Are PD-1 antibodies safe for use in metastatic uveal melanoma?

Katy K Tsai^{*1}

Alain P Algazi¹

“...patients with uveal melanoma have been historically excluded from the pivotal Phase III trials leading to approval of ipilimumab, pembrolizumab and nivolumab...”

First draft submitted: 17 March 2017; Accepted for publication: 4 April 2017; Published online: 10 May 2017

If we think back to the days of first-line chemotherapy for metastatic melanoma, it is easy to see how the development of molecularly targeted therapies and new immunotherapies have injected fresh optimism into the systemic treatment of melanoma. Targeted therapies blocking *BRAF* and *MEK* are indicated for the roughly 50% of patients with cutaneous melanomas (CM) harboring *BRAF* V600 mutations [1] and have shown high response rates of up to 70% and demonstrable survival benefit with 3-year overall survival (OS) rate of 45% [2]. Immune checkpoint inhibitors with antibodies against PD-1 (pembrolizumab and nivolumab) have demonstrated efficacy independent of *BRAF* mutation status and have been approved to be given for advanced melanoma either as monotherapy [3–5] or in combination with a CTLA-4 antibody (ipilimumab) [6,7]. Response rates with PD-1 monotherapy are as high as 40%, with 3-year OS rate reported at 40% [8].

While these data have been practice changing, none of the above breakthroughs

seem to apply to uveal melanoma (UM). UM arises from melanocytes in the uvea (comprised of the iris, ciliary body and choroid plexus) – but there, its similarities with CM end. UM is a rare form of melanoma, representing only 3–5% of the incidence of its cutaneous counterpart [9]. Its molecular pathogenesis is quite different, with genetic alterations found in *GNAQ* or *GNAI1* [10] rather than in *BRAF* [11] and its clinical behavior is also distinct: it has a propensity for liver and lung metastasis rather than locoregional spread. While localized disease can be managed with surgery or proton beam radiation therapy, metastasis is common and approximately 50% of patients go on to develop distant disease within 15 years of their initial diagnosis [12]. Outcomes for patients with metastatic disease are uniformly poor, with median OS of about 12 months [13]. Due to these biological differences, patients with UM have been historically excluded from the pivotal Phase III trials leading to approval of ipilimumab, pembrolizumab and nivolumab, and prospective data

KEYWORDS

- atezolizumab • immunotherapy
- nivolumab • PD-1 • PD-L1
- pembrolizumab • safety • toxicity
- uveal melanoma

¹Melanoma Center, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, 1600 Divisadero Street, San Francisco, CA 94115, USA

^{*}Author for correspondence: katy.tsai@ucsf.edu

“In the case of uveal melanoma, the benefits anticipated for any given patient treated with immunotherapy are modest, though arguably clinically meaningful in a proportion of patients who otherwise have no approved treatment options.”

describing the safety and efficacy of immune checkpoint inhibition in UM remain very limited. Despite this limitation, first-line treatment with pembrolizumab or nivolumab plus ipilimumab is widely used, with clinicians in many cases extrapolating from the outcomes of these drugs for CM, as well as due to the current lack of better standard of care options for metastatic UM. Here, we explore whether this approach is warranted from a safety perspective.

While Phase III studies of PD-1 monotherapy in CM (NCT01866319, NCT01721772, NCT01721746 and NCT01844505) have been shown to result in objective response in 30–40% of patients and with a favorable toxicity profile (grade 3–4 adverse events [AEs] occurring in 7–16%) [3–6], data regarding anti-PD-1 use specifically in UM patients remains limited to retrospective series at this time. One case series of ten patients treated with pembrolizumab reported three cases (33%) of grade 3–4 toxicities, including liver enzyme elevation, adrenal insufficiency and hyperbilirubinemia. Three of ten patients (33%) were noted to have objective response [14]. Another case series of 25 patients treated with pembrolizumab on an expanded access program noted 5 cases (20%) of grade 3–4 AEs leading to treatment discontinuation [15]. These AEs included grade 4 transaminitis and grade 3 skin rash, pruritus, hypophysitis, diarrhea and fatigue; objective responses were rare, with only 2 of 25 patients (8%) achieving partial response. The largest case series to date contains 56 patients treated with pembrolizumab, nivolumab and atezolizumab at various doses and described 25 cases (46%) with grade 1–2 AEs, 7 (13%) with grade 3 AEs and none with grade 4–5 AEs [16]. Grade 3 AEs reported by investigators included nausea, vomiting, hyperbilirubinemia, fatigue, colitis, arthralgia and lymphopenia. Only one patient discontinued treatment due to toxicity (arthralgia). Response outcomes were similarly poor, with objective response observed in only two (3.6%) patients, with median OS of 7.6 months.

How does this compare to ipilimumab? Ipilimumab was approved for advanced melanoma in 2011 and evolving Phase III data (NCT00094653, NCT01844505 and NCT01515189) have shown it to induce objective responses in CM of 11–19% [6,17–18] with an estimated 3-year OS rate of 23% [18]. The incidence of grade 3 AEs in CM patients

treated with ipilimumab has been reported to be as high as 27% [6]. As ipilimumab was developed and has been in clinical use for a longer period than pembrolizumab or nivolumab, the body of data regarding its use in metastatic UM is comparatively more robust. Several expanded access programs of ipilimumab for metastatic UM have reported incidence of grade 3–4 AEs between 10 and 22% (colitis, diarrhea and hepatitis), albeit with rare objective responses [19–22]. A large retrospective series of ipilimumab in 39 metastatic UM patients resulted in objective response in only two patients and median OS of 9.6 months. Twenty-one patients (54%) had grade 1–2 AEs, while 7 (18%) had grade 3–4 AEs consisting of hypophysitis, hepatitis, pancreatitis, uveitis and colitis [23]. All patients who required systemic steroids for management experienced symptom resolution without recurrence after steroid taper. An abstract from a second, smaller retrospective study did not detail adverse effects, but described similarly poor outcomes including median OS of 9.7 months in a cohort of 24 patients [24]. From a Phase II trial of ipilimumab 3 mg/kg in metastatic uveal melanoma patients (NCT01355120), prospective data support similar findings: 0 of 53 patients had objective response, 2-year OS rate was 7% and safety data showed 16 patients (30%) with grade 1–2 AEs and 19 patients (36%) with grade 3–4 AEs [25]. Grade 3–4 AEs were diarrhea, colitis and transaminitis. There was one possible treatment-related death in the setting of pancytopenia with subsequent cerebral hemorrhage and respiratory insufficiency. An abstract from a second Phase II study of ipilimumab 10 mg/kg (EudraCT 2010–024415–4) in 32 patients reported 15 patients (47%) with grade 3–4 AEs (abdominal pain, hypophysitis, emesis, diarrhea, asthenia, proctalgia, bone pain, urinary tract infection, hepatotoxicity, multi-organ failure, altered state of consciousness and vascular compression) [26]. Responses were similarly modest, with one partial response and six patients with stable disease at a median follow-up of 5.5 months.

In summary, currently published data suggest that grade 3–4 AEs occur in 13–33% of the metastatic UM patients treated with anti-PD-1/PD-L1 monotherapy [14–16] and in 10–22% [19–22] (or in up to 36–46% in prospective studies) of those treated with ipilimumab [25,26]. Objective responses to immune checkpoint inhibition remain rare. PD-1-based

therapies as single agents can thus be viewed as helpful in the management of metastatic UM: in the absence of prospective data, the PD-1 antibodies seem to be better tolerated than ipilimumab. Any discussion of therapeutic risk must be framed, however, in the context of potential benefit. In the case of UM, the benefits anticipated for any given patient treated with immunotherapy are modest, though arguably clinically meaningful in a proportion of patients who otherwise have no approved treatment options. Thus, one could make a case that treatment with a PD-1 antibody with a favorable side effect profile may be acceptable whereas ipilimumab, known to induce more severe autoimmunity, may not be. However, this risk-benefit analysis does not take into account the extreme needs of patients with advanced UM for more effective therapies and perhaps a better strategy might be to pursue aggressive combination therapies on clinical trials until better strategies are identified.

How best to go about this is a point of debate. While many have called for the inclusion of UM in the forthcoming melanoma trials, a more rational design might include dedicating separate studies to UM given its unique molecular and clinical characteristics. We are humbly reminded that melanoma remains a heterogeneous disease; while UM is quite distinct from CM, it is not alone – overall response rates in desmoplastic melanoma to anti-PD-1 monotherapy, for example, may be twice as

high as those seen for nondesmoplastic lesions [27] and the tumor microenvironment may be the key to understanding these differences [28].

The limitations of approved immunotherapies in UM underscore the constraints of traditional tumor classification systems based on histology and site of origin. The key to surpassing these limitations may instead lie in a deeper understanding of the roles of mutational burden, microenvironment and other aspects of immunogenicity associated with each tumor type. Rather than respecting the boundaries of histology, disrupting those boundaries and moving forward with intensive biomarker research, investigations into tumor immunogenicity and research into the underlying mechanisms of immune escape are likely to hold the answers to improving therapeutic strategies for metastatic uveal melanoma.

Financial & competing interests disclosure

KK Tsai reports clinical trial support from Roche and Takeda, outside the submitted work. AP Algazi reports grants for clinical trial support from Merck, Bristol-Myers Squibb, Medimmune, AstraZeneca, Oncosec, Acerta, Novartis and GlaxoSmithKline, outside the submitted work. 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 apart from those disclosed.

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

References

- McArthur GA, Ribas A. Targeting oncogenic drivers and the immune system in melanoma. *J. Clin. Oncol.* 31(4), 499–506 (2013).
- Robert C, Karaszewska B, Schachter J *et al.* Three-year estimate of overall survival in COMBI-v, a randomized Phase III study evaluating first-line dabrafenib (D) + trametinib (T) in patients (pts) with unresectable or metastatic BRAF V600E/K-mutant cutaneous melanoma. *Ann. Oncol.* 27(Suppl. 6), LBA40 (2016).
- Robert C, Schachter J, Long GV *et al.* Pembrolizumab versus ipilimumab in advanced melanoma. *N. Engl. J. Med.* 372(26), 2521–2532 (2015).
- Weber 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 randomised, controlled, open-label, Phase III trial. *Lancet Oncol.* 16(4), 375–384 (2015).
- Robert C, Long GV, Brady B *et al.* Nivolumab in previously untreated melanoma without BRAF mutation. *N. Engl. J. Med.* 372(4), 320–330 (2014).
- Larkin J, Chiarion-Sileni V, Gonzalez R *et al.* Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N. Engl. J. Med.* 373(1), 23–34 (2015).
- 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).
- Robert C, Ribas A, Hamid O *et al.* Three-year overall survival for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. *J. Clin. Oncol.* 34, Abstract 9503 (2016).
- Singh AD, Topham A. Incidence of uveal melanoma in the United States: 1973–1997. *Ophthalmology* 110(5), 956–961 (2003).
- Van Raamsdonk CD, Bezrookove V, Green G *et al.* Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. *Nature* 457(7229), 599–602 (2009).
- Davies H, Bignell GR, Cox C *et al.* Mutations of the *BRAF* gene in human cancer. *Nature* 417(6892), 949–954 (2002).
- Kujala E, Mäkitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. *Invest. Ophthalmol. Vis. Sci.* 44(11), 4651–4659 (2003).
- Rietschel P, Panageas KS, Hanlon C, Patel A, Abramson DH, Chapman PB. Variates of survival in metastatic uveal melanoma. *J. Clin. Oncol.* 23(31), 8076–8080 (2005).
- Kottschade LA, McWilliams RR, Markovic SN *et al.* The use of pembrolizumab for the

- treatment of metastatic uveal melanoma. *Melanoma Res.* 26(3), 300–303 (2016).
- 15 Karydis I, Chan PY, Wheeler M, Arriola E, Szlosarek PW, Ottensmeier CH. Clinical activity and safety of pembrolizumab in ipilimumab pre-treated patients with uveal melanoma. *OncoImmunology* 5(5), e1143997 (2016).
- 16 Algazi AP, Tsai KK, Shoushtari AN *et al.* Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies. *Cancer* 122(21), 3344–3353 (2016).
- 17 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).
- 18 Ascierto PA, Del Vecchio M, Robert C *et al.* Overall survival and safety results from a Phase III trial of ipilimumab at 3 mg/kg vs 10 mg/kg in patients with metastatic melanoma. Presented at: *The European Society for Medical Oncology 2016 Congress*. Copenhagen, Denmark, 7–11 October 2016 (Abstract 11060).
- 19 Kelderman S, Kooij van der MK, Eertwegh van den AJM *et al.* Ipilimumab in pretreated metastatic uveal melanoma patients. Results of the Dutch Working group on Immunotherapy of Oncology (WIN-O). *Acta Oncol.* 52(8), 1786–1788 (2013).
- 20 Khattak MA, Fisher R, Hughes P, Gore M, Larkin J. Ipilimumab activity in advanced uveal melanoma. *Melanoma Res.* 23(1), 79–81 (2013).
- 21 Danielli R, Ridolfi R, Chiarion-Sileni V *et al.* Ipilimumab in pretreated patients with metastatic uveal melanoma: safety and clinical efficacy. *Cancer Immunol. Immunother.* 61(1), 41–48 (2012).
- 22 Maio M, Danielli R, Chiarion-Sileni V *et al.* Efficacy and safety of ipilimumab in patients with pre-treated, uveal melanoma. *Ann. Oncol.* 24(11), 2911–2915 (2013).
- 23 Luke JJ, Callahan MK, Postow MA *et al.* Clinical activity of ipilimumab for metastatic uveal melanoma. *Cancer* 119(20), 3687–3695 (2013).
- 24 Deo MA. Long-term survival benefit from ipilimumab treatment in metastatic uveal melanoma patients. *J. Clin. Oncol.* 32(Suppl. 5s), Abstract 3060 (2014).
- 25 Zimmer L, Vaubel J, Mohr P *et al.* Phase II DeCOG-study of ipilimumab in pretreated and treatment-naïve patients with metastatic uveal melanoma. *PLoS ONE* 10(3), e0118564 (2015).
- 26 Rodriguez JMP, Olza MO de, Codes M *et al.* Phase II study evaluating ipilimumab as a single agent in the first-line treatment of adult patients (Pts) with metastatic uveal melanoma (MUM): the GEM-1 trial. *J. Clin. Oncol.* 32 (Suppl. 5s), Abstract 9033 (2014).
- 27 Eroglu Z, Kim DW, Johnson DB *et al.* Response to anti-PD1/PDL1 therapy in patients with metastatic desmoplastic melanoma. *J. Clin. Oncol.* 33, Abstract 9011 (2015).
- 28 Frydenlund N, Leone D, Yang S *et al.* Tumoral PD-L1 expression in desmoplastic melanoma is associated with depth of invasion, tumor-infiltrating CD8 cytotoxic lymphocytes and the mixed cytomorphological variant. *Mod. Pathol.* 30(3), 357–369 (2017).