Unraveling the puzzle: efficacy of PD-L1 inhibitors in esophageal squamous cell carcinomas with low PD-L1 expression—a comprehensive overview of challenges and limitations

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Esophageal cancer remains a formidable foe in the battle against malignancies, with more than 0.6 million cases diagnosed worldwide in 2020 (1). While surgical intervention and chemotherapy have been traditional mainstays in treating locally advanced esophageal squamous cell carcinomas (ESCC), Patients with metastatic ESCC are typically treated with chemotherapy, but they face a dismal prognosis, and those who progress on chemotherapy are left with even fewer options (2). In this challenging context, the utilization of programmed death-ligand 1 (PD-L1) inhibitors emerges as a beacon of hope. These inhibitors have shown substantial effectiveness in a spectrum of cancers (3-5). PD-L1 expression levels on cancer cells play a critical role in determining the effectiveness of immunotherapy. Most randomized controlled trials (RCTs) exploring the potency of these inhibitors for advanced ESCC concentrate on the broader, randomly selected participants and particularly PD-L1-positive [combined-positive score (CPS) ≥10 or tumor proportion score (TPS) ≥1%] subsets. However, a burning question lingers: Are PD-L1 inhibitors truly effective in treating ESCC patients with low PD-L1 expression? This editorial delves into the complexities and limitations of this critical question, shedding light on the intricate landscape of PD-L1 inhibitor usage in ESCC treatment.

To address this question, we first review the current guidelines and recommendations for the use of PD-L1 inhibitors based on published clinical trials, noting the variability in regulatory approvals and diverse clinical trial outcomes. This suggests that immunotherapies alone or in combination with other treatments may not be universally suitable for all patients. Here, we also briefly highlight the concept of CPS and TPS, which are measures used to determine PD-L1 expression levels.

(I) Pembrolizumab: the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved pembrolizumab for the treatment of adult patients with unresectable locally advanced or metastatic ESCC whose tumors express PD-L1 with a CPS of 10 or greater and who have received prior systemic therapy. In addition, the US FDA has also approved pembrolizumab for the treatment of advanced or metastatic ESCC that has not responded to or has progressed after previous treatment, regardless of the tumor's PD-L1 expression status (6).

(II) Nivolumab: the US FDA has approved nivolumab for the treatment of patients with unresectable advanced or metastatic ESCC that has progressed after fluoropyrimidine- and platinum-containing

chemotherapy, without regard to the PD-L1 status of the tumor. The EMA has approved nivolumab for the treatment of adult patients with unresectable advanced or metastatic ESCC whose tumors express PD-L1 with a CPS of 10 or greater and who have received prior systemic therapy (7).

(III) Combination therapy: the US FDA has approved the combination of nivolumab and ipilimumab with chemotherapy as first-line treatment for patients with unresectable advanced or metastatic ESCC, regardless of PD-L1 expression. The EMA has also approved the combination of nivolumab and chemotherapy as first-line treatment for adult patients with unresectable advanced or metastatic ESCC whose tumors express PD-L1 with a CPS of 10 or greater (7).

To gain deeper insights into the efficacy of PD-L1 inhibitors among individuals with low PD-L1 expression, a comprehensive meta-analysis encompassing nine distinct randomized clinical trials was undertaken. These studies assessed the performance of anti-programmed death 1 (PD-1) therapies in the context of advanced ESCC, focusing on metrics such as overall survival (OS), progression-free survival (PFS), and duration of response (DOR). Survival curves for the entire participant population, high PD-L1 subgroups, and low PD-L1 subgroups (when available) were compiled from the respective published studies. Also, time-to-event outcomes were calculated from these curves. For research instances where specific curves for low PD-L1 cohorts were not disclosed, a KMSubtraction technique was applied to estimate the survival figures. Subsequently, a detailed analysis pooling individual patient data (IPD) was executed, with a primary focus on OS, and secondary emphases on evaluating PFS and DOR (8).

OS

Two studies, CheckMate-648 and ESCORT, used TPS to determine the PD-L1 score (7,9). ESCORT evaluated the use of camrelizumab as a second-line therapy, while CheckMate-648 evaluated the use of nivolumab plus chemotherapy and nivolumab plus ipilimumab versus chemotherapy as a first-line agent. Both showed no difference in OS for immunotherapy-based groups compared with chemotherapy [hazard ratio (HR), 0.98; 95% confidence interval (CI): 0.75–1.28; P=0.89 and HR, 0.78; 95% CI: 0.59–1.02; P=0.07].

There was a variation in the OS among the studies employing CPS for PD-L1 scoring.

For example, both KEYNOTE-181 (pembrolizumab vs. chemotherapy) and KEYNOTE-590 (pembrolizumab + chemotherapy vs. chemotherapy) trials showed no significant difference in OS for immunotherapy compared with chemotherapy alone (HR, 0.90; 95% CI: 0.68–1.18; P=0.44 and HR, 0.91; 95% CI: 0.69–1.20; P=0.50) (6,10).

On the other hand, the ORIENT-15 trial, which evaluated sintilimab + chemotherapy vs. chemotherapy alone, showed a significant difference in OS for immunochemotherapy compared with chemotherapy in patients with CPS of less than 10 (HR, 0.62; 95% CI: 0.45–0.85; P=0.003) (11).

The observed differences between studies could be attributed to variations in study design, patient populations, or other factors that warrant further investigation.

PFS and DOR

Two studies, CheckMate-648 and ORIENT-15 provided data on PFS and DOR in patients with low PD-L1 expression (7,11). CheckMate-648 showed no significant PFS difference between nivolumab-chemotherapy and chemotherapy alone (HR, 0.98; 95% CI: 0.75–1.28; P=0.88), while dual immunotherapy exhibited inferior PFS. However, ORIENT-15 revealed improved PFS for immunochemotherapy in the CPS <10 subgroup (HR, 0.52; 95% CI: 0.39–0.70; P<0.001). Median DOR showed no significant differences in CheckMate-648 for subgroups with TPS <1% (P>0.05), while in ORIENT-15, sintilimab-based immunochemotherapy demonstrated a significant difference compared to chemotherapy (HR, 0.64; 95% CI: 0.43–0.96; P=0.03).

IPD pooled analysis

Two IPD pooled analyses in this meta-analysis were done, one based on the line of therapy and the other based on the scoring system. The analysis based on the line of therapy was done in two categories: First-line studies which showed a significant difference in OS and PFS for immunochemotherapy compared with chemotherapy alone in the overall population (HR, 0.70; 95% CI: 0.63–0.77; P<0.001 and HR, 0.64; 95% CI: 0.58–0.70; P<0.001) (7,10-12).

Second-line studies showed a statistically significant difference between immunotherapy and chemotherapy in terms of OS and PFS in the overall population. (HR, 0.72;

95% CI: 0.65–0.80; P<0.001 and HR, 0.89; 95% CI: 0.81–0.99; P=0.03) (6,9,13,14).

However, when IPD pooled analysis was conducted based on the scoring system, studies that used TPS with a cutoff of 1% showed a significant difference in OS between chemoimmunotherapy and chemotherapy alone that was not seen in the subgroup of TPS <1% (7,12). This suggests that the overall population's outcomes could be influenced by the favorable results observed in individuals with a TPS of more than 1%.

Interestingly, IPD pooled analysis of trials that used CPS of 10% as a cutoff showed a significant difference in OS between immunochemotherapy and chemotherapy in all subgroups (10,11). This might be attributed to the positive results seen in ORIENT-15, which was conducted on an Asian population, while KEYNOTE-590 was global.

In the context of the ongoing debate and investigation into the efficacy of PD-L1 inhibitors across varying expression levels, the JUPITER-06 trial provides a pertinent example. The trial demonstrated that the combination of toripalimab, a PD-1 antibody, to chemotherapy (cisplatin plus 5-fluorouracil) significantly improved both PFS and OS in patients with untreated, locally advanced, or metastatic ESCC, compared to chemotherapy alone. A subsequent analysis indicated that the efficacy threshold for both PFS and OS was met, with the addition of toripalimab to chemotherapy proving superior across the predetermined PD-L1 subgroups (CPS ≥1, CPS ≥10). This suggests that the clinical benefit was pronounced in both high and low PD-L1-expressing subgroups. However, the survival and its significance in the group of patients with PD-L1 CPS <10 was not presented, which if negative, might reflect that the overall positive outcome in the PD-L1 CPS of 1 or higher might be driven by the great outcome in patients with PD-L1 CPS ≥10 (15).

In summary, it is evident that the efficacy of immune checkpoint inhibitors (ICIs) tends to be reduced in patients exhibiting low PD-L1 expression. Nevertheless, it is crucial to acknowledge that a portion of this population still derives substantial clinical benefits from ICIs. This observation highlights the need for ongoing research into other factors, such as geographic variation, complementary predictive biomarkers, and the dynamism of PD-L1 expression, which can be used alongside PD-L1 to better identify responders. Furthermore, clinicians should keep in mind the differences between TPS and CPS scoring systems in terms of assessment focus and PD-L1 assays used.

As the field of immunotherapy continues to evolve, further studies are needed to identify new biomarkers and refine patient selection criteria. Ultimately, a more personalized approach to cancer treatment will enable clinicians to better tailor immunotherapies to individual patients, thereby maximizing therapeutic success and minimizing unnecessary side effects.

In conclusion, while the use of PD-L1 inhibitors in ESCC patients with low PD-L1 expression remains a complex and challenging issue, continued investigation into the factors that govern treatment response and the development of more targeted therapies hold promise for improving outcomes in this patient population. As the understanding of tumor biology and the immune response advances, it is anticipated that future breakthroughs in immunotherapy will contribute significantly to the arsenal of weapons in the fight against ESCC.

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