Utility of ipilimumab in melanoma patients who progress on anti-PD-1 therapy

“Metastatic melanoma has been historically associated with a poor prognosis; however, the therapeutic landscape has recently changed with rapid advances in the field of immune therapy.”

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First draft submitted: 6 April 2017; Accepted for publication: 10 May 2017; Published online: 26 July 2017

Metastatic melanoma has been historically associated with a poor prognosis; however, the therapeutic landscape has recently changed with rapid advances in the field of immune therapy. CTLA-4 was first identified as a crucial negative regulator of the immune system over 25 years ago [1] and in 1996 scientists from the University of California at Berkeley showed that *in vivo* administration of antibodies to CTLA-4 resulted in tumor rejection, suggesting that blockade of the inhibitory effects of CTLA-4 can potentiate immune responses against tumor cells and giving birth to the concept of ‘immune checkpoint blockade’ [2]. Another approach to activate the immune response involves PD-1, an immunoinhibitory receptor expressed on activated T cells that interact with its ligands PD-L1 and PD-L2 expressed on tumor cells to limit T-cell activity. Blocking the PD-1/PD-L1 pathway removes the inhibition of T-cell activation and leads to an enhanced anti-tumor immune response [3]. Ipilimumab, a

monoclonal antibody that targets CTLA-4, was approved by the US FDA in 2011 after Phase III data showed improved survival in patients with metastatic melanoma [4]. Pembrolizumab and nivolumab, monoclonal antibodies against PD-1, have proven superior to cytotoxic chemotherapy and also received FDA approval in 2014 for treatment-refractory patients [5,6].

Multiple prospective Phase III studies have demonstrated the superiority of anti-PD1 agents over ipilimumab in patients with metastatic melanoma [7,8]. In the first study, KEYNOTE-006, previously untreated patients with metastatic melanoma were randomized to either two different doses of pembrolizumab or ipilimumab [7]. In this study, patients who received pembrolizumab had improved objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). In the second study, CheckMate-067, previously untreated patients with metastatic melanoma were randomized to nivolumab, ipilimumab, or

KEYWORDS

- anti-CTLA-4 • anti-PD-1
- immunotherapy • ipilimumab
- metastatic melanoma
- nivolumab • pembrolizumab

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ipilimumab and nivolumab. The patients randomized to nivolumab or ipilimumab/nivolumab arms had superior ORR, PFS and OS when compared with ipilimumab. Based on the results of both of these studies, anti-PD-1 therapy alone or in combination with ipilimumab is the standard of treatment while single agent ipilimumab is no longer a recommended front-line agent for patients with metastatic melanoma.

In the front line, approximately 40% of patients with metastatic melanoma will achieve a partial or complete response to anti-PD1 agents, which unfortunately leaves the majority of patients in need of an option in the second line. At present, there is no prospective data published on the efficacy of ipilimumab in patients who progress on anti-PD1. A review of the literature identified four peer-reviewed retrospective case series and one presentation at an annual meeting reporting on the use of ipilimumab in patients with melanoma who had progressed on anti-PD1 agents.

In the first retrospective study, Jacobsoone-Ulrich *et al.* reported on eight patients with metastatic melanoma who progressed on anti-PD1 agents [9]. In this series, four out of eight patients (50%) achieved a response: three showed a complete response and one showed a partial response. In the second retrospective study, Bowyer *et al.* reviewed a cohort of 40 patients with metastatic melanoma treated with ipilimumab as the next treatment after progression on anti-PD1. Here, 4/40 patients (10%) achieved an objective response to ipilimumab, and an additional three patients (8%) experienced prolonged stable disease for more than 6 months [10]. In the third retrospective study, Aya *et al.* reported on nine patients who received ipilimumab after progression on anti-PD1 agents with a partial response occurring in two out of nine patients (22%) [11].

At the 2016 Society of Melanoma Research Annual Meeting, Long *et al.* presented the largest retrospective experience of the efficacy of ipilimumab after progression on front line pembrolizumab [12]. This presentation reviewed the experience of patients on KEYNOTE-006, which was a front-line study of patients with metastatic melanoma who were randomized to receive either pembrolizumab at two different doses or ipilimumab [7]. In this study, patients who received either dose of pembrolizumab did better than patients who received ipilimumab, thus establishing pembrolizumab as the new standard of care in front line metastatic melanoma. Despite the clinical success in patients

treated with front line pembrolizumab (n = 555), approximately 40% (n = 219) of patients who received pembrolizumab went on to receive additional treatments and of these patients, approximately 59% (n = 129) received ipilimumab with 75% (n = 97) receiving ipilimumab in the second line immediately following progression on pembrolizumab. In this cohort of 97 patients who received ipilimumab as the next therapy after progression on front-line pembrolizumab, there were 3% complete remissions, 10% partial remissions, 32% with stable disease, 32% with progressive disease and 23% unknown. In the 57 patients where survival data is known, the median overall survival from the time of randomization for the patients was 19.0 months.

More recently, a retrospective study by Zimmer *et al.* evaluated the efficacy of ipilimumab alone or in combination with nivolumab in patients who progressed on prior anti-PD-1 monotherapy. In this multicenter study, 47 patients that received ipilimumab after anti-PD-1 treatment failure had an ORR of 16%, a disease control rate of 42% and a 1-year survival rate of 54% [13]. These response rates are comparable to those of treatment naive patients. In contrast, the combination of ipilimumab and nivolumab after progression on prior anti-PD-1 therapy showed an ORR of only 21% compared with 58% reported in treatment-naïve patients [8].

In summary, while there are no prospective trials to assess the efficacy of ipilimumab in patients with metastatic melanoma who progress on front line anti-PD1 agents, we can surmise that approximately 10–20% of patients will achieve a response to second-line ipilimumab. Given this information, we believe ipilimumab should be considered as a viable treatment option for patients who progress on front line anti-PD1 agents.

Financial & competing interests disclosure

Dr RW Joseph is in the advisory/consulting boards for BMS, Merck, Exelixis, Incyte and Novartis. He has performed clinical trials with BMS, Merck, Roche, Amgen, X4P and Syndax. The authors have no other 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 Waterhouse P, Penninger JM, Timms E *et al.* Lymphoproliferative disorders with early lethality in mice deficient in CTLA-4. *Science* 270(5238), 985–988 (1995).
- 2 Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science* 271(5256), 1734–1736 (1996).
- 3 Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat. Rev. Cancer* 12(4), 252–264 (2012).
- 4 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).
- 5 Webber JS, D'Angelo SP, Minor D *et al.* Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomized, controlled, open-label Phase III trial. *Lancet Oncol.* 16(4), 375–384 (2015).
- 6 Ribas A, Puzanov I, Dummer DR *et al.* Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomized, controlled, Phase II trial. *Lancet Oncol.* 16(8), 908–918 (2015).
- 7 Robert C, Schachter J, Long GV *et al.* Pembrolizumab versus ipilimumab in advanced melanoma. *N. Engl. J. Med.* 372(26), 2521–2532 (2015).
- 8 Larkin J, Hodi FS, Wolchok JD. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N. Engl. J. Med.* 373(13), 1270–1271 (2015).
- 9 Jacobsoone-Ulrich A, Jamme P, Alkeraye S *et al.* Ipilimumab in anti-PD1 refractory metastatic melanoma: a report of eight cases. *Melanoma Res.* 26(2), 153–156 (2016).
- 10 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).
- 11 Aya F, Gaba L, Victoria I *et al.* Ipilimumab after progression on anti-PD-1 treatment in advanced melanoma. *Future Oncol.* 12(23), 2683–2688 (2016).
- 12 Long GV, Robert C, Arance A *et al.* Outcomes in patients treated with ipilimumab after pembrolizumab in KEYNOTE-006. *Society of Melanoma Research 2016 Congress*. Boston, MA, USA, 2016.
- 13 Zimmer L, Appuri 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).