hormone receptor-positive disease and hormone receptor-negative disease, with the hormone receptor-positive group having a lower proportion of disease-free survival events earlier in follow-up.[3] Data show that disease-free survival events occurring later in follow-up are more likely to be contralateral breast cancers and non-breast cancer deaths and are less likely to be locoregional and distant recurrences.[6] The possible influence of non-breast cancer death on the surrogacy of disease-free survival is supported by data in Saad and colleagues' analysis showing both improved patient-level and improved trial-level association between disease-free survival and breast cancer-specific survival (which excludes deaths unrelated to breast cancer) compared with overall survival (which is agnostic to cause of death). This finding highlights the importance of competing risks of death in the interpretation of trials over long-term follow-up.

With many registration trials in early breast cancer using disease-free survival as the primary endpoint, a question that needs to be answered is whether the data reported by Saad and colleagues can be extrapolated to other settings. Triple-negative breast cancer is associated with a high frequency of disease-free survival events similar to that seen in HER2-positive disease untreated with trastuzumab. However, the magnitude of relative treatment effect in this subgroup is smaller.[7] For hormone receptor-positive, HER2-negative disease, the low event frequency and higher proportion of disease-free survival events unrelated to breast cancer would probably result in reduced performance of disease-free survival as a surrogate for overall survival.

Saad and colleagues should be congratulated for their work to assess the use of disease-free survival as a primary endpoint in a defined subgroup of early-stage breast cancer, and for providing a blueprint for the validation of disease-free survival in this setting. Attempts to validate disease-free survival as a surrogate for overall survival should be pursued in a broader group of breast cancers while ensuring (as in Saad and colleagues' analysis) that assessment includes not only the strength and consistency of correlation between the surrogate and definitive endpoints at the trial level, but also the prediction of the net effect of treatment at a patient level.

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1 Zhao F. Surrogate end points and their validation in oncology clinical trials. *J Clin Oncol* 2016; **34:** 1436–37.
2 Saad ED, Squifflet P, Burzykowski T, et al. Disease-free survival as a surrogate for overall survival in patients with HER2-positive, early breast cancer in trials of adjuvant trastuzumab for up to 1 year: a systematic review and meta-analysis. *Lancet Oncol* 2018; published online Jan 29. http://dx.doi.org/10.1016/S1470-2045(18)30750-2.
3 Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; **353:** 1673–84.
4 von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med* 2017; **377:** 122–31.
5 Tolaney SM, Barry WT, Guo H, et al. Seven-year (yr) follow-up of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC). *J Clin Oncol* 2017; **35** (suppl)**:** 511 (abstr).
6 Algorashi I, Goldvaser H, Ribnikar D, Cescon DW, Amir E. Evolution in sites of recurrence over time in breast cancer patients treated with adjuvant endocrine therapy. *Cancer Treat Rev* 2018; **70:** 138–43.
7 Esserman LJ, Berry DA, DeMichele A, et al. Pathologic complete response predicts recurrence-free survival more effectively by cancer subset: results from the I-SPY 1 TRIAL--CALGB 150007/150012, ACRIN 6657. *J Clin Oncol* 2012; **30:** 3242–49.

Improving the outcomes of checkpoint inhibitors in breast cancer

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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

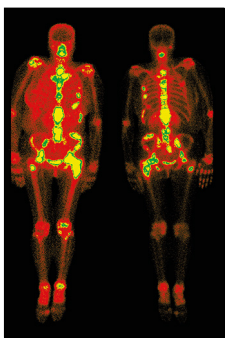
subtypes. Of substantial interest, the recently reported IMPASSION-130 study[1] showed improvements in progression-free survival in patients with metastatic triple-negative breast cancer treated with atezolizumab (a programmed cell death 1 ligand 1 [PD-L1] inhibitor) plus nab-paclitaxel, compared with 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 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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1 Schmid P, Adams S, Rugo HS,et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med* 2018; **379:** 2108–21.

2 Dirix LY, Takacs I, Jerusalem G, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. *Breast Cancer Res Treat* 2018; **167:** 671–86.

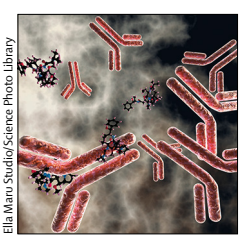
3 Loi S, Giobbie-Hurder A, Gombos A, et al. Pembrolizumab plus trastuzumab in trastuzumab-resistant, advanced, HER2-positive breast cancer (PANACEA): a single-arm, multi-centre, phase 1b–2 trial. *Lancet Oncol* 2019; published online Feb 11. http://dx.doi.org/10.1016/S1470-2045(18)30812-X.

4 Hale DF, Mittendorf EA, Brown TA, et al. Pre-specified interim analysis of a randomized phase IIb trial of trastuzumab + nelipeptimut-S (NeuVax) vs trastuzumab for the prevention of recurrence demonstrates benefit in triple negative (HER2 low-expressing) breast cancer patients. *Ann Oncol* 2018; published online Oct 23. DOI:10.1093/annonc/mdy288.001.

5 Gall VA, Philips AV, Qiao N, et al. Trastuzumab Increases HER2 uptake and cross-presentation by dendritic cells. *Cancer Res* 2017; **77:** 5374–83.

6 Ott PA, Bang YJ, Piha-Paul SA, et al. T-cell-inflamed gene-expression profile, programmed death ligand 1 expression, and tumor mutational burden predict efficacy in patients treated with pembrolizumab across 20 cancers: KEYNOTE-028. *Proc Am Soc Clin Oncol* 2018; published online Dec 13. DOI:10.1200/JCO.2018.78.2276.

Targeting tissue factor in advanced solid tumours



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Despite the development of more effective therapies that modulate antitumour immune responses, target oncogenic mutations, and block key hormonal and cell cycle pathways, outcomes remain poor in many patients with metastatic cancers. Antibody–drug conjugates—which are therapeutics composed of an antibody that targets receptors overexpressed on cancer cells, a cytotoxic agent or payload, and a linker molecule—are an intriguing approach in these settings. Antibody–drug conjugates might offer advantages over both conventional chemotherapy (by permitting delivery of the cytotoxic molecule to the tumour microenvironment, while limiting systemic absorption) and classical antibody-directed therapy (by the addition of a cytotoxic payload). So far, four antibody–drug conjugates have been approved by the US Drug and Food Administration for cancer treatment.[1] Gemtuzumab ozogamicin, an anti-CD33 antibody linked to calicheamicin, is approved for acute myeloid leukaemia. Inotuzumab ozogamicin, an anti-CD22 antibody linked to calicheamicin, is approved for acute lymphoblastic leukaemia. Brentuximab vedotin, an anti-CD30 antibody linked to monomethyl auristatin E (MMAE), is approved for Hodgkin lymphoma (both relapsed refractory and untreated disease in combination with chemotherapy), both systemic and cutaneous anaplastic large cell lymphomas, and CD30-expressing mycosis fungoides. In 2013, ado-traztuzumab emtansine, which is a human epidermal growth factor receptor 2-targeted antibody linked to DM1 (a microtubule inhibitor), was approved for human epidermal growth factor receptor 2-positive metastatic breast cancer, becoming the first antibody–drug conjugate approved for treatment of solid tumours. The success of these antibody–drug conjugates has spurred further interest in evaluating different antibodies and cytotoxic molecules, with more than 60 of these therapeutics currently under investigation.[2]

Tissue factor is a 47-kDa transmembrane glycoprotein that activates the extrinsic coagulation pathway, and is overexpressed in numerous cancers as a result of hypoxia, loss of tumour suppressor genes (such as *TP53* and *PTEN*), and overactivity of MAPK signaling.[3] Tissue factor is of interest as an anticancer therapy because of its overexpression in various cancers, its perceived role in oncogenesis, and its association with inferior clinical outcomes.[4,5] The targeting of tissue factor with tisotumab vedotin and other agents had only minimal effects on coagulant and bleeding parameters in pre-clinical models, providing some reassurance that this approach could be feasible in patients.[6]

In *The Lancet Oncology*, Johann S de Bono and colleagues[7] report the outcomes of a phase 1–2, open-label, dose-escalation and dose-expansion study evaluating the safety, tolerability, pharmacokinetics, and preliminary antitumour activity of tisotumab vedotin in patients with advanced cancer. Tisotumab vedotin is an antibody–drug conjugate that links a fully human monoclonal antibody targeting tissue factor with MMAE. Although the study was done in cancers with relatively high concentrations of tissue factor expression, patients were not selected for eligibility on the basis of this marker. The dose-escalation phase showed a maximum tolerated dose of 2·0 mg/kg given intravenously every 3 weeks. In the dose-expansion phase, some preliminary