Improving the outcomes of checkpoint inhibitors in breast cancer

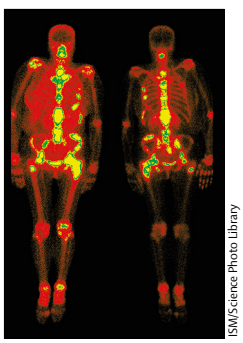
Checkpoint inhibitors have revolutionised the way that cancer is treated in all developed countries, with numerous checkpoint inhibitors approved to treat multiple tumour types. Unfortunately, the results for checkpoint inhibitors in breast cancer have been less successful. Most of the positive results to date in this setting have been reported in triple-negative breast cancer, which comprises only 15% of breast cancers, but is known to induce a higher level of endogenous immune response than other breast cancer subtypes. Of substantial interest, the recently reported IMPASSION-130 study[1] showed improvements in progression-free survival in patients with metastatic triple-negative breast cancer treated with atezolizumab (a programmed cell death 1 ligand 1 [PD-L1] inhibitor) plus nab-paclitaxel, compared with nab-paclitaxel alone. However, there was no difference in overall survival.

Much less has been done with checkpoint inhibitors in HER2-positive breast cancers, because multiple effective HER2-targeted therapies are available for these patients. A phase 1 trial[2] of avelumab (anti-PD-L1) alone in 26 PD-L1-unselected, HER2-positive patients with metastatic breast cancer, showed no objective responses. In *The Lancet Oncology*, Sherene Loi and colleagues[3] have taken a different approach, and tested a programmed cell death protein 1 (PD-1) inhibitor (pembrolizumab) in combination with anti-HER2 therapy (trastuzumab) in patients with HER2-positive, metastatic breast cancer who had progressed on a previous trastuzumab-containing regimen. In the single-arm, PANACEA trial, the authors report six (15%) of 40 patients with freshly biopsied, PD-L1-positive metastatic tumours had an objective response and ten (25%) achieved durable disease control with pembrolizumab plus trastuzumab, which seems to translate to good overall survival outcomes in these heavily pre-treated patients. Sequentially enrolled patients with PD-L1-negative tumours had no objective responses with the same combination therapy.

Although these results are encouraging and will inform the next confirmatory trial, the authors highlight some of the limitations of the study. It is difficult to truly compare the PD-L1-positive and PD-L1-negative cohorts because they were not concurrently enrolled. Furthermore, the PD-L1-negative patients were older, with a lower performance status, and treated later in their disease course than their PD-L1-positive patients. PD-L1 status (positive *vs* negative, or degree of expression) has been difficult to consistently correlate with response to PD-1 inhibitors. Although it might appear that this inconsistency is related to tumour histology, it is more probably related to the testing method used, the interpretation of these results, the tumour quality tested, or the timing of the testing in relation to lines of therapy because PD-L1 expression is known to be a dynamic marker.

In PANACEA, it is unclear whether trastuzumab is necessary to achieve the reported activity. All 58 patients in the trial showed disease progression after trastuzumab and 51 (88%) had received at least one additional HER2-targeted therapy. Therefore, the continued benefit from trastuzumab is in question. However, given the results of PD-L1 monotherapy with avelumab in this setting,[2] pembrolizumab might be acting synergistically with trastuzumab through an immune-mediated mechanism. Indeed, at the 2018 ESMO Congress, Hale and colleagues[4] reported results from a randomised, phase 2b trial of a HER2 vaccine that showed a significant reduction in recurrence in patients with triple-negative breast cancer when combined with trastuzumab, compared with trastuzumab alone. Additionally, preclinical data have underscored the immune mechanisms of trastuzumab and its synergy with T-cell-eliciting therapies.[5] Therefore, a follow-on trial should randomly assign patients to pembrulizumab plus trastuzumab versus pembrolizumab alone, to confirm the contribution of the individual drugs and reduce patient exposure to toxicities associated with long-term trastuzumab therapy if unnecessary.

One of the more important features of the PANACEA trial is its correlative work on tumour-infiltrating lymphocytes. Using a simple assessment of tumour-infiltrating lymphocytes on haematoxylin and eosin-stained slides, the authors showed that tumour-infiltrating lymphocyte levels were higher in responding patients than in those who did not respond. Furthermore, by arbitrarily setting the tumour-infiltrating lymphocyte



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level at 5%, the frequency of response doubled. This finding could substantially improve the results of future trials by enriching for patients more likely to respond to this combination. Ongoing studies of checkpoint inhibitors are assessing not only PD-L1 and tumour-infiltrating lymphocytes, but also tumour mutational burden as a prognostic biomarker.[6] Once better understood, these factors, probably in combination, will help improve trial design, select target patient populations, limit toxicities, and improve outcomes in future trials of checkpoint inhibitors alone or in combination therapies.

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