Editorial

Is there a role for adjuvant pertuzumab in HER2-positive breast cancer?

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The outcomes of human epidermal growth factor receptor 2 (HER2)-positive breast cancer was dramatically changed by the introduction of targeted therapies against the HER2 receptor (1). The monoclonal antibody trastuzumab was the first HER2-directed treatment that demonstrated, together with chemotherapy, a significant improvement in treatment outcomes of this subgroup of patients, both in the metastatic (2) and neo-/adjuvant (3-7) settings, thus becoming the mainstay of treatment in HER2 positive breast cancer. The remarkable results achieved led to the development of additional HER2-targeted drugs, raising the hypothesis of a double-HER2 blockade against breast cancer.

Pertuzumab, a humanized monoclonal antibody binding different domain of HER2 receptor compared with trastuzumab (8), showed impressive results in prolonging progression-free survival (PFS) and overall survival (OS) when added to trastuzumab and docetaxel as first-line treatment for metastatic HER2-positive breast cancer, as described by the CLEOPATRA study, with an acceptable toxicity profile (9). Findings in metastatic disease were translated into the neo-adjuvant setting, as described in the phase 2, randomized, multicenter, open-label, NeoSphere trial (10). The addition of pertuzumab to standard of care (trastuzumab plus chemotherapy) resulted in a significant increase in the pathological complete response rate, which switched from 29.0% to 45.8% (10). Moreover, neoadjuvant treatment with pertuzumab resulted in more favorable 5-year PFS and disease-free survival (DFS) (11), even if the trial was not powered to detect differences in survival. These favorable assumptions open the way to the investigation of pertuzumab plus trastuzumab and chemotherapy in the adjuvant setting for HER2-positive breast cancer.

Recently, von Minckwitz *et al.* have reported the results of APHINITY (12), a prospective, randomized, multicenter, double-blind, placebo-controlled trial. From November 2011 through August 2013, a total of 4,805 patients with non-metastatic, adequately excised, histologically confirmed invasive HER2-positive breast cancer were randomly assigned to receive chemotherapy and 1 year of treatment with trastuzumab plus pertuzumab (N=2,400) or chemotherapy and 1 year of treatment with trastuzumab plus placebo (N=2,405) as adjuvant treatment. Either node-positive disease or node-negative with a tumor diameter greater than 1.0 cm were eligible. Patients with node-negative tumors between 0.5 and 1.0 cm in diameter were initially included if at least one high-risk feature was present. The primary end point was invasive DFS, an acceptable surrogate of long term outcomes in the adjuvant setting (13).

Consistently with what observed in the metastatic and neoadjuvant settings, the addition of pertuzumab to trastuzumab and chemotherapy in the adjuvant setting led to significant outcome improvement.

In the overall population, disease recurrence occurred in 171 (7.1%) and 210 (8.7%) patients in the pertuzumab and placebo group, respectively [hazard ratio (HR), 0.81; 95% confidence interval (CI), 0.66–1.00; P=0.045]. The 3-year rates of invasive DFS were 94.1% and 93.2% in the pertuzumab and placebo arm, respectively. These findings

are encouraging but not impressive. In the attempt of clarifying the results observed, we may consider patient- and disease-characteristics, along with relevant methodological aspects. In the pre-planned subgroup analyses, results are statistical significant in patients with node-positive disease: 139 patients (9.2%) in the pertuzumab group and 181 patients (12.1%) in the placebo group had invasive-disease events; the 3-year rate of invasive-DFS was 92.0% in the pertuzumab group and 90.2% in the placebo group (HR 0.77; 95% CI, 0.62–0.96; P=0.02). Similarly, in the cohort of patients with hormone-receptor-negative tumors, 71 patients (8.2%) in the pertuzumab group and 91 patients (10.6%) in the placebo group had invasive-disease events (HR 0.76; 95% CI, 0.56–1.04; P=0.08); the 3-year rate of invasive-DFS was 92.8% in the pertuzumab group and 91.2% in the placebo one (12). No significant differences were found in the node-negative subgroup (P=0.64) or in the subgroup of patients with hormone-receptor-positive disease (P=0.28).

These results suggest that, in a specific group of patients, the addition of pertuzumab to standard adjuvant treatment may be clinically relevant, with patients with node-positive and hormone-receptor-negative tumors showing more favorable outcomes. In this regard, it is mandatory to remember that the study was amended after the enrollment of 3,655 patients to limit patients with node-negative disease. As reported in the manuscript, the reason of the amendment was to yield a patient population whose nodal status distribution was comparable to that anticipated at the time of the study design. Indeed, the HR graphically displayed by the inherent forest plot did not show significant differences for the outcomes considered (3-year invasive-DFS) by protocol version (P=0.69). However, although well justified from a methodological standpoint, we cannot completely exclude a potential impact of this protocol amendment on long term outcomes.

Moreover, the predicted rate of 3-year invasive-DFS of 89.2% for the placebo group was lower than that actually observed (93.2%). This under-estimated rate leads to the need of a higher number of events in both groups for the primary statistical analysis. In this regard, the median period of follow-up for the primary analysis was only 45.4 months. Consistently with what reported by the authors in the discussion concerning the length of follow up, this latter may be not sufficiently extended in the adjuvant setting.

Regarding safety, as in the other studies of combination between pertuzumab and trastuzumab, patients were accurately monitored especially for cardiac toxicity. Primary cardiac events occurred in 17 patients (0.7%) in the pertuzumab group and in 8 patients (0.3%) in the placebo group, most of them during treatment with anthracyclines. Moreover, cardiotoxic events were reported for all patients in the placebo arm from the entire treatment start. Conversely, for patients in the experimental arm, cardiac toxicity was reported only for patients receiving pertuzumab. Therefore, in this latter arm patients who had experienced a previous cardiac event while on chemotherapy treatment were excluded from the analysis.

Relevant differences were registered for diarrhea, with grade 3 or higher, reported almost exclusively during chemotherapy, in 9.8% of the patients in the pertuzumab group and 3.7% in the placebo group, rising to 71.2% and 45.2% for diarrhea of all grades in the two groups, respectively. These findings are consistent with the previous results from the combined analysis of toxicity data of pertuzumab trials (14). Overall, treatment discontinuation for adverse events was 1.1 percentage points higher with pertuzumab than with placebo.

Another key point to be critically considered is the "financial toxicity" affecting the dual HER2 blockade in this setting. Adding 1 year of pertuzumab to adjuvant trastuzumab and chemotherapy increases the cost of treatment of approximately three times. This topic will be likely fully addressed in shortly upcoming risk-benefit analysis including economic aspects which may widely vary by country and inherent regulations.

All these statements bring us back to the initial question of our editorial, namely, "Is there a role for adjuvant pertuzumab in HER2-positive breast cancer?". Overall, APHINITY is a trial with positive findings in terms of invasive-DFS, whose results have to be translated into the clinical practice. The HR reached with the addition of pertuzumab to standard of care (trastuzumab plus chemotherapy) in the adjuvant setting must be weighed against the absolute risk of recurrence. Indeed, as described in the original article, to avoid an invasive disease event, the numbers of patients needed to treat were 112 for the overall population, 56 for the node-positive population, and 63 for hormone-receptor-negative population.

A further topic of potential interest is that the APHINITY trial was conceived on the basis of the results of the previously described neoadjuvant NeoSphere trial (10). Patients included in the NeoSphere study had HER2-positive non-metastatic breast tumors, larger than 2 cm, with any nodal status. When explored in light of its

baseline characteristics, the APHINITY trial population (N=4,804) includes 2,879 (59.9%) patients with a pathologic tumor size larger than 2 cm (mean size 2.4 cm), and 3,005 (62.6%) patients with at least 1 axillary positive node. Thus, more than a half of the population in the APHINITY study could have been candidate for neoadjuvant therapy. In addition, the better outcomes observed with adjuvant pertuzumab were related to patients with node-positive disease. In clinical practice, patients with early HER2-positive, node-positive and/or cT2 cancer are usually candidates for neoadjuvant treatment, aiming at pathological complete response (pCR), a reliable predictor of favorable long-term outcome in high-risk breast cancer (15).

Notwithstanding the previously addressed issues, the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) was recently published to help the clinicians critically consider the clinical significance of research findings from randomized clinical studies (16). Using this reference, the APHINITY trial is placed in the category B of curative setting, thus, clinically relevant for patients' care.

Other studies have investigated the efficacy of the combination of two HER2-directed therapies in early HER2-positive breast cancer, with discrepant results. In the neoadjuvant TRYPHAENA trial, pCR rates of 57.3% to 66.2% were described with regimens combining chemotherapy with trastuzumab and pertuzumab (17). In the NeoALTTO trial, the addition of the HER1/HER2 tyrosine-kinase inhibitor lapatinib to trastuzumab and chemotherapy resulted into a significantly improvement of pCR (18). Conversely, the ALTTO adjuvant trial failed to show a clinical benefit when lapatinib was added to trastuzumab and chemotherapy, which may be partly explained by the numerous limitations of the study (19). Another intriguing study in the adjuvant setting was the ExteNET trial, where neratinib, a pan-HER inhibitor, was investigated for 1 year after the conventional 1-year-treatment with trastuzumab. In the recently published 5-year follow-up analysis (20), in the group of patients treated with neratinib the authors described a significant improvement in terms of invasive-DFS, even if at the expense of increased toxicity, confirming the results of the 2-year follow-up analysis (21).

When globally considered, these data suggest that, despite success in the neoadjuvant setting, the use of HER2 blocking agents other than trastuzumab in addition to this latter has translated in quite discouraging outcomes. Moreover, the improvement in breast treatment outcomes when using trastuzumab *per se* is associated with acceptably low rates of recurrence. On this basis, the design and conduct of adequately powered adjuvant clinical trials may be particularly difficult (22), and demonstrating the efficacy of new drugs and/or combo treatments may take a long time.

In conclusions, following the supportive evidence emerged from the double blockade in the metastatic and neoadjuvant setting, data from the trial carried out by von Minckwitz and colleagues show that the use of pertuzumab and trastuzumab plus chemotherapy in the adjuvant treatment modestly improves treatment outcomes in early HER2-positive breast cancer, with an acceptable toxicity profile. In the clinical practice, this could be a good option, particularly in patients with node-positive or hormone-receptor-negative disease. More mature data are awaited to orient the physician choice relatively to the use of adjuvant pertuzumab across subgroups of patients differing by disease-related key features and patient characteristics.

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Footnote

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