Abstract While in general, not immediately praxis changing, results of various relevant clinical trials were presented at the 2014 ASCO Annual Meeting. Indeed, the ALTTO study provided first (albeit negative) data on the activity of dual Her2 inhibition with trastuzumab and lapatinib (either sequentially or concomitantly) in the adjuvant setting, while a combined analysis of the SOFT and TEXT studies suggested, for the first time, that a combination of ovarian function suppression (OFS) plus exemestane might be superior to OFS plus tamoxifen in premenopausal early breast cancer patients. Results of the POEMS trial investigating the role of the gonadotropin-releasing hormone-analog goserelin in the prevention of chemotherapy-induced amenorrhea led to lengthy debates, as the trial reported a survival benefit in hormone-receptor-negative breast cancer patients receiving goserelin. A subgroup analysis of German Breast Group trial GeparSixto as well as several other phase II trials again emphasized the role of carboplatin in neoadjuvant therapy of triple-negative breast cancer patients. These and other studies will be reviewed within this article.

Keywords ASCO Annual Meeting 2014 · Breast cancer · Highlights · Review

ALTTO
Dual Her2 inhibition is well established in the metastatic setting and is evolving to become a standard in the neoadjuvant setting as well. The NeoALTTO trial reported a significant increase in terms of pathologic complete remission (pCR) rates in early-stage breast cancer patients receiving paclitaxel plus the monoclonal Her2 antibody trastuzumab in combination with the Her2 tyrosine kinase inhibitor (TKI) lapatinib as compared with paclitaxel with either trastuzumab or lapatinib alone [1]. A similar effect was observed with a combination of two Her2 antibodies, trastuzumab and pertuzumab [2, 3]. Other studies, such as APHINITY and ALTTO, aimed to improve outcome in the adjuvant setting by adding either pertuzumab or lapatinib to trastuzumab-based therapy. At the 2014 ASCO Annual Meeting, first results of the ALTTO trial were presented.

Initially, ALTTO was designed as prospective randomized phase III trial including four treatment arms: a standard arm consisting of trastuzumab for 1 year, and three experimental arms consisting of lapatinib for 1 year as well as two combination arms in which lapatinib was added to trastuzumab either in a sequential (i.e., after 12 weeks of trastuzumab) or concomitant manner. Importantly the lapatinib-alone arm was closed at first interim analysis due to futility. Results of the remaining three arms with approximately 6000 patients were now presented [4].

In contrast to the neoadjuvant setting, neither sequential nor concomitant addition of lapatinib to trastuzumab was associated with improved outcome. Of note, 4-year disease-free survival (DFS; 86–88 %) as well as overall survival (OS; 94–95 %) were excellent in all treatment groups, with a lower event rate than anticipated; a significant rate of dose modifications was once more evident in patients receiving a combination of chemotherapy and lapatinib.
Based on these results, adjuvant therapy with trastuzumab for a duration of 1 year remains the standard of care. Lapatinib will continue to have a role in the palliative (and potentially) neoadjuvant settings, while results of the APHINITY study of adjuvant trastuzumab plus pertuzumab need to be awaited before closing the chapter on dual Her2 blockade in the adjuvant setting. Why the obvious benefit observed in the neoadjuvant setting could not be translated into an adjuvant treatment benefit remains currently open for debate, and several explanations exist. First, the ALTTO study accrued a good risk population with a high rate of node-negative patients. This is shown by the excellent outcome, and such patients might derive less benefit from dual blockade. Second, neoALTTO included a nonstandard chemotherapy backbone of paclitaxel alone, which might have increased the relative effect of anti-Her2 therapy. Finally, TKIs such as lapatinib might require a relevant amount of tumor tissue for their activity.

**SOFT and TEXT**

Results of the combined analysis of the SOFT and TEXT trials were awaited with great interest as well [5]. Currently, adjuvant endocrine therapy with tamoxifen is usually regarded as the standard of care in premenopausal women; the exact role of additional ovarian function suppression (OFS) could not be established henceforth, and Austrian Breast and Colorectal Cancer Study Group trial ABCSG-12 failed to show a benefit of anastrozole plus OFS over tamoxifen plus OFS [6]. SOFT and TEXT re-evaluated the role of aromatase inhibitors in combination with OFS in premenopausal early breast cancer patients. Of note, differences existed in between the two trials as well as between SOFT/TEXT and ABCSG-12.

While TEXT was a two-arm trial directly comparing tamoxifen plus OFS with exemestane plus OFS, SOFT included a third arm of tamoxifen without OFS, which may be regarded as standard arm. In contrast to ABCSG-12, no bisphosphonate arm was included, treatment was scheduled for 5 years (as opposed to three years), a high rate of patients had received prior adjuvant chemotherapy, and OFS was conducted with triptorelin, irradiation, or surgery as opposed to goserelin.

In this combined analysis, a significant benefit in terms of DFS was observed in favor of the exemestane group (hazard ratio (HR): 0.72; \(p=0.0002\)), which did not translate into an OS benefit (HR: 1.14; not significant).

As outlined, several factors may explain the differential outcome of SOFT/TEXT and ABCSG-12. While exemestane plus OFS was superior to tamoxifen plus OFS, it appears too early to accept exemestane plus OFS as novel treatment standard in premenopausal patients. Indeed, tamoxifen alone is commonly regarded as standard therapy, and the third (tamoxifen alone) arm of SOFT has not been yet reported. Furthermore, it should be remembered that OFS for 5 years is associated with relevant toxicity in a premenopausal patient population.

**POEMS**

Another trial of interest was POEMS [7], a study analyzing the role of goserelin in the prevention of premature ovarian failure (POF). Of note, POF has evolved to become a relevant problem in young women with breast cancer as the age of first pregnancy increases. Henceforth, studies as well as meta-analyses with regard to the role of gonadotropin-releasing hormone agonists in the prevention of POF have brought up inconclusive or conflicting results. Therefore, results of POEMS were eagerly awaited.

Disappointingly, the planned number of patients could not be accrued, as only 257 premenopausal patients were finally included (218 evaluable for response). All patients had steroid-receptor-negative breast cancer and received cyclophosphamide-containing chemotherapy and were randomized to goserelin once every 4 weeks starting at least 1 week prior to first chemotherapy dose until the completion of chemotherapy (±2 weeks) or control. Rate of POF was chosen as primary study end point and defined as amenorrhea and follicle-stimulating hormone serum levels within the postmenopausal range during the last 6 months at 2 years after randomization. A significantly lower POF rate was observed in the intervention group (22 versus 8%; \(p=0.03\) for unadjusted analysis, \(p=0.08\) for adjusted logistic regression analysis), suggesting activity of goserelin in the prevention of chemotherapy-induced ovarian failure. Furthermore, a higher rate of pregnancies was observed in the goserelin group as well (22 versus 13; \(p=0.05\)). It was, however, another secondary end point that caused heated discussions: authors reported a significant benefit in terms of DFS (HR: 0.49; \(p=0.04\)) as well as OS (HR: 0.43; \(p=0.05\)) in patients receiving goserelin.

In summary, interpretation of these data appears difficult. Clearly, the biological mechanism causing an OS benefit with anti-hormonal therapy in steroid-receptor-negative patients awaits further clarification. Taking into consideration that in other recent studies (including thousands of patients), a lower than anticipated event rate was observed causing problems with statistical analysis, a bias might have caused the OS benefit in POEMS. In this light, the higher rate of pregnancies may also indicate a healthy mother bias casting doubts on the trial’s results.

**Evaluating the role of bevacizumab and carboplatin in the neoadjuvant setting**

The neoadjuvant AVATAXHER trial [8] evaluated the effect of adding bevacizumab to docetaxel plus trastuzumab in Her2-positive early breast cancer patients. This phase II study had an interesting design: patients received one cycle of standard docetaxel plus trastuzumab therapy and were then re-evaluated with positron emission tomography–computed tomography. Patients without clear reduction in tumor metabolism were randomized to docetaxel plus trastuzumab with or
without bevacizumab. In the bevacizumab group, a significant increase in pCR rates was observed (42.5 versus 24%), again indicating that bevacizumab offers activity in selected patients also in the neoadjuvant setting. The well-rehearsed drawback—the lack of reliable predictive factors—of course remains.

Three trials presented in a “poster highlights” session evaluated the respective roles of carboplatin and bevacizumab in neoadjuvant therapy of Her2-negative breast cancer patients. A randomized phase II study indicated that the addition of carboplatin to weekly paclitaxel yielded a significant increase in pCR rates, with the largest benefit shown in triple-negative patients (entire population: pCR: 31.8 versus 17.6%; p = 0.01; triple-negative population: 61.2 versus 26.3%; p = 0.003) [9]. These results were well in line with another study evaluating a combination of docetaxel and carboplatin in the neoadjuvant setting. Of note, a relevant activity of this regimen was shown in both, patients with and without BRCA mutations, as a pCR rate of 50% in sporadic triple-negative patients was reported [10]. Finally, the phase II ARTemis study indicated that the addition of bevacizumab to standard chemotherapy (without carboplatin) yielded a significant improvement in terms of pCR; of note, this effect was limited to patients with low or entirely without steroid receptor expression, similar to data from the GeparQuinto trial [11, 12]. In summary, these data once again suggest relevant activity of carboplatin in the neoadjuvant setting at least in triple-negative early breast cancer patients. The exact role of bevacizumab in this setting, however, awaits further clarification. Still, these results once more showed that a subset of patients evidence benefits from neoadjuvant bevacizumab.

Of note, the role of carboplatin was also emphasized by a subgroup analysis of German Breast Group trial GeparSixto: addition of carboplatin yielded an increase in pCR rates in patients with BRCA germ-line mutations (odds ratio (OR): 2.75), patients with positive family history lacking BRCA germ-line mutations (OR: 2.29), and also (albeit to a lesser extent) in sporadic triple-negative patients (OR: 1.79) [13]. While final evidence from a phase III trial is still lacking, available data from numerous phase II trials now indicate that carboplatin has a role in the neoadjuvant treatment of triple-negative breast cancer patients.

Summary

In summary, no single trial presented at the 2014 ASCO Annual Meeting will change clinical practice by itself. Still, results provided relevant information and may eventually help in optimizing current treatment strategies.

Take-home massage

The ALTTO trial could not provide evidence of superior activity of lapatinib plus trastuzumab (administered either sequentially or concomitantly) over trastuzumab alone in the adjuvant therapy of early-stage Her2-positive breast cancer. A combined analysis of SOFT and TEXT suggested superiority of exemestane plus OFS over tamoxifen plus OFS, but data are yet insufficient to define a novel treatment standard. Results of several phase II studies underscored the role of carboplatin in neoadjuvant therapy of triple-negative early-stage breast cancer.

Conflict of interest

The authors declare that there is no conflict of interest.

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