Editorial

Nivolumab for chemorefractory oesophageal squamous cell carcinoma

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Although immunotherapy has radically changed the treatment paradigm for a variety of tumours including melanoma, non-small cell lung cancer and renal cell carcinoma, until now it has been less successful in tumours of the gastrointestinal tract. In a recent report in *Lancet Oncology*, Kudo *et al*. described the results of the first trial assessing immune checkpoint blockade in OSCC patients (1). The study enrolled 65 Japanese patients with platinum and taxane refractory OSCC in a standard open-label phase II design, the primary endpoint of which was centrally assessed objective response rate (ORR). OSCC patients treated with nivolumab on the trial had an ORR of 17% [95% confidence interval (CI), 10–28%] by central radiological review. However, a further proportion of patients appeared to benefit from anti-PD-1 therapy but did not reach RECIST criteria for response; a reduction in overall tumour burden was observed in 45% of participants by the trial investigators. In keeping with many studies of immunotherapy, median progression-free survival (PFS) did not appear to be substantially improved by nivolumab (median PFS, 1.5 months; 95% CI, 1.4–2.8 months), however, median overall survival (OS) was promising for a chemorefractory patient population at 10.8 months (95% CI, 7.4–13.3 months). These results are potentially important because if validated in a randomised controlled trial, nivolumab could provide a new treatment option for advanced OSCC, a cancer for which very little evidence is available to guide clinical management.

Historically, few trials have focused on treatment for metastatic OSCC patients, and most treatments for OSCC are based on data derived from trials of gastric or gastroesophageal adenocarcinoma. Phase III randomised trials support the use of single agent taxane or irinotecan chemotherapy in the second-line setting; the absolute benefit associated with salvage chemotherapy is approximately 6 weeks, with median OS of less than 6 months expected (2-4). Two small studies of combination chemotherapy for chemorefractory OSCC suggest higher response rates of 23–30% for taxane-gemcitabine or taxane-fluoropyrimidine combinations; however, these regimens have not been validated in larger, randomised trials (5,6). Considering the generally poor radiological response rates associated with single agent salvage chemotherapy, in the trial reported by Kudo and colleagues, it is impressive that nivolumab was able to achieve a radiological response rate of 17% in a heavily pretreated population refractory to both cisplatin and taxane chemotherapy. Furthermore, the median OS associated with nivolumab therapy appears to be longer than that seen with taxanes in the in second-line setting. Importantly, in a patient group which may have co-morbidities associated with tobacco and alcohol use, the toxicity profile of nivolumab was not different from what is already known. Although standard immunotherapy-related side effects were observed (i.e., diarrhea, rash, abnormal hepatic function and fatigue), serious adverse events were uncommon (n=11, 17%) and relatively few patients (n=7, 11%) discontinued treatment due to toxicity. Prior to the publication of Kudo and colleagues in *Lancet Oncology*, few data on immune checkpoint blockade (i.e.,

PD-1, PD-L1 and CTLA-4 inhibitors) were available relating specifically to OSCC. The KEYNOTE 028 study, which was reported in abstract form only, assessed the efficacy of pembrolizumab in PD-L1 positive oesophageal cancer (of both adenocarcinoma and OSCC histology) (7). In KEYNOTE 028, 17 patients with PD-L1 positive OSCC were treated with pembrolizumab, of whom 29% (n=5) had an objective radiological response. In particular, although emerging data supports the routine use of nivolumab in chemorefractory gastric and gastroesophageal adenocarcinoma, the biological distinctions between oesophageal adenocarcinoma and OSCC mean that results from gastroesophageal adenocarcinoma trials cannot be readily extrapolated to patients with OSCC (8). The work of The Cancer Genome Atlas (TCGA) demonstrates that whereas from an oncogenomic perspective oesophageal adenocarcinoma is strongly reminiscent of chromosomally unstable gastric cancer, OSCC resembles squamous cell carcinoma of other organs, including head and neck squamous cell carcinoma (HNSCC) and squamous non-small cell lung cancer (SqNSCLC) (9).

Because aetiologically and pathologically OSCC is more closely molecularly related to HNSCC and sqNSCLC than gastric or gastroesophageal adenocarcinoma, the results of immune checkpoint blockade in HNSCC and SqNSCLC may be of relevance for development of anti-PD-1 therapy in OSCC. In the CheckMate 141 trial which evaluated nivolumab *vs.* methotrexate, docetaxel or cetuximab in a unselected platinum-refractory HNSCC population, the ORR associated with nivolumab treatment was 13.3%, and nivolumab significantly increased median overall and 1-year survival compared to standard therapy [median OS, 7.5 *vs.* 5.1 months; hazard ratio (HR), 0.70; P=0.01 and 36.6% *vs.* 16.0%, respectively] (10). In a subgroup analysis of Checkmate 141, median OS was statistically significantly improved only for HNSCC patients who were PD-L1 positive in ≥1% of tumour cells. Although results of nivolumab efficacy in OSCC according to PD-L1 expression are not reported by Kudo *et al*., the PD-L1 expression associated survival benefit demonstrated in HNSCC for nivolumab might suggest that evaluation of PD-L1 status in OSCC could select a subgroup of patients with increased benefit from PD-1 inhibition. However conversely, results in sqNSCLC trials did not support a predictive role for tumoural PD-L1 expression (at the 1–10% level) for nivolumab therapy, but did for pembrolizumab (at 50% PD-L1 positivity using a different assay) (11,12). Therefore, it is evident that each tumour site, even if molecularly similar, must be evaluated independently for the interaction between PD-L1 expression, which may be antibody dependent, and efficacy of immune checkpoint blockade. Interestingly, in the largest retrospective series evaluating the prognostic role of PD-L1 expression in patients with surgically resected OSCC, PD-L1 expression in ≥5% of immune infiltrating cells but not tumour cells was positively prognostic for OS (13). Therefore, in future trials, evaluation of PD-L1 status on immune infiltrating cells rather than tumour cells may be of more value for OSCC patients.

Notably, the results presented by Kudo *et al*. were achieved in a clinical trial which recruited only Japanese patients. Therefore, whether these results are generalizable to non-Asian patients is a relevant question. However, the TCGA assessment of oesophageal cancer included a global patient population and found no significant differences in genomic signatures between Eastern and non-Asian patients, although some regional trends were noted (9). Moreover, although there is evidence suggesting that the immune microenvironment varies between Asian and non-Asian gastric cancer patients, there are no data suggesting the same in the OSCC setting (14). Finally, in an early report of the efficacy of pembrolizumab in PD-L1 positive gastric cancer, there was no difference in efficacy between Asian and non-Asian patients, nor has there been any suggestion of differential efficacy of anti-PD-1 in Asian NSCLC patients (12,15). Therefore, future trials of anti-PD-1 therapy for OSCC might reasonably combine patients from different geographic regions worldwide. Ongoing and upcoming trials examining immunotherapy agents, either as a single agent or in various combination strategies, in the OSCC setting are summarised in *Table 1*.

In conclusion, the results presented by Kudo and colleagues are encouraging for patients with OSCC. By focusing their analysis on OSCC patients, they have set an important benchmark in separating the two oesophageal cancer histologies. In doing so, it should be possible to derive stronger conclusion from trials and ultimately provide benefit to patients. Identification and validation of predictive biomarkers to establish which patients are likely to benefit from immune checkpoint inhibitors remains a priority in all cancers, including OSCC. Equally, understanding the mechanisms of resistance to anti-PD-1 therapy in OSCC is essential, as the majority of patients do not benefit from immune checkpoint blockade. This knowledge will be important in designing future trials, in particular combination strategies.

Table 1 Upcoming trials targeting the PD-1/PD-L1 pathway in advanced oesophageal squamous cell cancer

Clinicaltrial.gov ID	Name	Treatment	Cohort	Setting	Biomarker assessment	Phase	Planned enrollment	Expected completion
Pembrolizumab (anti-PD-1)								
NCT02971956	–	Single-agent	OSCC, OAC	Relapsed/refractory, unselected	Yes	Phase 2	50	June 2020
NCT02559687	Keynote 180	Single-agent	OSCC, OAC	Relapsed/refractory, unselected	Yes	Phase 2	100	September 2017
NCT02564263	Keynote 181	Single-agent *vs.* ICT	OSCC, OAC	Relapsed/refractory, unselected	Yes	Phase 3	720	August 2018
NCT03189719	Keynote 590	Cisplatin/5-FU +/– pembrolizumab	OSCC, OAC	First line, unselected	Yes	Phase 3	700	November 2020
NCT02642809	–	Pembrolizumab + brachytherapy	OSCC, OAC	First line, unselected	Yes	Phase 2	15	April 2018
NCT02830594	–	Pembrolizumab + external RT	OSCC, OAC, GC	All lines, unselected	Yes	Phase 2	14	October 2018
Nivolumab (anti-PD-1)								
NCT02971956	ONO-4538	Single-agent *vs.* taxane	OSCC, OAC	Relapsed/refractory, unselected	No	Phase 3	390	September 2019
NCT02559687	CheckMate 648	Nivo/ipi *vs.* nivo/chemo *vs.* chemo	OSCC	All lines, unselected	Yes	Phase 3	939	May 2020
Durvalumab (anti-PD-L1)								
NCT02735239	–	Durva/chemo, durva/treme/chemo	OSCC, OAC	First line, unselected	No	Phase 1/2	75	April 2021
NCT03212469	ABBIMUNE	Durva/treme + SBRT	OSCC, HNSCC, squamous NCLSC	Relapsed/refractory, unselected	Yes	Phase 1/2	40	February 2018
JS001 (anti-PD1)								
NCT02915432	Junshi-JS001-Ib/II	Single-agent	OSCC, OAC, GC, HNSCC, NPC	Relapsed/refractory, unselected	Yes	Phase 1/2	448	October 2017
SHR-1210 (anti-PD1)s								
NCT03187314	HangzhouCH08	SHR-1210 + external RT	OSCC	First line, unselected	Yes	Phase 2	21	June 2018
NCT03099382	301-ESC	SHR-1210 *vs.* docetaxel or irinotecan	OSCC	Relapsed/refractory, unselected	Yes	Phase 3	438	June 2018

OSCC, oesophageal squamous cell carcinoma; OAC, oesophageal adenocarcinoma; ICT, integrative cancer therapies; SBRT, stereotactic body radiation therapy; RT, radiation therapy; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; NPC, nasopharyngeal carcinoma; GC, gastric cancer.

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Footnote

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Conflicts of Interest: EC Smyth declares honoraria for advisory role from Five Prime Therapeutics, Bristol Meier-Squibb, Gritstone Oncology and Servier. M Chénard-Poirier 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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