Editorial

Immune checkpoint inhibition in advanced esophageal squamous cell carcinoma: how can we personalise management?

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Esophageal cancer comprises two main histological subtypes, esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). ESCC is the most common subtype worldwide, and has a dismal prognosis—5-year overall survival (OS) is ~15% (1). The majority of cases are diagnosed when curative treatment is not an option. For those who are eligible for and undergo curative treatment, relapse rate is high, either loco-regional tumour persistence or recurrence. When this occurs, first-line palliative systemic therapy comprises platinum-based chemotherapy with or without an immune checkpoint inhibitor (ICI) (2,3). On progression, options for second-line systemic therapy include chemotherapy or an ICI (4-7).

In this issue of *Journal of Thoracic Disease*, Zhu *et al.* (8) report findings from a meta-analysis of five randomised controlled trials investigating the role of ICIs as second-line therapies in advanced ESCC. Their meta-analysis of five phase 2 and 3 trials demonstrates, convincingly, that second-line therapy based on ICIs is more effective than chemotherapy for patients with advanced ESCC, with a lower side-effect burden. This finding was consistent across objective response rate [odds ratio (OR) =2.07; 95% CI: 1.22–3.52] and OS [hazard ratio (HR) =0.73; 95% CI: 0.66–0.81], although not progression-free survival (HR =0.93; 95% CI: 0.77–1.12).

ICI therapy has become a powerful tool to treat many solid-organ malignancies (9,10). For the proportion of patients whose disease shows response to ICI therapy, these drugs can offer durable tumour control, prolonged survival and are relatively well tolerated (10). In advanced ESCC, Zhu and colleagues' meta-analysis demonstrates the benefit of ICI over chemotherapy in the second-line setting. Given the superiority of ICI to chemotherapy in the second-line setting, attention has already turned to the use of ICIs as a first-line treatment. Both the CheckMate 648 and KEYNOTE-590 trials (3,11) showed that a combination of ICI and chemotherapy was superior to chemotherapy alone as a first-line treatment for advanced ESCC; the investigators of CheckMate 648 further showed that a combination of two different ICIs, without chemotherapy, was superior to chemotherapy alone (3).

Despite this, only approximately 10–20% of all patients respond to single-agent ICI therapy (primary resistance) (8). For those that do respond, the majority subsequently progress (acquired resistance). Understanding the reasons underlying this differential response and identifying biomarkers is essential to improving patient outcomes (12).

Individualised treatment approaches must be based on patients' specific tumour biology, but unfortunately the main biomarker studied in these trials [programmed death ligand-1 (PD-L1) expression] seems to muddy rather than clarify the waters. Zhu and colleagues (8) stratified their meta-analysis on the basis of two established measures of PD-L1 expression: the tumour proportion score (TPS), which measures the proportion of tumour cells that stain positive for PD-L1; and the combined positivity score

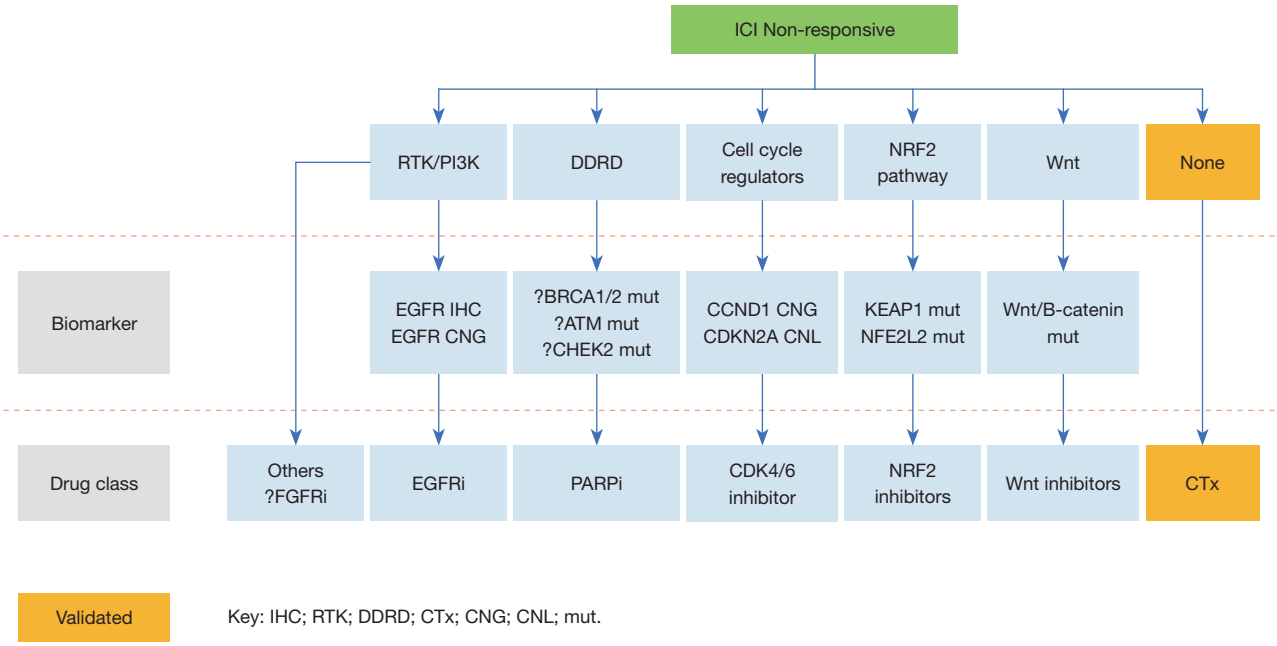

Figure 1 Emerging approaches to improve immune checkpoint inhibitor responses in ESCC. Figure adapted from Baxter *et al.* (14) under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0). ICI, immune checkpoint inhibitor; RTK, receptor tyrosine kinase; DDRD, DNA Damage Response Deficient; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; CNG, copy number gain; CNL, copy number loss; mut, mutation; CTx, chemotherapy.

(CPS), which counts not only PD-L1-positive tumour cells but also PD-L1-positive tumour-associated immune cells.

Their findings suggest a potentially greater impact on OS among patients with TPS ≥1% (versus TPS <1%) and among those with TPS ≥10% (versus TPS <10%). By contrast, in a pooled analysis of ICIs in the first-line setting, Yap *et al.* similarly found a greater OS benefit for ICI for patients with TPS ≥1% but no survival advantage at all for patients with TPS <1% (13).

In addition, while Zhu and colleagues showed greater benefit for patients with CPS ≥10 (versus CPS <10) and no benefit for patients with CPS <10, Yap *et al.* found survival benefits both for CPS ≥10 and (albeit smaller) with CPS <10 (13). Standardisation of CPS and TPS between studies is almost impossible to establish, and where these findings leave researchers, clinicians, and patients is unclear.

Zhu and colleagues' analyses, and the more recent studies of ICIs as first-line palliative therapies and in patients with residual disease after radical therapy, support the role of ICI as a therapeutic option in patients with advanced ESCC. However, they do not answer the important questions of what to do after ICI treatment has failed and how do we improve patient selection and response to ICI therapy? To answer these questions, we need a precision approach both with targeted therapies and better biomarkers.

Most research so far has understandably focused on the role of PD-L1/PD-1. However, other biomarkers within the tumour microenvironment warrant investigation (*Figure 1*) (12,14). For example, epidermal growth factor receptor (EGFR) is overexpressed in 30–70% of ESCC tumours (15,16). EGFR activation is associated with depleted tumour-infiltrating lymphocytes and resistance to ICIs (15). This suggests that further investigation of the role of and precision targeting of EGFR-driven ESCC in combination with ICI could be a therapeutic strategy to overcome ICI resistance.

Overall, the authors should be congratulated on completing a study which adds to the literature and confirms the safety and efficacy of ICI therapy after failure of first-line chemotherapy in patients with advanced ESCC. Considering the unmet clinical need and lack of targets for precision medicine in ESCC, research attention must now turn to better understanding the mechanisms underlying ICI resistance (12). This will enable individualised treatment strategies for the majority of patients who progress despite ICI treatment.

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