PD-1 antagonist antibody treatment for patients with oesophageal squamous-cell carcinoma

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The recent exciting publication by Kudo \textit{et al}. (Nivolumab treatment for oesophageal squamous-cell carcinoma: an open-label, multicentre, phase 2 trial) (1) has added yet another high mutational load tumor to the list of advanced cancers that benefit from immune check-point inhibition, and provides a greater impetus for clinical trials in these patients. The 1990’s saw several studies out of Japan utilizing the “original” immune check-point inhibitor, Interleukin-2, in new and imaginative ways for patients with advanced esophageal cancer (2-5). An interest in immune activation continues, with strategies to block immune check-points or infuse activated tumor infiltrating lymphocytes following in the footsteps of such pioneering trials. Reports such as this not only give us insight into the potential benefits from this class of antibodies, but also provide an impetus to pursuing other avenues of targeted immune activation.

As more patients become eligible for such novel trials, we should not lose sight of an important consideration to maximize not only our knowledge, but also patient benefit. As Kudo and colleagues point out, profiling pre-treatment tumor samples for the expression of immune check-point proteins (PD-L1, CTLA-4, etc.) in future trials may help investigators personalize treatment, and increase the response rate to a particular drug regimen. We know that the expression of PD-L1 and PD-L2, members of the B7-H1 family of molecules, in esophageal cancer varies substantially by institution and technique, and has been an important determinant in indicated use of PD-1 inhibitors for patients with lung cancer and melanoma (6). The cited study by Ohigashi \textit{et al}. found protein or mRNA expression of PD-L1/2 in just over 40% of between 31 and 41 samples, but this represents a small number of patients from a single study (7). A patient specific strategy should be considered, as the current trial did not use PD-L1 expression as a criterion for enrollment. Hopefully future trials will take this into account. In addition, we now understand that radiation and chemotherapy will change the expression profiles of these immune check-points in esophageal cancer, so the timing of tumor sampling will be critical prior to initiating treatment (8).

The future is bright for immune activation in esophageal and other cancers, and we look forward to more trials that pave the way for the next evolution in treatment. As more sophisticated options emerge, and a greater understanding of the underlying tumour biology behind immune evasion emerges, it will be critical to drive T-cell therapies that enhance deep and durable benefit for our patients. The notion that T-cells might also promote tumour growth through the release of exosomes driving the epithelial mesenchymal transition (9) or promoting autophagy and survival pathways should also be considered. Other B-7H1 family members including B7-H3 and B7-H4 should also be studied for their important prognostic information (10) and as potential targets for inhibition.
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Footnote

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