Editorial Commentary

Anal cancer and immunotherapy—are we there yet?

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Anal cancer is a rare malignancy. An estimated 48,541 new cases were diagnosed in 2018, comprising 0.3% of all worldwide cancer diagnoses (1). The incidence of anal cancer has been increasing over the past 30 years (2). Squamous cell carcinoma of the anal canal (SCCA) is associated with HPV infection and is the most common histologic type of anal cancer.

The majority of patients diagnosed with SCCA present with localized disease. 5-fluorouracil (5-FU) plus mitomycin with concurrent radiation has been the standard of care for non-metastatic SCCA for decades (3). Approximately 10–30% of patients develop metastatic disease, with the most common sites of metastases being liver, lung, and bone (4). The expected 5-year overall survival for patients with stage IV SCCA is expected to be 15.2% (5).

Historically, there has been no clear consensus on the optimal first-line regimen for metastatic SCCA (6). Cisplatin/5-FU has been one of the most widely published regimens for metastatic disease. Recent results of the randomized phase II "InterAACT" trial comparing carboplatin/paclitaxel to cisplatin/5-FU in treatment-naïve patients with advanced SCCA supports carboplatin/paclitaxel as the preferred regimen (7). Carboplatin/paclitaxel demonstrated a similar response rate with fewer toxicities and longer overall survival as compared to cisplatin/5-FU (20 versus 12.3 months, respectively) (8).

Over 80% of SCCA is attributable to high-risk HPV infection (9). HPV infection has been well established as a predictive marker of favorable outcomes in oropharyngeal cancer, and has been linked to an increased immune response to chemoradiation (10,11). HPV status has been correlated with clinical outcomes in SCCA in some studies, but has not yet been established as a reliable prognostic biomarker. This may be due to inconsistent HPV detection methods between studies and limited sample sizes due the rarity of the disease (12,13).

The immune microenvironment in SCCA is an area of active research. High intratumoral and peritumoral CD8+ T cell density has been associated with improved outcomes in SCCA (14). Tumor-infiltrating lymphocyte (TIL) scores have been shown to effectively stratify outcomes after chemoradiation in p16 positive patients with non-metastatic SCCA. In a retrospective cohort study of 284 patients, tumors with high TIL scores had a 92% relapse-free rate compared to 63% in patients with absent or low TIL scores (15). It follows that immune-based therapies have emerged as a promising treatment for metastatic SCCA.

The recognition and destruction of cancer cells by the adaptive and innate immune system is the overarching goal of cancer immunotherapy. Immune checkpoint inhibitors (ICIs) promote antitumor immune responses by interrupting immune inhibitory signaling pathways, often by blocking PD-1, PD-L1, or CTLA-4 (16). ICIs have improved outcomes in a variety of solid tumors, most notably melanoma and non-small cell lung cancer (17,18). Clinical studies of ICIs in SCCA have thus far focused on the use of the anti-PD-1 antibodies nivolumab and pembrolizumab in patients with chemotherapy-refractory disease. The first major reports on the efficacy of nivolumab and pembrolizumab in SCCA were both published in February 2017.

Morris *et al.* reported safety and efficacy results of a

single-arm, multicenter phase II trial of nivolumab in patients with refractory metastatic SCCA. Of 37 enrolled patients, there were 2 complete responses and 7 partial responses, for a response rate of 24% (95% CI, 15–33%). The median duration of response was 5.8 months among responders, median progression-free survival was 4.1 months, and median overall survival was 11.5 months (19). PD-L1 expression was not required, although it was evaluated in an exploratory analysis of pretreatment tumor samples from 13 patients. Higher PD-L1 expression was observed on tumor samples of responders (4 patients) compared to non-responders (9 patients), but interpretation of this exploratory result is limited by small sample size.

KEYNOTE-028 was a multi-cohort, phase Ib trial evaluating the safety and antitumor activity of pembrolizumab in patients with PD-L1 positive advanced SCCA. Four partial responses were observed in a cohort of 24 patients with advanced SCCA, for a response rate of 17% (95% CI, 5–37%). Additionally, 10 patients had stable disease (42%). Median progression-free survival was 3.0 months and median overall survival was 9.3 months (20). Toxicities from nivolumab and pembrolizumab were in keeping with the established toxicity profile of ICIs, with fewer than 20% grade 3 adverse events reported in each trial.

Based on these two trials, nivolumab and pembrolizumab were added to the NCCN guidelines for subsequent systemic therapy for anal carcinoma in 2018.

Ongoing immunotherapy studies in SCCA are evaluating nivolumab after combined modality therapy in patients with high-risk stage II-IIIB anal cancer (NCT03233711), nivolumab with or without ipilimumab in metastatic refractory anal cancer (NCT02314169), and a phase II trial of pembrolizumab in refractory metastatic anal cancer (NCT02919969) is underway. Investigators are also looking at the combination of the anti-EGFR antibody cetuximab with the anti-PD-L1 antibody avelumab versus avelumab alone in refractory locally advanced or metastatic SCCA (NCT03944252). Chemoimmunotherapy is a future direction for clinical trials in SCCA. The ongoing phase II "SCARCE" study will investigate the combination of docetaxel, cisplatin, and 5-FU (mDCF) with or without the anti-PD-L1 antibody atezolizumab in advanced SCCA (NCT03519295).

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Footnote

Conflicts of Interest: Dr. K Almhanna has a consulting agreement with Merck. JJ Bian has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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