Reply to the letter to the editor

‘Duration of endocrine therapy and its impact on the results of adjuvant trials in premenopausal breast cancer patients’

by Fouad et al.

We appreciate the interest of Fouad et al. [1] in ABCSG-12. However, several comments have to be made: despite looking closely, we were unable to identify comments of Fouad et al. with respect to the claimed ‘various shortcomings’ of ABCSG-12—in fact, we note a single concern only: protocol-violating treatment extension in the ovarian function suppression (OFS) plus tamoxifen (TAM) arm may have confounded trial results.

Treatment continuation outside of an adjuvant protocol would indeed constitute a potential confounder, however did not occur in ABCSG-12: clearly, such a confounder would lead to a difference in disease-free survival (DFS), not in postrelapse overall survival (OS). The TAM–Anastrozol DFS outcome in ABCSG-12 was similar throughout the long-term follow-up of the trial, with superimposable curves in all respective publications [2–4]. The claims by our colleagues are thus not supported by the data, which up to a median of almost 95 months have matured remarkably well; all hazard ratios (HRs) of DFS and OS have been highly stable at all times of analysis. On a further note, although the existence of a confounder can never be completely ruled out, it does seem highly unlikely in light of the accurate documentation about any postprotocol therapy received in this FDA-inspected trial database.

While intertrial comparisons between SOFT and ABCSG 12 should be (as always) interpreted with great caution, Fouad et al. also err in stating that ABCSG-12 contradicts the analysis of the SOFT trial: in the subgroup of SOFT patients who did not receive adjuvant chemotherapy, there is no significant DFS difference between TAM and exemestane [5], a result that is highly similar to ABCSG-12. Likewise, the striking deterioration of postrelapse survival in patients who had adjuvant OFS and aromatase inhibitors (AIs) is both present in ABCSG-12 and the combined SOFT/TEXT analysis, with respective HRs of 0.72 for DFS and 1.14 for OS [6]. As a result, many international opinion leaders have recently voiced their concerns about potential long-term adverse effects of the OFS+AI combination at the occasion of the recent St Gallen Breast Cancer Consensus in Vienna [7].

Finally, it remains less than clear that 5 years are in fact an inevitable ‘standard’ duration in premenopausal breast cancer: treatment durations within pivotal clinical trials of OFS have increased over time [8], starting historically with 6 months, 18 months [9], 2 years [10], 3 years [11] to 5 years. While in general adjuvant endocrine treatment durations increase particularly for postmenopausal breast cancer [12], there is considerable concern that extending endocrine therapy severely impairs patients’ quality of life, particularly in younger patients [13]. Dramatic side-effects on bone have been well described even after only 3 years of endocrine therapy [14], and the true impact of hormonal treatments in young women with active personal and professional lives may be well hidden between the lines of clinical trial data, but can loudly be heard by clinicians who take an active interest during patient follow-up. Identifying better selection criteria, either based on molecular or clinical parameters [15], to avoid highly displeasing overtreatment, is the task at hand [16].

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References

An activating ALK gene mutation in ALK IHC-positive/FISH-negative nonsmall-cell lung cancer

ALK inhibitors (i.e. crizotinib and alectinib) exhibit marked anti-tumor activity against nonsmall-cell lung cancer (NSCLC) with ALK rearrangements [1, 2]. The detection of ALK rearrangements is mainly carried out using fluorescence in situ hybridization (FISH). However, such analyses can yield false-positive and false-negative results [3, 4]. Other ALK diagnostic techniques have been developed, including immunohistochemistry (IHC) for the detection of the ALK protein [5]. Several studies have shown that IHC is sensitive and specific for the determination of ALK protein expression and is an accessible, cost-effective, and rapid alternative to the ALK FISH assay. In addition, some authors have reported significant clinical improvement with crizotinib in patients with tumors that were designated as ALK-negative using FISH but were found to be ALK-positive using IHC, raising the possibility that the FISH assay may miss cases that could benefit from ALK inhibitors [4]. Recently, Ilie et al. reported that the discrepancies observed between IHC and FISH data can reflect unexpected biological events, rather than technical issues, which could potentially have a major impact on therapeutic strategies involving ALK inhibitors [3]. In our present study, we discovered an ALK kinase domain mutation (R1192G) in an ALK IHC-positive but FISH-negative NSCLC specimen (Figure 1A). ALK was phosphorylated when this mutation was overexpressed in the HEK293 cell line (Figure 1B). A focus formation assay using the NIH-3T3 cell line showed that the ALK R1192G mutation had transformational abilities, compared with the controls (Figure 1B). The ALK mutation-overexpressed Ba/F3 cell line showed IL-3-independent growth and was sensitive to ALK inhibitors (crizotinib and alectinib) (Figure 1C). The sensitivity of the cell lines to drugs was consistent with the suppression of phospho-ALK (Figure 1C). In vivo, the growth of tumors from the Ba/F3-ALK R1192G cell line was reduced by alectinib treatment in a dose-dependent manner (Figure 1D). These findings indicate that ALK inhibitors are effective against NSCLC cells carrying the ALK R1192G mutation. To the best of our knowledge, this is the first study to show that a clinical sample with ALK IHC-positive/FISH-negative findings has an ALK-activating mutation. Although this patient has not been treated with any ALK inhibitors because of no recurrence, ALK inhibitors can be effective against such NSCLC cells. Indeed, preliminary data showed that ALK IHC-positive/FISH-negative patients responded to crizotinib [4]. In clinical samples, however, no additional ALK mutation was detected in the other surgically resected NSCLC specimens using next-generation sequencing (supplementary Table S1, available at Annals of Oncology online).

In conclusion, we identified an ALK-activating mutation in an NSCLC clinical sample with ALK IHC-positive/FISH-negative findings and showed that ALK inhibitors can be effective against NSCLC cells carrying this mutation. Because clinical data are lacking, further clinical testing to validate the use of ALK inhibitors for patients with NSCLC carrying this ALK mutation should be carried out. To ensure that candidates for treatment with ALK inhibitors are not missed, further comprehensive analyses, such as NGS, should be introduced into clinical practice.

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