Editorial

Immune checkpoint blockade in esophageal squamous cell carcinoma: is it ready for prime time?

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Esophageal cancer is a lethal disease with limited treatment options, particularly in the metastatic setting. While the incidence of esophageal squamous cell carcinoma (ESCC) has declined worldwide, it remains a major cause of morbidity and mortality in Asia, Africa and South America (1). In contrast to esophageal adenocarcinoma, which develops in the lower esophagus and is related to gastric reflux and Barrett's esophagus, ESCC occurs in the upper/mid esophagus and is associated with tobacco and alcohol use (2). Despite their differences, a common feature of both ESCC and adenocarcinoma is the presence of chronic inflammation and an abundance of tumor-infiltrating lymphocytes and other immune cell populations. As shown in other malignancies, infiltration of the tumor by CD8+ T cells was associated with improved outcomes (3,4), while the presence of regulatory T cells and myeloid-derived suppressor cells was correlated with worse overall survival (5,6). Furthermore, a small number of studies have evaluated the role of immune inhibitory signals, specifically the programmed cell death-1 (PD-1) protein and its ligands PD-L1 and PD-L2, in ESCC. One such study used gene expression to investigate the clinical significance of PD-L1 and PD-L2 in 41 cases of ESCC. In this series, 43.9% of patients had PD-L1 or PD-L2-positive tumors, determined by real-time quantitative PCR. PD-L1 and PD-L2 positivity was found to be a poor prognostic factor, in both univariate and multivariate analysis (7). A more recent study confirmed these findings. Of 106 patients with ESCC who underwent surgery without prior chemotherapy or radiation, 63 (59.4%) had tumors positive for either or both PD-L1 and PD-L2. PD-L1 and PD-L2 positivity predicted for worse overall survival (8). Furthermore, PD-L1 positivity has been associated with advanced stage, nodal metastasis, poor response to neoadjuvant chemoradiotherapy and locoregional recurrence (9).

Immune checkpoint blockade has changed the treatment landscape for a variety of cancers, most prominently melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma and cancers. These marked successes have led to an increased interest in evaluating these agents in several other malignancies. Given the high unmet need for effective therapies in advanced or metastatic ESCC and its prominent immunologic features, testing of immune checkpoint inhibitors in this cancer was a reasonable step.

Prior to their evaluation in advanced ESCC, the anti-PD-1 antibodies nivolumab and pembrolizumab demonstrated good efficacy in other squamous cancers and were FDA approved for the treatment of metastatic squamous cell NSCLC and head and neck squamous cell carcinoma (HNSCC). Specifically, nivolumab was compared with docetaxel in a randomized phase III trial of patients with advanced squamous cell NSCLC (CheckMate-017) (10). Nivolumab significantly improved the objective response rate (ORR) (20% *vs*. 9%; P=0.008) and prolonged the median OS (9.2 *vs*. 6.0 months; P<0.001). The expression of PD-L1 was neither prognostic nor predictive of benefit.

In contrast to nivolumab, pembrolizumab was shown to be effective in PD-L1 positive advanced NSCLC (expression in ≥50% of tumor cells), not only in the refractory but also in the first-line setting. In the phase III KEYNOTE-024 trial, patients with PD-L1 positive advanced, untreated NSCLC were randomized to pembrolizumab or platinum-based chemotherapy (11). Of 305 patients, 56 (18.4%) had squamous cell NSCLC. The ORR was higher in the pembrolizumab group than in the chemotherapy group (44.8% *vs.* 27.8%), and the median progression-free survival (PFS) was 10.3 months in the pembrolizumab group *vs.* 6.0 months in the chemotherapy group (P<0.001). In patients with previously treated, PD-L1 positive, advanced NSCLC, the phase II/III KEYNOTE-010 trial compared pembrolizumab (2 and 10 mg/kg) with docetaxel (12). Among patients with at least 50% of tumor cells expressing PD-L1 (22% of whom had squamous cell NSCLC), overall survival was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (median 14.9 *vs.* 8.2 months; P=0.0002) and with pembrolizumab 10 mg/kg than with docetaxel (17.3 *vs.* 8.2 months; P<0.0001). Although the difference for squamous cell disease was not statistically significant, the lack of benefit was likely due to the small sample size. Based on the results of these trials, both nivolumab and pembrolizumab were FDA approved for advanced squamous cell NSCLC.

Similar to squamous cell NSCLC, immune checkpoint inhibitors have shown marked clinical activity in HNSCC. In the phase III CheckMate-141 trial, patients with recurrent HNSCC, whose disease had progressed within 6 months after platinum chemotherapy, were randomized to nivolumab or standard, single-agent systemic therapy (13). Nivolumab led to a significant prolongation of the median OS (7.5 *vs.* 5.1 months; P=0.01) and improvement in ORR (13.3% *vs.* 5.8%). Even though there was preliminary evidence of greater benefit from nivolumab in patients with tumor PD-L1 expression of ≥1%, the test for interaction was not significant. In contrast to nivolumab and despite promising results of early-phase results, pembrolizumab failed to prolong OS in patients with previously treated recurrent or metastatic HNSCC in the phase III KEYNOTE-040 trial (14).

Although there are currently no randomized trial data on immune checkpoint inhibitors in ESCC, results of a phase II study conducted in Japan were reported in *Lancet Oncology* by Kudo and colleagues (15). Patients with advanced ESCC refractory or intolerant to fluoropyrimidine-, platinum- and taxane-based chemotherapy were treated with nivolumab 3 mg/kg every 2 weeks. Of the 64 patients assessable for the primary endpoint of ORR, 11 (17%) had an objective response (1 complete response), while 27 patients (42%) achieved disease control. Median PFS was 1.5 months, and median OS was 10.8 months. Median duration of response was not reached. Treatment was well tolerated with grade 3 or worse events in 17% of patients. The most common serious treatment-related adverse event was interstitial lung disease in three patients, which resolved with supportive care. No biomarker analysis (PD-L1, tumor mutation burden, CD8 cells, etc.) was reported for this trial. In this heavily pretreated population (38% of patients had received 3 or more systemic therapies), nivolumab showed remarkable activity compared to historical controls of systemic therapy, in terms of both ORR and OS (16,17). It is also important to note that PD-L1 positivity was not required for enrollment in this study. However, biomarker analysis, including PD-L1 expression, may identify predictors of response to nivolumab and enable better patient selection for future immune checkpoint inhibitor trials.

Another recent study confirmed the promising clinical activity of PD-1 inhibition in advanced esophageal cancer. The results from the esophageal cancer cohort of KEYNOTE-028, a multicohort, phase IB trial of pembrolizumab in patients with PD-L1 positive advanced solid tumors, were reported in the *Journal of Clinical Oncology* (18). The study included patients with either ESCC or esophageal adenocarcinoma, in whom standard therapy failed. PD-L1 positivity was defined as membranous staining on at least 1% of cells or the presence of a distinctive interface pattern in both neoplastic cells and contiguous mononuclear inflammatory cells. Patients were treated with pembrolizumab 10 mg/kg every 2 weeks. Of 83 patients, 37 patients had PD-L1 positive tumors, and 23 of those were enrolled. The majority of patients (18 patients, 78%) had ESCC, and 87% received ≥2 prior therapies for advanced/metastatic disease. ORR was 28% (5 of 18 patients) for patients with ESCC and 40% (2 of 5 patients) for those with adenocarcinoma. Median duration of response was 15 months, median PFS was 1.8 months and median OS was 7.0 months. Toxicity was manageable with the most common treatment-related adverse event being rash. In an effort to identify a biomarker of response to pembrolizumab, tumors were assayed for a six-gene interferon-γ expression signature (*CXCL9*, *CXCL10*, *HLA-DRA*, *IDO1*, *IFNG*, and *STAT1*), which has been shown to predict response in melanoma, head and neck

Table 1 Ongoing phase III clinical trials of immune checkpoint inhibitors in advanced ESCC

Agents	Treatment	Patient population	NCT identifier
Nivolumab	Nivolumab *vs*. docetaxel/paclitaxel	ESCC or esophageal/GEJ adenocarcinoma in 2nd line setting	NCT02569242
	Nivolumab + ipilimumab *vs*. nivolumab + fluorouracil + cisplatin *vs*. fluorouracil + cisplatin	ESCC in 1st line setting	NCT03143153
Pembrolizumab	Pembrolizumab *vs*. docetaxel/paclitaxel/irinotecan	ESCC or esophageal/GEJ adenocarcinoma in 2nd line setting	NCT02564263

ESCC, esophageal squamous cell carcinoma; GEJ, gastroesophageal junction.

and gastric cancer. The signature score showed trends toward an association with PFS (P=0.053, one-sided) and ORR (P=0.107, one-sided) in patients treated with pembrolizumab.

Both studies demonstrated encouraging preliminary efficacy of PD-1 blockade in advanced, refractory ESCC, a disease for which new, better therapies are sorely needed. The Kudo *et al.* study was larger and included only patients with ESCC, whereas KEYNOTE-028 was smaller and included both ESCC and adenocarcinoma patients. However, Kudo and colleagues conducted the trial only in Japan, whereas KEYNOTE-028 was a global trial which enrolled patients in Asia, Europe and the United States. The major difference between the two trials was that KEYNOTE-028 enrolled only patients with PD-L1 positive tumors, whereas in the Kudo *et al.* study patients were not preselected based on PD-L1 expression. It will be important to evaluate patient samples from both studies to identify biomarkers that could predict response to PD-1 inhibition. A potential biomarker of response to pembrolizumab, the interferon-γ gene signature, was suggested in KEYNOTE-028. However, this signature needs further exploration in a larger patient population. Finally, these data are only suggestive of efficacy of PD-1 blockade in esophageal cancer and need to be validated in the currently ongoing randomized phase III clinical trials (*Table 1*). However, as responses to PD-1 inhibitor monotherapy are still low, it will be important to test combination approaches with other immunotherapies, cytotoxic chemotherapy or radiation therapy to enhance its efficacy. An additional strategy is to test PD-1 blockade in earlier lines of therapy, as it seems to be more effective in patients who are not heavily pretreated, based on preliminary data in gastroesophageal adenocarcinoma (19,20).

In conclusion, both the Kudo and colleagues study in *Lancet Oncology* and the KEYNOTE-028 study in the *Journal of Clinical Oncology* suggest that PD-1 checkpoint blockade may be an effective therapeutic approach that could improve outcomes of patients with advanced ESCC. However, these results need to be confirmed in randomized phase III trials that are currently ongoing.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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