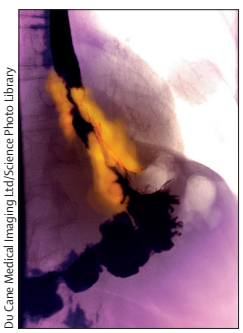
Nivolumab for previously treated squamous oesophageal carcinoma



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Despite accounting for more than 90% of oesophageal cancers globally, oesophageal squamous cell carcinoma has historically been underserved by research. High-quality data to support therapeutic decision making in patients with advanced oesophageal squamous cell carcinoma are scarce, and treatment is frequently extrapolated from gastroesophageal adenocarcinoma trials. Encouragingly, the molecular distinction of oesophageal squamous cell carcinoma from adenocarcinoma has paved the way for clinical trials focusing exclusively on oesophageal squamous cell carcinoma.[1]

In *The Lancet Oncology*, Ken Kato and colleagues[2] present the results of ATTRACTION-3, an international, randomised, phase 3 trial comparing nivolumab with taxane chemotherapy (paclitaxel or docetaxel) in patients with oesophageal squamous cell carcinoma (including adenosquamous histology), which was refractory or intolerant to one previous platinum or fluoropyrimidine chemotherapy regimen.[2] After a median follow-up of 10·5 months (IQR 4·5–19·0) for the nivolumab group and 8·0 months (4·6–15·2) for the chemotherapy group, the primary endpoint of overall survival was significantly improved for nivolumab-treated patients compared with chemotherapy-treated patients (median 10·9 months, 95% CI 9·2–13·3, *vs* 8·4 months, 7·2–9·9; hazard ratio 0·77, 95% CI 0·62–0·96; p=0·019). There were numerically fewer grade 3 or grade 4 treatment-related adverse events in the nivolumab group than in the chemotherapy group (grade 3, 33 [16%] *vs* 85 [41%]; grade 4, five (2%) *vs* 46 [22%]), and a prespecified exploratory analysis showed improved health-related quality of life for patients receiving nivolumab compared with those receiving chemotherapy. These findings are important for patients, especially because of the longer duration of treatment associated with effective nivolumab therapy. As a result of these landmark findings, nivolumab might be adopted as a standard second-line treatment option for patients with oesophageal squamous cell carcinoma, who have had few options available so far.

Despite these game-changing results, ATTRACTION-3 also highlighted several, now familiar, challenges associated with immunotherapy in modestly sensitive patient populations.[3] There was no incremental increase in the number of patients achieving an objective response for nivolumab compared with chemotherapy (33 [19%] *vs* 34 [22%]), and median progression-free survival did not statistically differ between treatment groups. Accordingly, the overall survival curves crossed early. However, even with a higher proportion of patients who had initial disease progression, patients treated with nivolumab were not disadvantaged in terms of treatment with third-line therapy.

Although early progression is a concern, there is not yet enough information to accurately gauge which patients with oesophageal squamous cell carcinoma will benefit from nivolumab. In ATTRACTION-3,[2] the patients who appeared to derive the most advantage from nivolumab were younger (<65 years) and did not have recurrent disease following previous treatment. However, older patients and patients previously treated with radiotherapy and surgery also had improved overall survival with nivolumab, albeit with a smaller magnitude of benefit, and therefore these subgroup results should be used to inform conversations about risks and benefits with patients, rather than to select patients for treatment.

The relationship between PD-L1 expression and anti-PD-1 therapy outcome in oesophageal squamous cell carcinoma is variable. In ATTRACTION-3, the level of PD-L1 expression on tumour cells did not correlate with nivolumab benefit according to a prespecified interaction test. However, the degree of benefit from nivolumab did appear to favour patients who had PD-L1-expressing tumours, although higher levels of PD-L1 expression did not provide any further advantage. Here, the results of ATTRACTION-3 differ from those of the KEYNOTE-181 study,[4] in which pembrolizumab did not improve overall survival compared with chemotherapy for patients with oesophageal squamous cell carcinoma and a PD-L1 expression combined positive score of 1 or more on tumour and immune cells. In KEYNOTE-181 overall survival in oesophageal squamous cell carcinoma was one of three co-primary endpoints and therefore subject to stringent correction for α splitting, which might

have obscured a clinically relevant benefit. By further contrast with ATTRACTION-3, in KEYNOTE-181, high-level PD-L1 expression (ie, combined positive score ≥10) on tumour and immune cells predicted a significant improvement in overall survival with pembrolizumab compared with chemotherapy. In oesophageal cancer, as in other tumour types, the value of PD-L1 staining might be equally dependent on an antibody and testing compartment.[5]

Finally, although ATTRACTION-3 potentially sets a new standard for previously treated patients with oesophageal squamous cell carcinoma, the inclusion of few non-Asian participants might undermine the trial's global generalisability. The main drivers of non-endemic oesophageal squamous cell carcinoma pathogenesis (tobacco and alcohol) are similar in Asian and non-Asian countries, suggesting an underlying common biology. However, subgroup analysis of the more global KEYNOTE-181 trial suggests anti-PD-1 therapy is more effective in Asian patients with oesophageal squamous cell carcinoma than in non-Asian patients.[4] Determining whether tumour or host factors, including ethnicity or region of origin, have precedence in response to immune checkpoint blockade in oesophageal cancer will be crucial for future trial design and from a regulatory perspective. However, these issues should not detract from the large number of patients with oesophageal squamous cell carcinoma for whom the results of ATTRACTION-3 will provide renewed hope. In future, it is possible that perioperative immunotherapy or combinations of immunotherapy and chemotherapy or chemoradiation might ultimately improve long term survival in patients with early and locally advanced oesophageal squamous cell carcinoma.

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Quality of life considerations in the treatment of metastatic hormone-sensitive prostate cancer

Globally, the incidence and prevalence of prostate cancer are increasing, with more than 1·2 million men now estimated to be diagnosed every year.[1] Although in countries such as the USA and Australia, most men will be diagnosed with localised disease,[2] the burden of metastatic disease is still substantial and unevenly distributed.[3] Furthermore, men with advanced or metastatic disease experience poorer quality of life, and higher psychological morbidity and risk of suicide than men with localised disease.[4,5] Therefore, for these men, a consideration of the patient experience is crucial. In *The Lancet Oncology*, Neeraj Agarwal and colleagues[6] present patient-reported outcomes from the TITAN study, providing insight into the effects on quality of life when apalutamide is used as an adjunctive therapy to androgen deprivation in men with metastatic castration-sensitive prostate cancer. The question of treatment burden is important to men diagnosed with metastatic castration-sensitive prostate cancer, for whom overall survival, as well as radiographic progression-free survival and delay to cytotoxic therapy, are critical. But do treatments that improve these outcomes come at a cost of compromised quality of life?

In the TITAN study,[6] 1052 patients with metastatic castration-sensitive prostate cancer who were on continuous androgen deprivation therapy were randomly assigned to receive apalutamide (n=525) or a placebo (n=527). The previously reported primary


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