Editorial Commentary

Pembrolizumab for recurrent/metastatic head and neck cancer: equally promising for Asian patients?

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Provenance: This is an invited article commissioned by Guest Section Editor Hengrui Liang (Department of Thoracic Surgery, Guangzhou Medical University, Guangzhou, China).

Comment on: Tahara M, Muro K, Hasegawa Y, *et al.* Pembrolizumab in Asia-Pacific patients with advanced head and neck squamous cell carcinoma: Analyses from KEYNOTE-012. Cancer Sci 2018;109:771-6.

Submitted Jan 03, 2019. Accepted for publication Jan 18, 2019.
doi: 10.21037/atm.2019.01.46
View this article at: http://dx.doi.org/10.21037/atm.2019.01.46

Head and neck squamous cell carcinoma (HNSCC) is the fifth most common cancer worldwide, with more than half a million new cases every year (1). Over half of these originate from the Asia Pacific region, where HNSCC accounts for a much greater proportion of newly diagnosed cancers (2). While the annual incidence of HNSCC in North America and Europe ranges from 5–10% of new cancer cases, this figure may be as high as 37.5% in some areas of Asia (3). These epidemiologic differences are largely attributed to geographical variations in tobacco and alcohol exposure, which is implicated in up to 80% of HNSCC diagnoses worldwide (4). Other well-established risk factors include human papillomavirus (HPV) infection, betel nut chewing and Epstein-Barr (EBV) infection. Persistent infection with high risk HPV subtypes is responsible for the increasing incidence of oropharyngeal squamous cell carcinoma in many countries despite reductions in tobacco use (2). On the other hand, EBV-associated nasopharyngeal carcinoma (NPC), despite being from a similar cell/tissue lineage as other epithelial head and neck tumors, is a biologically distinct disease entity endemic to east and southeast parts of Asia (5). As a result, with the heavy burden of disease associated with head and neck malignancies in the Asia Pacific region, and the significant toxicities associated with platinum chemotherapy, there is a need for new and improved treatment modalities. Recent landmark trials on anti-programmed death-1 (PD-1) checkpoint inhibitors pembrolizumab and nivolumab in recurrent/metastatic HNSCC (KEYNOTE-012 and CHECKMATE-141 respectively) demonstrated promising clinical anti-tumor response, subsequently leading to Food and Drug Administration (FDA) approval for their use in recurrent or metastatic disease (6,7). Other ongoing clinical trials are exploring the use of checkpoint inhibitors in upfront therapy.

In a recent article by Tahara *et al.* in *Cancer Science*, the authors conducted a subgroup analysis of Asia-Pacific patients from the KEYNOTE-012 clinical trial expansion cohort (8). KEYNOTE-012, a phase Ib, study with multiple cohorts, investigated the safety and efficacy of pembrolizumab in advanced solid tumors (6). In the original cohort of 60 patients with programmed death ligand-1 (PD-L1) positive head and neck tumors, pembrolizumab was well-tolerated and effective, with 17% of patients experiencing grade 3–4 drug-related adverse events and an overall response rate (ORR) of 18% (25% of patients with HPV-related tumors and 14% in patients with HPV-negative tumors). An expansion cohort of 132 patients, enrolled regardless of PD-L1 status, demonstrated similar safety and efficacy profiles, with 9% of patients experiencing grade 3–4 drug-related adverse events and an ORR of 18% (9). In the Asia-Pacific subgroup analysis, Tahara *et al.* included a total of 26 patients enrolled from one of five

centers in the Asia Pacific region (8). When compared to the overall expansion and original cohorts, safety and efficacy measures in this subgroup analysis were similar, with 8% of patients experiencing grade 3 drug-related adverse events and an ORR of 19%. Furthermore, duration of response was not reached after a median follow-up of 12 months, with 80% of treatment responses still ongoing at data cut-off. Taken together, these data suggest that the safety and efficacy of pembrolizumab in advanced HNSCC is consistent in patients from the Asia Pacific region.

In this study, 19 (73%) patients were current or former smokers, and the vast majority of tumors were HPV-negative (92%) (8). In contrast, HPV-negative disease comprised 62% and 79% of tumors in the original and overall expansion cohorts respectively (6,9). Furthermore, primary tumor location in the oropharynx affected 15% of patients in the Asian subgroup *vs.* 27% and 45% in the original and overall expansion cohorts. These differences likely mirror the geographic variations in environmental exposures and risk factors, with higher rates of HPV-negative HNSCC in Asia compared with North America and Europe (10). In a similar study, Kiyota *et al.* conducted a subgroup analysis of Asian patients (n=34) in the CheckMate-141 phase III trial to evaluate nivolumab *vs.* investigator's choice in this population (11). Interestingly, they found an increased 9-month overall survival rate in Asian patients *vs.* the global population (76.7% *vs.* 43.4%) while 9-month progression-free survival rate was similar between the Asian and global groups (8.3% *vs.* 11.4% respectively). The authors suggest that the observed difference could be attributed to the increased percentage of patients in the Asian subgroup with PD-L1 positive tumors (62% *vs.* 55% in the entire study population) as well as to the increased frequency of subsequent therapy in the Asian population *vs.* overall study population. Importantly, this study was able to show that nivolumab, like pembrolizumab, was as effective in the Asian population as in the global population.

In addition to this, in the subgroup analysis by Tahara *et al.*, there were two cases (8%) of NPC, an EBV-associated cancer caused by a combination of viral, genetic and environmental factors (8,12). NPC has a distinct disease biology compared to other forms of HNSCC and a geographical predominance in Southeast Asia, making it a particularly important area of study in the Asia Pacific region. In the phase Ib KEYNOTE-028 trial, pembrolizumab was studied in 27 patients with PD-L1 positive recurrent/metastatic NPC (13). In this clinical trial, the ORR was 25.9%, suggesting that the promising antitumor activity of pembrolizumab in HNSCC trials also extends to patients with advanced NPC (6). As for the safety profile, although 29.6% of patients experienced grade 3+ drug-related adverse events, with one drug-related death (sepsis), the higher rate of drug-related adverse events compared to other trials in HNSCC was attributed to the trial patients having more advanced and/or treatment-resistant disease (6,13).

In conclusion, the findings from Tahara *et al.* attempted to address the question of whether the results from KEYNOTE-012 remain consistent across racial groups, particularly in patients from the Asia Pacific region. While the cohort of Asian patients is small, this study, along with the CheckMate-141 Asian subgroup analysis by Kiyota *et al.* and the NPC trial by Hsu *et al.*, solidifies the promising role of checkpoint inhibitors in the treatment of advanced head and neck malignancies in the Asian population. With the high incidence and burden of disease associated with head and neck cancers in Asia, this study reaffirms the potential that pembrolizumab and other immune therapies have in this region of the world. Additional analyses with larger sample sizes may be warranted in future studies to delineate more nuanced differences in treatment response for head and neck cancer in Asia.

Acknowledgements

None.

Footnote

Conflicts of Interest: NC Schmitt has received research funding from Astex Pharmaceuticals, which is not relevant to this submission. W Ye has no conflicts of interest to declare.

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Cite this article as: Ye W, Schmitt NC. Pembrolizumab for recurrent/metastatic head and neck cancer: equally promising for Asian patients? Ann Transl Med 2019;7(Suppl 1):S14. doi: 10.21037/atm.2019.01.46

