Immunotherapy for Advanced Esophageal Squamous Cell Carcinoma—Renewed Enthusiasm and a Lingering Challenge

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Esophageal cancer is the sixth leading cause of cancer-related mortality worldwide, with an estimated 544,076 deaths in 2020. It is also the seventh most incident cancer globally, with more than 50% of cases occurring in China alone. The diagnosis typically occurs in patients with locally advanced unresectable or metastatic disease, when palliative chemotherapy is the primary treatment option, and the 5-year survival rates can be as low as 5%. Esophageal cancer can be classified by histology as esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Esophageal adenocarcinoma is the most common among Western populations, occurs most often in the lower esophagus near the gastric junction, and is associated with obesity, gastric reflux, and a precursor state termed Barrett esophagus. Esophageal squamous cell carcinoma occurs predominantly in the upper and mid-esophagus and is associated with smoking and alcohol exposure, although ESCC risk factors among non-Western populations are less known. These histologies differ in risk factors, prognosis, and genetics. Despite ESCC’s high incidence, to our knowledge, robust clinical trials are scarce, and most of the evidence guiding its treatment comes from studies assessing ESCC and EAC combined. There has been little progress in treating esophageal cancer over the last 2 decades, with median overall survival (OS) for these patients remaining close to 11 months.

The results from ESCORT-1st, published in JAMA, thus represent a welcome new piece of evidence in a critical turning point in the treatment landscape of ESCC. In this large, double-blind, phase 3 clinical trial, Luo and colleagues evaluated the efficacy and safety of camrelizumab (200 mg) vs placebo combined with up to 6 cycles of paclitaxel (175 mg/m², 3 days, every 3 weeks). The authors included 596 patients with unresectable, locally advanced, or metastatic ESCC who had received no systemic treatment for at least 6 months before enrollment. There were 298 participants (median age, 62 years; 87.2% men) randomly assigned to the camrelizumab plus chemotherapy (camrelizumab-chemotherapy) group and 298 participants (median age, 62 years; 88.3% men) allocated to the placebo plus chemotherapy group. ESCORT-1st met its coprimary endpoints of progression-free survival (PFS) and OS, irrespective of programmed cell death ligand 1 (PD-L1) expression. Immune checkpoint inhibition (ICI) plus chemotherapy significantly improved survival compared with chemotherapy alone, with an OS of 15.3 vs 12.0 months (hazard ratio [HR], 0.70; 95% CI, 0.56-0.88), and a PFS of 6.9 vs 5.6 months (HR, 0.56; 95% CI, 0.46-0.68). All-grade treatment-related adverse events were highly incident in both groups, affecting 296 of 298 participants (99.3%) receiving camrelizumab-chemotherapy vs 288 of 297 (97.0%) receiving placebo plus chemotherapy. There was a higher rate of severe adverse events and treatment discontinuation with camrelizumab-chemotherapy than with chemotherapy alone (30% vs 23.2% and 45.3% vs 23.9%, respectively). The addition of checkpoint inhibition to chemotherapy also increased the rate of immune-related adverse events (84.6% vs 33%); however, severe immune-related adverse events, such as pneumonitis and liver toxic effects, were uncommon in both arms. There was no significant difference in health-related quality of life between treatment groups, although patients receiving camrelizumab-chemotherapy tended to report more financial distress.

The prespecified exploratory analysis according to PD-L1 tumor proportion score (TPS) revealed a survival benefit from camrelizumab plus chemotherapy across all strata, leading to no statistically significant association of the PD-L1 expression with treatment efficacy. For participants with a TPS of 1 or greater, OS improved from 11.5 to 15.3 months (HR, 0.59; 95% CI, 0.43-0.80) and PFS from 5.6 to 6.9 months (HR, 0.51; 95% CI, 0.39-0.67); for those with a TPS of 10 or greater, the OS HR was 0.52 (95% CI, 0.35-0.79) and the PFS HR was 0.51 (95% CI, 0.36-0.72). Notably, patients with a TPS lower than 1 still had a survival gain with camrelizumab plus chemotherapy, with OS increasing from 12.0 to 15.0 months (HR, 0.79; 95% CI, 0.57-1.11) and a PFS of 5.7 vs 6.9 months (HR, 0.51; 95% CI, 0.39-0.67). Curiously, while survival curves clearly separated early in the subgroup with a TPS of 1 or greater, the curves among PD-L1-negative patients were alike and crossed multiple times during the first months of follow-up. Considering these findings, PD-L1 TPS was a predictive factor rather than a trigger biomarker, endorsing the urgent need for more standardized and robust tests to select patients with upper gastrointestinal tumors who will benefit most from chemoimmunotherapy.

Another concern regarding PD-L1 assessment is the lack of standardization of the results from different assays. ESCORT-1st used a TPS assay (6E8 antibody; Shuwen Biotech) that measured the proportion of viable tumor cells expressing PD-L1. Other trials in this setting used different antibodies and scores. CheckMate-648 reported TPS obtained with the Dako PD-L1 IHC 28-8 assay, whereas KEYNOTE-590 used the Dako 22C3 assay and reported a combined positive score (CPS). The CPS incorporates the percentage of PD-L1 expression among tumor cells and inflammatory cells inside tumor nests and the adjacent supporting stroma, unlike the TPS. Currently, there

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is real-world evidence of the concordance of 28-8 and 22C3 assays on various tumor types, but, to our knowledge, data specific to gastroesophageal tumors are lacking.

Several differences have to be noted in the landscape of trials assessing immunotherapy in ESCC, all of which may limit the generalizability and the comparability of the results in ESCORT-1st with other studies. First, the study recruited only Chinese patients, and there is evidence that Asian individuals with ESCC have different genetic and clinical profiles than White individuals, showing higher immunotherapy response rates. Second, the chemotherapy regimen was distinct from the usually adopted combinations fluorouracil and cisplatin. The choice of paclitaxel in ESCORT-1st was based on the relatively less robust evidence of activity from phase 2 and retrospective studies. However, the survival rates with the combination of cisplatin with paclitaxel were comparable with those obtained with fluorouracil plus cisplatin, with the advantage of a more feasible administration.

In this regard, ESCORT-1st corroborates a fortunate trend of positive results in trials of ICI for patients with esophagus carcinoma. Specifically, KEYNOTE-590 randomized 749 patients with EAC, ESCC, and esophagus near the gastric junction carcinoma to receive a combination of either pembrolizumab or placebo with fluorouracil, 800 mg/m², from days 1 to 5, plus cisplatin, 80 mg/m², every 3 weeks, for up to 6 doses. Seventy-three percent of these patients had ESCC; the addition of pembrolizumab to chemotherapy in this group prolonged OS from 9.8 to 12.6 months (HR, 0.72; 95% CI, 0.60-0.88) irrespective of PD-L1 expression and from 9.4 to 13.5 months (HR, 0.62; 95% CI, 0.49-0.78) by selecting those with a CPS of 10 or greater. CheckMate-648 was another global study to bring encouraging results in its first interim analysis. The trial assigned patients with ESCC to 3 arms: nivolumab plus chemotherapy fluorouracil + cisplatin every 4 weeks (n = 321); nivolumab, 3 mg/kg, plus ipilimumab, 1 mg/kg, every 6 weeks (n = 325); and chemotherapy alone (n = 324). The OS with nivolumab plus chemotherapy vs chemotherapy alone was 15.4 vs 9.1 months (HR, 0.54; 95% CI, 0.54-0.80) for those with a CPS 1 or greater and 13.2 vs 10.7 months (HR, 0.74; 95% CI, 0.58-0.96) for all randomized patients. Moreover, the survival gains from dual checkpoint inhibition in CheckMate-648 were likewise favorable, endorsing the option of a chemotherapy-free treatment, although there were more progression events and deaths among dual checkpoint inhibition patients during the first 6 months of the study.

Camrelizumab plus chemotherapy will become a new standard of care for patients with advanced ESCC in China, which carries one of the highest burdens of this disease. Likewise, ICI plus chemotherapy, and even dual checkpoint inhibition, will become a feasible option for many patients with ESCC worldwide. Nevertheless, besides the challenge of selecting the patients most likely to benefit from immunotherapy approaches, it will be paramount to tackle issues of access, especially in low-resource settings.

ARTICLE INFORMATION

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