Editorial Commentary

Immunotherapy for head and neck cancer: where are we now and where are we going?

Joshua M. Bauml, Charu Aggarwal, Roger B. Cohen

Division of Hematology Oncology, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
Correspondence to: Joshua M. Bauml, MD. Perelman Center for Advanced Medicine, 10th Floor, 3400 Civic Center Blvd, Philadelphia, PA 19104, USA. Email: Joshua.bauml@uphs.upenn.edu.

Provenance: This is an invited article commissioned by Guest Section Editor Tao Shi (Clinical Cancer Institute of Nanjing University, Nanjing, China).

Comment on: Mehra R, Seiwert TY, Gupta S, *et al.* Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. Br J Cancer 2018;119:153-9.

Submitted Mar 06, 2019. Accepted for publication Mar 25, 2019.
doi: 10.21037/atm.2019.03.58
View this article at: http://dx.doi.org/10.21037/atm.2019.03.58

Head and neck squamous cell carcinoma (HNSCC) is a relatively common cancer (1). While many patients with locally advanced disease are cured with some combination of surgery, radiation, and chemotherapy, others will develop recurrent/metastatic disease (R/M) and are considered incurable. Cytotoxic chemotherapy has limited efficacy and substantial toxicity in metastatic HNSCC, with a median overall survival of less than a year (2).

Immunotherapy with PD-1 and PD-L1 inhibitors has recently revolutionized the treatment of multiple cancers. The first trial evaluating the PD-1 inhibitor pembrolizumab in R/M HNSCC was KEYNOTE 012 (3,4). In this multicohort Phase I study, 132 patients with R/M HNSCC received pembrolizumab. The overall response rate was 18%, with a median duration of response not reached at the time of initial report. Responses were seen regardless of human papilloma virus (HPV) status. Outcomes were numerically superior among patients with a greater tissue PD-L1 Composite Proportion Score (CPS), which includes assessment of tumor and stroma, whereas Tumor Proportion Score (TPS) did not seem predictive. Consistent with other trials, pembrolizumab was relatively well tolerated, with only 9% of patients experiencing a grade 3 or greater treatment related adverse event. The results of KEYNOTE 012 were confirmed in KEYNOTE 055, a phase II trial that focused exclusively on patients with R/M HNSCC after progression on both platinum and cetuximab (5). In this phase II study, 171 patients received pembrolizumab. The overall response rate in this more heavily pretreated population was 16%.

Based upon these promising results, two randomized phase III studies were initiated to definitively evaluate immunotherapy in platinum refractory R/M HNSCC. In CHECKMATE 141, 361 patients were randomized to the PD-1 inhibitor nivolumab or investigator's choice of docetaxel, cetuximab or methotrexate (6). Nivolumab was associated with a significantly longer overall survival (7.5 *vs.* 5.1 months, P=0.01) with less toxicity. In KEYNOTE 040, 247 patients were randomized to pembrolizumab or investigator's choice of docetaxel, cetuximab, or methotrexate (7). At the time of the preplanned survival analysis, the median overall survival was 8.4 months for pembrolizumab and 6.9 months for chemotherapy. While this result did not meet the pre-specified cutoff for survival improvement, longer follow-up has demonstrated a statistically significant improvement in overall survival. Based upon these data, both pembrolizumab and nivolumab have been approved by the FDA for the treatment of platinum refractory metastatic HNSCC.

One of the major advantages of immunotherapy over other forms of systemic cancer therapy is that responses can be quite durable—with clinical benefit sometimes measured in years. In non-small cell lung cancer, for example, we have recently observed that 16% of patients originally treated on the phase I study of nivolumab were alive at 5 years (8). In 2018, Mehra *et al.* published the first long-term follow-up data for survival outcomes following immunotherapy for R/M HNSCC based on data from KEYNOTE 012 (9). With a median of 9 months follow-up (range, 0.2–32 months),

the authors noted that the overall response rate was 18%—similar to the original report. What was most striking was the duration of these responses: 85% of responses had lasted 6 months or more and 71% of responses had lasted a year or more. They also reported a higher overall response rate and progression free survival among patients with PD-L1 positive tumors by CPS, but not when measured by TPS. No new toxicity signals were seen for pembrolizumab with longer follow-up.

While these data are very exciting for the minority of patients who respond to immunotherapy, a clear gap remains for most patients. Over 80% of patients with metastatic HNSCC do not respond to PD-1 blockade, and we must continue research efforts to improve outcomes for these patients. We believe there are two key pathways to improving outcomes for such patients—rational combination immunotherapy approaches and improved biomarkers to inform patient selection.

There are currently thousands of ongoing combination immunotherapy trials for the treatment of various cancers. Many of these trials are designed around convenience of drug availability, rather than robust science. With a traditional P value cutoff of 0.05, it is inevitable that we will see multiple phase I/II studies that are positive due to statistical chance alone, only to be proven ineffective in a phase III trial. This may explain the fate of epacadostat, an IDO1 inhibitor with apparent efficacy in early phase trials (including in HNSCC) (10). The Phase III trial was negative in melanoma, and many other trials were stopped early as a result.

Patient selection is going to be key in designing successful clinical trials of immunotherapy. These targets are not always easy to identify or validate but there are some emerging targets of interest. With the emergence of HPV-associated HNSCC as a health epidemic (11), an approach targeting HPV specific epitopes may provide a unique opportunity to harness the immune system and potentially eradicate cancer cells. Our group recently tested a DNA-based immunotherapeutic HPV vaccine, which had previously shown efficacy in patients with premalignant cervical lesions (12), in patients with locally advanced HPV-related HNSCC. We found that this immunotherapeutic vaccine led to induction of tumor specific immune responses (13). A trial evaluating this targeted immunotherapeutic approach in combination with PD-L1 blockade is currently underway for patients with HPV related R/M HNSCC. A peptide-based immunotherapeutic HPV vaccine has also been evaluated in combination with nivolumab for HPV-related metastatic HNSCC (14). Those investigators reported an overall response rate of 33%, nearly double what would be expected from single agent PD-1/PD-L1 inhibition. We believe that this type of trial design, which evaluates immunotherapeutic agents in populations that may be most likely to benefit from them, is key to advancing the field.

At the most recent ESMO meeting, we saw the first hints of patient selection for IO in a phase III trial of R/M HNSCC when Burtness *et al.* presented preliminary data for KEYNOTE 048 (15). In this study, patients with untreated R/M HNSCC were randomized to pembrolizumab monotherapy, platinum/5-Fluorouracil/cetuximab (the EXTREME regimen) (2), or platinum/5-fluorouracil/pembrolizumab. The authors reported that among patients with a PD-L1 CPS ≥1% or CPS ≥20% that pembrolizumab monotherapy was associated with a superior overall survival to chemotherapy alone. Data about CPS subgroups were not presented to compare chemoimmunotherapy to chemotherapy, but in the intention to treat population the use of chemoimmunotherapy led to improved overall survival. We anxiously await further results to inform how best to incorporate these findings into clinical practice.

Most patients with metastatic HNSCC, and indeed, most patients with metastatic cancer in general, do not have a clear tumor-specific target. Discovery of new biomarkers will be essential to improving their outcomes with immunotherapy. Currently available biomarkers have serious limitations. PD-L1 immunohistochemistry has apparent face validity—PD-L1 is the main ligand for PD-1, so it stands to reason that overexpression would be associated with response to therapy. Unfortunately, PD-L1 is dynamic over time and heterogeneous throughout tumors (16). Beyond that, each PD-1/PD-L1 inhibitor was developed alongside its own PD-L1 assay. While correlation between these assays is reasonable for staining on tumor cells (at least in lung cancer), substantially more variability between assays is present when surrounding immune cells are incorporated into the assay (17). The observation that CPS seems to be much more predictive for immunotherapy benefit in patients with HNSCC compared to TPS, renders this disparity particularly relevant for patients with HNSCC. Tumor mutation burden (TMB) has long been known to be associated with response to immunotherapy (18,19). The rationale is straightforward: a greater number of mutations leads to an increased repertoire of neoepitopes that can be targeted by an activated immune system. Unfortunately, many of the same

limitations that impact PD-L1 also affect TMB; tumor heterogeneity, dynamism, and assay harmonization are just some of the challenges as we consider the incorporation of TMB into our decision-making process (20,21). Both PDL-1 and TMB are surrogate biomarkers—they are measuring factors that are associated with response to immunotherapy rather than measuring directly the likelihood of response to immunotherapy. Biomarkers that more directly assess the interactions of the individual host immune system with tumor(s) will be needed in order to manipulate the immune response and achieve greater clinical benefit for individuals and populations.

In conclusion, immunotherapy now has an established role in the management of patients with metastatic HNSCC. PD-1 inhibitors have substantial activity in a minority of patients leading in some cases to dramatic and durable responses in a select group of patients. Future research focusing on biomarkers to inform the development of rational combinations and more refined patient selection is essential to expand the population that can benefit from these exciting drugs.

Acknowledgments

None.

Footnote

Conflicts of interest: JM Bauml discloses research funding to his institution from Merck, Incyte, Carevive Systems, Novartis, Bayer, Janssen, Astra Zeneca and Takeda. He discloses that he has performed consultative services for Bristol Myers Squibb, Astra Zeneca, Celgene, Merck, Janssen, Genentech, Guardant Health, Boehringer Ingelheim and Takeda; C Aggarwal discloses research funding to her institution from Genentech/Roche, Incyte, Macrogenics and Medimmune. She has performed consultative services for Genentech, Bristol Myers Squibb, and Lilly. An immediate family member is on a speakers' bureau with Genentech, Novartis, and Pfizer; RB Cohen discloses research funding to his institution from Merck, Celldex, Innate, Macrogenics, HEAT, Genocea, and Xencor. He discloses that he has performed consultative services for Takeda, HEAT, Innate, and Genocea.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7-30.
2. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-27.
3. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol 2016;17:956-65.
4. Chow LQM, Haddad R, Gupta S, et al. Antitumor Activity of Pembrolizumab in Biomarker-Unselected Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: Results From the Phase Ib KEYNOTE-012 Expansion Cohort. J Clin Oncol 2016;34:3838-45.
5. Bauml J, Seiwert TY, Pfister DG, et al. Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: Results From a Single-Arm, Phase II Study. J Clin Oncol 2017;35:1542-49.
6. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016;375:1856-67.
7. Cohen EEW, Soulieres D, Le Tourneau C, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. Lancet 2019;393:156-67.
8. Gettinger S, Horn L, Jackman D, et al. Five-Year Follow-Up of Nivolumab in Previously Treated Advanced Non-Small-Cell Lung Cancer: Results From the CA209-003 Study. J Clin Oncol 2018;36:1675-84.
9. Mehra R, Seiwert TY, Gupta S, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. Br J Cancer 2018;119:153-9.
10. Mitchell TC, Hamid O, Smith DC, et al. Epacadostat Plus Pembrolizumab in Patients With Advanced Solid Tumors: Phase I Results From a Multicenter, Open-Label Phase I/II Trial (ECHO-202/KEYNOTE-037). J Clin Oncol 2018. [Epub ahead of print].
11. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011;29:4294-301.
12. Bagarazzi ML, Yan J, Morrow MP, et al. Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. Sci Transl Med 2012;4:155ra138.
13. Aggarwal C, Cohen RB, Morrow MP, et al.

Immunotherapy Targeting HPV16/18 Generates Potent Immune Responses in HPV-Associated Head and Neck Cancer. Clin Cancer Res 2019;25:110-24.
14. Massarelli E, William W, Johnson F, et al. Combining Immune Checkpoint Blockade and Tumor-Specific Vaccine for Patients With Incurable Human Papillomavirus 16-Related Cancer: A Phase 2 Clinical Trial. JAMA Oncol 2019;5:67-73.
15. Burtness B, Harrington KJ, Greil R, et al. LBA8_ PRKEYNOTE-048: Phase III study of first-line pembrolizumab (P) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Ann Oncol 2018;29:Abstract LBA8_PR.
16. McLaughlin J, Han G, Schalper KA, et al. Quantitative Assessment of the Heterogeneity of PD-L1 Expression in Non-Small-Cell Lung Cancer. JAMA Oncol 2016;2:46-54.
17. Hirsch FR, McElhinny A, Stanforth D, et al. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. J Thorac Oncol 2017;12:208-22.
18. Snyder A, Makarov V, Merghoub T, et al. Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma. N Engl J Med 2014;371:2189-99.
19. Rizvi NA, Hellmann MD, Snyder A, et al. Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer. Science 2015;348:124-8.
20. Riaz N, Havel JJ, Makarov V, et al. Tumor and Microenvironment Evolution during Immunotherapy with Nivolumab. Cell 2017;171:934-49.e15.
21. Vanderwalde A, Spetzler D, Xiao N, et al. Microsatellite instability status determined by next-generation sequencing and compared with PD-L1 and tumor mutational burden in 11,348 patients. Cancer Med 2018;7:746-56.

Cite this article as: Bauml JM, Aggarwal C, Cohen RB. Immunotherapy for head and neck cancer: where are we now and where are we going? Ann Transl Med 2019;7(Suppl 3):S75. doi: 10.21037/atm.2019.03.58

