Everolimus, when combined with exemestane, adds toxicity with minimal benefit for women with breast cancer

The lead editorial in the April 2014 issue of *Annals of Oncology* sets appropriate standards for acceptance of manuscripts: they should be reproducible, innovative, global and balanced. Yet in this issue are two articles that comment on adverse events associated with everolimus and exemestane in the BOLERO-2 trial [1, 2]. That trial was innovative and global, but these reports are not balanced.

The original report of BOLERO-2 showed a substantial difference in progression-free survival (PFS) in favour of everolimus and exemestane compared with exemestane alone; the hazard ratio (HR) was 0.43 ($P < 0.001$) [3]. That analysis was subject to bias because of informative censoring, which was not balanced between the arms: almost 40% of locally assessed PFS events were deemed non-events upon central review. Further, 24% versus 6% of women on experimental versus control arms withdrew from treatment before disease progression because of toxicity or other reasons. Most patients who withdraw from treatment are not doing well and many will refuse to continue with scheduled radiologic assessments, resulting in a bias which favours the more toxic therapy [4]. Finally, an improvement in PFS is not an effective measure of benefit to patients, nor has it been shown to be a valid surrogate for overall survival or its quality. Analysis of overall survival of the BOLERO-2 trial was presented at the 2014 European Breast Cancer Conference with the finding of a modest (HR = 0.89) and non-significant difference between the arms of the study [5].

The articles by Aapro et al. [1] and by Rugo et al. [2] evaluating toxicity and its management show that there was greater toxicity in the combined everolimus and exemestane arm of the BOLERO-2 trial, including stomatitis, pneumonitis, hyperglycaemia and fatigue. Some women on the experimental arm might have had improved or maintained quality of life (QoL), and a previous analysis suggested slower decline in QoL, but this was also confounded by unbalanced informative censoring [6]. Therefore, one can only conclude that the combination of everolimus and exemestane has greater biological activity than exemestane alone, but unfortunately, adds substantial toxicity with only a small improvement in survival.

Then there is the question of balanced reporting. The final sentence of one article [1] states: 'Overall everolimus is an effective treatment option, with manageable toxicity, among patients with HR^+ advanced breast …'. The second article [2] ends with the statement: 'Understanding the time course of AEs … is particularly important given the clinical benefit obtained from adding everolimus to exemestane and the differential toxicities associated with this targeted agent'. In our lexicon, therapies that increase toxicity with minimal improvement in survival are not 'effective treatment options' and they do not provide 'clinical benefit'.

We suggest an alternative concluding sentence to these articles: 'Although the combination of everolimus and exemestane has greater anti-tumour activity than exemestane alone, it leads to only a modest improvement in survival in an unselected population and it adds substantial toxicity'.

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disclosure

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Reply to the letter to the editor 'Everolimus, when combined with exemestane, adds toxicity with minimal benefit for women with breast cancer' Tannock and Pond

Thank you for your comments [1] regarding our papers [2, 3]. We appreciate the opportunity to respond in detail to your letter that in our opinion contains statements that do not reflect the actual Bolero-2 data. Our papers are balanced and accurately present available data. One paper reviews in detail the incidence and time course of toxicity from the combination of everolimus (EVE) and exemestane (EXE) [2], and the other gives practical guidance on how to manage these side-effects [3]. We believe these papers provide an objective assessment of both efficacy and toxicity of this novel therapy, and also represent an