in the literature for use of immune-checkpoint inhibitors for organ transplant recipients. For treatment of melanoma with ipilimumab alone, two cases of liver transplant recipients have been reported without significant graft complications [14,15]. In renal transplant recipients, both uncomplicated administration [16] as well as graft failure [17] have been reported. For sequential monotherapy administrations, one case report described acute renal allograft rejection [18], while another reported no graft dysfunction [19]. Of interest, in both cases the patients received ipilimumab followed by nivolumab due to on-treatment progression. However, in the former case reported by Spain *et al.*, tacrolimus was ceased at baseline and continued on prednisolone (5 mg daily) alone. Acute rejection occurred following cycle 1 of anti-PD-1 and was followed by ongoing disease control. In contrast, in the case reported by Herz *et al.*, sequential immunotherapy was administered with concurrent tacrolimus (2 mg b.i.d.) and prednisolone (5 mg daily). While there were no significant complications, the patient attained no therapeutic response in this setting. Overall, the use of checkpoint inhibitors in organ transplantation is not yet fully characterized; in particular, the outcomes of combination therapy are undefined.

Those with HIV and viral hepatitis B/C (HCV/HBV) infections have traditionally been excluded from immunotherapy clinical trials in melanoma, and the published experience is limited. Ravi *et al.* described a series of nine patients with melanoma treated with ipilimumab who had either HCV or HBV co-infections with hepatoxicity rates comparable to the known toxicity profile of ipilimumab [20]. Davar *et al.* reported two cases of patients with melanoma treated with pembrolizumab [21]. The first patient with HCV demonstrated no viral exacerbations during anti-PD-1 therapy. The second patient was co-infected with both HCV and HIV, which were well controlled via HCV antiviral treatment, prior to pembrolizumab and continuous antiviral therapy for HIV, and experienced no significant viral load increase. Interestingly, the role of anti-PD-1 blockade has been evaluated in a randomized trial for the treatment of chronic hepatitis C [22], with suggestion of viral suppression efficacy for a proportion of patients. Ongoing studies (NCT02576509, NCT02595866) are assessing nivolumab in advanced hepatocellular carcinoma in the setting of hepatitis B/C and pembrolizumab in the setting of advanced malignancy for those with HIV. No reports of combination checkpoints used in both HCV/HBV and HIV have been published.

Consideration of brain metastases

Clinical activity of immune checkpoint inhibitors, both as single agents and in combination has been demonstrated in Phase II trials for melanoma brain metastases (BM). In term of single agent efficacies, in a cohort of 72 patients, 51 with both asymptomatic BM and 21 on stable doses of steroids were treated with ipilimumab in an open-label Phase II study [23]. After 12 weeks of treatment, intracranial disease control rates were 24 and 10%, respectively. Pembrolizumab given at 10 mg/kg was trialed in an open-label Phase II study involving 18 melanoma patients with melanoma BM, with 22% achieving a partial response [24]. Results from two Phase II studies addressing the question of intracranial efficacy for combination therapy have been recently reported. First, in a three-arm study of 76 patients, 53 with asymptomatic BM and no prior local therapy were randomized in a 1:1 fashion to nivolumab only (n = 33, dosed at 3 mg/kg every 2 weeks) versus nivolumab (n = 27, dosed at 1 mg/kg every 3 weeks, then 3 mg/kg every 2 weeks) with ipilimumab (3 mg/kg every 3 weeks, 4 doses) [25]. The third arm included 16 patients with either symptomatic or leptomeningeal disease or prior failure of local therapy, and were treated with nivolumab alone. In the treatment-naive (systemic and intracranial local therapy) cohort, combination therapy demonstrated a 50% intracranial response rate, and 21% for nivolumab alone. Of note is the low efficacy for those previously treated with targeted therapies (16% in both groups) as well as those with disease refractory

"Both anti-PD-1 and combination immunotherapy have improved patient outcomes beyond traditional chemotherapeutics, with high response rates and durable responses."

to prior local treatment, symptomatic or leptomeningeal disease (6%). CheckMate 204 is a Phase II single-arm efficacy and safety study of combination therapy in patients with asymptomatic BM [26]. Tawbi *et al.* reported a similar intracranial response rate of 55%. Overall, the current evidence suggests an increased intracranial efficacy for combination therapy compared with single agent.

Conclusion

Both anti-PD-1 and combination immunotherapy have improved patient outcomes beyond traditional chemotherapeutics, with high response rates and durable responses. Beyond survival end points reported in clinical trials, the choice of therapy should be considered in the context of clinically relevant disease characteristics such as LDH, tempo and critical sites of disease weighed up against the pros and cons of each approach. Clearly the volume, pace and symptoms of BM would contribute to the overall clinical picture. A balanced assessment of potential tolerance for the increased toxicities of combination therapy, and taking into account 'at-risk' characteristics is needed in the therapeutic recommendation. Cumulative clinical trials, prospective registry data, retrospective case and cohort studies will all be important in guiding treatment decisions in the 'real-world' setting.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Hodi FS, O'Day SJ, McDermott DF *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* 363(8), 711–723 (2010).

2 Robert C, Thomas L, Bondarenko I *et al.* Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N. Engl. J. Med.* 364(26), 2517–2526 (2011).

3 Robert C, Schachter J, Long G *et al.* Pembrolizumab versus ipilimumab in advanced melanoma. *N. Engl. J. Med.* 372(26), 2521–2532 (2015).

4 Robert C. Long-term outcomes in patients with ipilimumab-naive advanced melanoma in the Phase III KEYNOTE-006 study who completed pembrolizumab treatment. Presented at: *ASCO Annual Meeting 2017.* Chicago, IL, USA, 2–6 June 2017.

5 Larkin J. Overall survival (OS) results from a Phase III trial of nivolumab (NIVO) combined with ipilimumab (IPI) in treatment-naive patients with advanced melanoma (CheckMate 067). Presented at: *AACR Annual Meeting 2017.* Washington, MA, USA, 1–4 April 2017.

6 Larkin J, Chiarion-Sileni V, Gonzalez R *et al.* Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N. Engl. J. Med.* 373, 23–34 (2015).

7 Postow MA, Chesney J, Pavlick AC *et al.* Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N. Engl. J. Med.* 372(21), 2006–2017 (2015).

8 D'Angelo SP, Larkin J, Sosman JA *et al.* Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: a pooled analysis. *J. Clin. Oncol.* 35(2), 226–235 (2017).

9 Bowyer S, Prithviraj P, Lorigan P *et al.* Efficacy and toxicity of treatment with the anti-CTLA-4 antibody ipilimumab in patients with metastatic melanoma after prior anti-PD-1 therapy. *Br. J. Cancer.* 114(10), 1084–1089 (2016).

10 Diem S, Kasenda B, Martin-Liberal J *et al.* Prognostic score for patients with advanced melanoma treated with ipilimumab. *Eur. J. Cancer* 51(18), 2785–2791 (2015).

11 Zimmer L, Apuri S, Eroglu Z *et al.* Ipilimumab alone or in combination with nivolumab after progression on anti-PD-1 therapy in advanced melanoma. *Eur. J. Cancer* 75, 47–55 (2017).

12 Menzies AM, Johnson DB, Rmanujam S *et al.* Anti-PD-1 therapy in patients with advanced melanoma and pre-existing autoimmune disorders or major toxicity with ipilimumab. *Ann. Oncol.* 28(2), 368–376 (2017).

13 Johnson DB, Sullivan RJ, Ott PA *et al.* Ipilimumab therapy in patients with advanced melanoma and pre-existing autoimmune disorders. *JAMA Oncol.* 2(2), 234–240 (2016).

14 Morales RE, Shoushtari AN, Walsh MM *et al.* Safety and efficacy of ipilimumab to treat advanced melanoma in the setting of liver transplantation. *J. Immunother. Cancer* 3, 22 (2015).

15 Ranganath HA, Panella TJ. Administration of ipilimumab to a liver transplant recipient with unresectable metastatic melanoma. *J. Immunother. Cancer* 38(5), 211 (2015).

16 Lipson EJ, Bodell MA, Kraus ES *et al.* Successful administration of ipilimumab to two kidney transplantation patients with metastatic melanoma. *J. Immunother. Cancer* 32(19), e69–e71 (2014).

17 Jose A, Yiannoullou P, Bhutani S *et al.* Renal allograft failure after ipilimumab therapy for metastatic melanoma: a case report and review of the literature. *Transplant Proc.* 48(9), 3137–3141 (2016).

18 Spain L, Higgins R, Gopalakrishnan K *et al.* Acute renal allograft rejection after immune checkpoint inhibitor therapy for metastatic melanoma. *Ann. Oncol.* 27(6), 1135–1137 (2016).

19 Herz S, Hofer T, Papapanagiotou M *et al.* Checkpoint inhibitors in chronic kidney failure and an organ transplant recipient. *Eur. J. Cancer.* 67, 66–72 (2016).

20 Ravi S, Spencer K, Ruisi M *et al.* Ipilimumab administration for advanced melanoma in patients with pre-existing hepatitis B or C infection: a multicenter, retrospective case series. *J. Immunother. Cancer* 2(1), 33 (2014).

21 Davar D, Wilson M, Pruckner C *et al.* PD-1 blockade in advanced melanoma in patients with hepatitis C and/or HIV. *Case Rep. Oncol. Med.* 2015, 737389 (2015).

22 Gardiner D, Lalezari J, Lawitz E *et al.* A randomized, double-blind, placebo-controlled assessment of BMS-936558, a fully human monoclonal antibody to programmed death-1 (PD-1), in patients with chronic hepatitis C viral infection. *PLoS ONE* 8(5), e63818 (2013).

23 Margolin K, Ernstoff M, Hamid O *et al.* Ipilimumab in patients with melanoma and brain metastases: and open-label, Phase II trial. *Lancet Oncol.* 13(5), 459–465 (2012).

24 Goldberg S, Gettinger S, Mahajan A *et al.* Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: an early analyses of an unrandomised, open-label Phase II study. *Lancet Oncol.* 17(7), 976–983 (2016).

25 Long GV *et al.* A randomized Phase II study of nivolumab and nivolumab combined with ipilimumab in patients (pts) with melanoma brain metastases: the Anti-PD1 Brain Collaboration (ABC Study). Presented at: *ASCO Annual Meeting 2017.* Chicago, IL, USA, 2–6 June 2017.

26 Tawbi H *et al.* Efficacy and safety of nivolumab plus ipilimumab in patients with melanoma metastatic to the brain: results of the Phase II study CheckMate 204. Presented at: *ASCO Annual Meeting 2017.* Chicago, IL, USA, 2–6 June 2017.