Beware trial end point comparisons

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Neoadjuvant systemic therapy is the standard-of-care for patients with locally advanced breast cancer, but is increasingly used in those with early stage disease. Nobody can deny that neoadjuvant treatment offers considerable benefits over adjuvant therapy, including the ability to downstage the primary tumour and axillary disease, and to adapt subsequent treatment according to response and post-treatment disease biology. The neoadjuvant period also provides a window of opportunity for drug-development efforts: intermediate end points, chiefly pathological complete response (pCR) rates, can expedite drug approval. For example, the addition of pertuzumab to trastuzumab and docetaxel in the neoadjuvant setting received accelerated approval based on an improvement in the pCR rate. In fact, the FDA has issued a draft guidance for using pCR as a surrogate end point for accelerated drug approval. Caution must be applied, however, when considering drug approval for entire patient populations based on this end point. In this issue, De Mattos-Arruda *et al.* compare and contrast the current findings from neoadjuvant and adjuvant trials of dual-agent anti-HER2 therapy comprising trastuzumab and lapatinib in patients with breast cancer, highlighting that ‘one size does not fit all’ when translating neoadjuvant therapy into survival benefits.

The authors outline the potential reasons why treatments that improve pCR rates in the neoadjuvant setting do not translate into survival benefits when used in the adjuvant setting, using results of the NeoALTTO and ALTTO trials to emphasize this disparity; important considerations include differences in trial designs (for example, treatment regimens, statistical power, end points), the patient populations enrolled, and the effects of treatment on disease biology. While editing this article, it became apparent that questions surrounding the translation of dual-agent anti-HER2 therapy into survival benefits apply not only to the adjuvant setting, but also to neoadjuvant treatment. Indeed, analysis of the evidence revealed important differences in the conclusions that are prominent in reports of neoadjuvant and adjuvant trial results.

The key issue is the use of the intermediate end point, pCR rate, as the primary end point in neoadjuvant trials. Although pCR rates were improved — and thus the primary end point met — in the NeoALTTO trial, this end point is fundamentally different to that used in adjuvant trials, which is usually disease-free survival (DFS) and approximates to event-free survival (EFS). Thus, we are not comparing apples with apples. If we compare apples with apples (or rather DFS with EFS), a different picture

emerges: DFS/EFS survival was not improved with the addition of lapatinib to trastuzumab in either the NeoALTTO or ALTTO trials.

The relationship between the extent of tumour regression and survival end points following tumour resection is an important question, considering the goal of surgery for early stage breast cancer is to remove all detectable disease. Patients with a pCR to neoadjuvant therapy do tend to have better survival outcomes, although this relationship varies across disease subtypes: in NeoALTTO, a pCR to dual-agent anti-HER2 therapy was associated with longer survival in patients with HER2+/ER– disease, but not in those with HER2+/ER+ disease. No differences in survival outcomes were reported, however, between the ER– and ER+ disease subgroups as a whole, mirroring findings in the adjuvant setting. Moreover, in NeoALTTO, pCR was independently associated with EFS in patients treated with dual-agent HER2 therapy, but not in the other treatment groups. This finding suggests that the strength of the correlation between pCR rates and survival outcomes might vary between treatments.

Thus, a more important question is whether pCR should form the basis for approval of treatments for use in entire patient populations, many of who might not gain benefit and will be at risk of financial and biological toxicities. Addition of lapatinib to trastuzumab increases pCR rates by approximately 20–25%, depending on ER status, but the lack of patient stratification potentially exposes all patients to the costs and adverse effects of lapatinib. The drawbacks of dual-agent HER2 blockade might be acceptable to patients with a pCR; however, since only an extra ~20% of patients will experience a pCR and currently these patients cannot be identified *a priori*, should this treatment be approved for use in all patients — bearing in mind the links between pCR and survival remain unclear? In the absence of biomarkers of response, decision-making is based on survival improvements observed for entire treatment cohorts, which would not be reflected in an approval based on pCR rates. Defining a threshold for improvement in pCR rates might be a better approach to determine whether neoadjuvant therapy will translate into survival benefits.

The preoperative period remains useful to test novel therapies, owing to the relatively short treatment durations and the possibility to obtain biopsies. Identification of biomarkers with good predictive performance would not only spare patients from futile treatment, but could also enable the design of novel trials that demonstrate the benefits of therapy for appropriately selected patients.

David Killock is a Senior Editor and Lisa Hutchinson is the Chief Editor of *Nature Reviews Clinical Oncology*.

Competing interests
The authors declare no competing interests.