Improving clinical outcomes with pembrolizumab in patients with advanced melanoma

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Provenance: This is a Guest Editorial commissioned by Section Editor Bin Lian, MD, (Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China).

Comment on: Ribas A, Hamid O, Daud A, *et al.* Association of Pembrolizumab With Tumor Response and Survival Among Patients With Advanced Melanoma. JAMA 2016;315:1600-9.

Submitted Nov 27, 2016. Accepted for publication Nov 29, 2016.

doi: 10.21037/cco.2017.01.04

View this article at: http://dx.doi.org/10.21037/cco.2017.01.04

The discovery of key regulators of T cell response and the development of checkpoint inhibitors have rapidly changed the treatment landscape of metastatic melanoma. Pembrolizumab is the first PD-1 blockade agent approved by the U.S. Food and Drug Administration (FDA) following a large phase Ib study which demonstrated clinical efficacy of pembrolizumab in patients with metastatic melanoma refractory to ipilimumab (1). Recently, an analysis of pooled data was reported from 655 patients with advanced melanoma enrolled in this open-label multicohort phase Ib study (KEYNOTE-001); the aim was to assess long term clinical outcomes with pembrolizumab (2). Among the heterogeneous 655 patients in the study, 173 were included in the randomized dose comparison cohort with ipilimumab refractory disease (1), 135 were included in the nonrandomized cohort (3), and 347 were not included in prior reports. Overall, 152 patients were received no prior therapy, 342 had prior ipilimumab and 110 had prior BRAF and/or MEK inhibitors. Pembrolizumab was well tolerated with 14% rate of grade 3–4 toxicities, and no significant differences in toxicity were observed between ipilimumab naïve and ipilimumab treated cohorts. The objective response rates (ORR) and the median overall survival (OS) was 33% and 23 months in the total population, and 45% and 31 months in the treatment naïve patients. Among all responders, 44% had response duration for at least 1 year. This study confirmed the safety and efficacy of pembrolizumab in patients with advanced melanoma. In particular the duration of response and survival data of this analysis suggests that the durable clinical responses with pembrolizumab may be at least similar to high dose interleukin 2 (4) and ipilimumab (5) treatment in patients with advanced melanoma. The clinical activity of pembrolizumab reported in the study is also similar with nivolumab, another anti-PD-1 antibody which demonstrated a 40% of ORR in previously untreated patients with advanced melanoma (6).

While this study confirmed the remarkable clinical activity of pembrolizumab in patients with advanced melanoma, there are some limitations to pembrolizumab's efficacy. Approximately, 50% of all patients did not have clinical benefit from pembrolizumab treatment, and 26% of the responders developed disease progression in the KEYNOTE-001 study. Various biomarkers and tumor characteristics to predict clinical response have been evaluated for appropriate selection of patients most likely and least likely to benefit from immune checkpoint blockade treatment including pembrolizumab. Several biomarkers have been suggested for checkpoint inhibitors including preexisting CD8 T cells in tumor (7), high tumor mutational loads (8), neoantigen heterogeneity (9), tumor T cell clonality and T cell fraction (10), mutations in the DNA repair gene BRCA2 (8), high relative eosinophil count (11), high relative lymphocyte count (11), low LDH (11) and absence of metastasis other than soft tissue and lung (11). In the KEYNOTE-001 study, normal LDH, stage IV (M1b) disease and small baseline tumor size (median <102 mm) were associated with higher response rates (42–56%) than

observed in patients without these characteristics (22–29%). A subsequent analysis of KEYNOTE-001 examined likelihood of durable responses in patients with elevated LDH (>1×ULN) at baseline. While not surprisingly an elevated LDH decreased the ORR (42.3% with normal LDH *vs.* 20.6% for elevated LDH), patients with elevated baseline LDH who respond to pembrolizumab nevertheless had long duration of response (median 34.6 months), overlapping the duration of patients with normal baseline LDH (12).

Compared to cutaneous melanomas, less common subtypes of melanoma such as mucosal melanoma were also found to have lower response rates (ORR of 19%) and shorter median PFS (2.8 months) in another pooled analysis that included KEYNOTE-001, along with KEYNOTE-002 (phase 2 trial of patients randomized to pembrolizumab *vs.* chemotherapy) and KEYNOTE-006 (phase 3 trial of patients randomized to pembrolizumab *vs.* ipilimumab) (13). In a retrospective analysis of 470 patients treated with pembrolizumab, the likelihood of progression on pembrolizumab was also noted to significantly decrease with increasing age in patients, which may be accounted by differences in infiltrating immune cells between the aged and young tumor microenvironment (14). As such, a large number of variables such as tumor type, size, age, and LDH, and additional ones such as BMI, microbiome, concurrent medications, etc. may need to be considered to understand outcomes seen in these immunotherapy clinical trials. While PD-L1 expression on tumor cells is routinely used in patients with metastatic non-small cell lung cancer as a biomarker for pembrolizumab treatment, this is not yet routine practice in patients with melanoma. PD-L1 data were not included in the KEYNOTE-001 study; regardless, other analyses have demonstrated that increased expression of PD-L1 on melanoma tumors measured via immunohistochemistry staining correlated with a higher response rate, longer progression free survival and longer OS with anti-PD-1 therapies (15). However, further studies are needed to delineate the role of PD-L1 expression in PD-1 inhibitor treatment for advanced melanoma, as durable responses are observed in patients with PD-L1 negative tumors; in addition there are different methods for PD-L1 staining or cut-off points for PD-L1 expression positivity, and tumor expression of PD-L1 may also be dynamic, depending upon changes in the tumor microenvironment.

Therefore, improving the clinical outcome in patients with anti-PD-1 therapy resistant tumors remains a challenge. Innate and acquired resistance mechanisms of PD-1 inhibitors have been extensively studied and suggested resistance mechanisms include: (I) constitutive activation of WNT/β-catenin signaling pathway leading to lack of T cell infiltration (16); (II) loss of PTEN increasing expression of immunosuppressive cytokines (17); (III) expression of indoleamine 2,3-dioxygenase (IDO) which suppresses effector T cells and activates regulatory T cells (18); (IV) a special transcriptional signature (upregulation of genes involving mesenchymal transition, cell adhesion, extracellular matrix remodeling, angiogenesis and wound healing) (8); (V) loss of function mutation in the genes encoding *Janus kinase 1* (*JAK1*) or *Janus kinase 2* (*JAK2*) resulting in insensitivity to the antiproliferative effects of interferon γ on cancer cells (19); (VI) mutation in the gene encoding beta 2 microglobulin leading to loss of expression of major histocompatibility complex (MHC) class I (19).

Currently, ipilimumab is a treatment option for patients who have progressed on anti-PD-1 therapies, with an ORR of 14% observed in 129 patients treated with ipilimumab after treatment with pembrolizumab in the KEYNOTE-006 trial, similar to ORR observed with front-line ipilimumab (20). Chemotherapy and high dose IL-2 remain the only other FDA-approved treatment options. With the improved understanding of resistance mechanisms, several combination approaches of anti-PD-1 antibodies with other therapeutic modalities are undergoing evaluation to overcome the resistance and improve clinical outcomes, as anti-PD-1 antibodies are combined with immune checkpoint targets such as Lag-3, TIM-3, OX-40, or CD137 agonists, or combined with talimogene laherparepvec, cancer vaccines or adoptive T cell therapies. As dual checkpoint inhibition with ipilimumab plus nivolumab has demonstrated promising clinical outcomes with improved ORR and prolonged PFS compared with nivolumab alone (21,22), ipilimumab is also undergoing studies in combination with pembrolizumab (23). Trials combining anti-PD-1 therapies with BRAF and MEK-inhibitor targeted therapies are also ongoing, given enhanced antitumor response following targeted inhibition, such as increases in melanoma antigen expression, CD8 T cell infiltration, PD-L1 expression, class I MHC upregulation, and decreased immunosuppressive cytokine production (24,25). Pembrolizumab and nivolumab are also moving to earlier stage melanomas, with several ongoing neoadjuvant and adjuvant clinical trials, as earlier-stage melanoma may have less systemic immune inhibition

compared to late-stage disease (26).

PD-1 blockade remains the most effective immunotherapy to date with durable clinical responses and relatively safe toxicity profiles. Despite the remarkable success of PD-1 blockade in metastatic melanoma however, the clinical activity is still limited in subgroups of patients, and studies are ongoing to try to improve clinical outcomes in patients with metastatic melanoma.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Kim DW, Zager JS, Eroglu Z. Improving clinical outcomes with pembrolizumab in patients with advanced melanoma. Chin Clin Oncol 2017;6(1):2. doi: 10.21037/cco.2017.01.04

