Editorial

Switching gear and looking from a different angle in the treatment of HER2-positive disease

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The results of the APHINITY trial were recently reported in the *New England Journal of Medicine* by von Minckwitz *et al.*, wherein adjuvant pertuzumab was combined with trastuzumab plus chemotherapy in the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer (1). The addition of pertuzumab produced a 0.9% lower recurrence rate and death at 3 years (1). However, the absolute benefit was better in patients with lymph node metastases; in these patients, the rate of invasive disease-free survival (DFS) was 1.8% higher in the pertuzumab group than in the placebo group (1). Pertuzumab might have a position in adjuvant treatment for patients with multiple lymph node involvement or those willing to allow considerable adverse side effects in return for questionable benefit (1). Real-world clinical significance is perhaps subtler than the rigid numbers that determine statistical significance in clinical trials. The results for pertuzumab in the APHINITY trial were statistically significant with reference to the primary endpoint of invasive DFS (1). However, compared to results of pertuzumab treatment in the context of advanced breast cancer (CLEOPATRA) and the neoadjuvant setting (NeoSphere), the results of APHINITY were a clinical and scientific disappointment (1-3).

After overexpression of HER2 was identified as a significant risk factor for recurrence or death from breast cancer, targeted therapeutic exploitation has gradually evolved (4). Trastuzumab, the first HER2-targeted monoclonal antibody, improved overall survival (OS) when combined with conventional chemotherapy for patients with HER2-positive breast cancer (4). Trastuzumab also enhances DFS and OS more dramatically when combined with chemotherapy for HER2-positive early-stage breast cancer (4). Mature results from the NSABP B-31, NCCTG 9831, and the BCIRG 006 trials all indicated OS rates of 83–86% at 8–10 years for a HER2-positive subtype that was previously associated with poor prognosis (5,6). The recommended standard adjuvant therapy for patients with HER2-positive early-stage breast cancer is chemotherapy plus trastuzumab for 1 year (7). Importantly, around 25% of these patients still experience disease recurrence (8).

Different strategies have been evaluated to improve additional outcomes (1,9). Pertuzumab inhibits dimerization of HER2 and HER3; preclinically, it synergistically increases the benefits of trastuzumab against HER2-positive breast cancer (1). In clinical trials, the combination of pertuzumab and trastuzumab results in positive outcomes with remarkable pathological complete response (pCR) rates as well as OS rates in metastatic disease (1-3). Combination of pertuzumab with trastuzumab and docetaxel improved OS 15.7 months longer in metastatic breast cancer (2). For patients treated with neoadjuvant strategies, dual HER2-targeted therapies approximately doubled the rate of pCR, leading to accelerated regulatory approval (3).

Some might consider the positive results of the APHINITY trial as validation of the neoadjuvant NeoSphere trial results, which regarded pCR as a surrogate measure for DFS (1,3). Similar to the results observed in the APHINITY trial, the Neo Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (NeoALTTO) study reported increases in pCR with the addition of Lapatinib; however, trials involving the use of this agent as adjuvant therapy reported negative results (10,11). Lapatinib is a small-molecule receptor tyrosine kinase inhibitor of HER1 and HER2 (12). Preclinical data indicated that the combination of

lapatinib with trastuzumab led to synergistic inhibition (12). Although lapatinib in combination with trastuzumab improved outcomes in patients with advanced breast cancer and generally improved pCR rates in the neoadjuvant setting, there were no significant differences among treatment groups (lapatinib *vs.* trastuzumab *vs.* lapatinib plus trastuzumab) (10,13). In the ALTTO trial, the combination of lapatinib did not improve DFS, and treatment with lapatinib monotherapy was closed early owing to poor outcomes (11). Despite the successful neoadjuvant studies of dual HER2-targeted therapies for HER2-positive breast cancer (14), improvement of OS benefits over trastuzumab alone have not been elucidated so far (1,11,15).

An analysis of several trials did not find an association between increased pCR and improved event-free survival (EFS) (9,11). The Food and Drug Administration distributed industry guidance on how pCR might be useful evidence of clinical improvement leading to adjuvant therapy approval (16). Positive outcomes have been observed in neoadjuvant trials, at least in terms of pCR (16). Neoadjuvant therapies in patients with breast cancer have been evaluated, particularly in the context of HER2-positive breast cancer (14,16). Significant outcomes in the pCR rate in response to anti-HER2 treatment, a suggested alternative endpoint for durable clinical benefit, have been noted with neoadjuvant dual-agent HER2 inhibitors (3,14). It was speculated that this strategy would lead to extra survival outcome beyond standard-of-care treatment with trastuzumab in the adjuvant setting (14). The accomplishment of a pCR, although the accomplishment of a pCR is hard to correlate with EFS and OS after neoadjuvant therapy but is known to be a defective alternative for prediction of outcomes in patients with breast cancer (17).

Two large randomized trials—the ExteNET and the HERA trials—have investigated adjuvant HER2-targeted treatment in the therapy of early breast cancer for >12 months (15,18). Neratinib is an effective, irreversible oral tyrosine-kinase inhibitor of HER1, HER2, and HER4, with monotherapy value complicated by clinically severe diarrhea in advanced disease stages (18). The phase 3 ExteNET study investigated neratinib therapy over 12 months following 1-year of trastuzumab-based adjuvant treatment in 2,840 patients with early-stage HER2-positive breast cancer (18). At 2 years, 70 invasive-DFS events had been counted in patients in the neratinib group (n=1,420) *vs.* 109 events in those in the placebo group [n=1,420; stratified hazard ratio (HR), 0.67; 95% confidence interval (CI), 0.50–0.91] (18). The absolute reduction in invasive DFS rate was 2.3% (93.9% in the neratinib group *vs.* 91.6% in the placebo group); the endocrine receptor-positive subset of patients experienced the most benefit because the invasive DFS rate improved by 4.2% (95.4% in the neratinib group and 91.2% in the placebo group) (18). Grade 3 diarrhea resulted in 40% of patients treated with neratinib, and diarrhea of at least grade 2 resulted in 72%; 17% of patients discontinued neratinib because of diarrhea (18). The ExteNET study enrolled a population with greater risk of recurrence, that was treated with non-cross-resistant oral tyrosine-kinase inhibitors, resulting in a significant outcome on invasive DFS (18). The obvious better improvement of neratinib in the endocrine receptor-positive subset compared with the endocrine receptor-negative subset is especially fascinating, given that combination of HER2-targeted treatment has already shown either similar advantage independent of endocrine receptor status or significant effect in the neoadjuvant endocrine receptor-negative subset (18). The significant effect in individuals with endocrine receptor-positive tumors in the ExteNET trials made the rationale that the biological response of neratinib could be related to reversal of endocrine resistance (18).

HERA is the unique study that assessed adjuvant trastuzumab for longer than 1 year (15). Between 2001 and 2005 after completion of chemotherapy, 1,552 patients with HER2-positive early breast cancer were assigned to 1 year of trastuzumab treatment and 1,553 patients to 2 years (15). The patients had been investigated for a median of 8 years when the initial results were reported (15). At this mature period, 367 patients in each group had recurrent disease or had died occurring in an HR of 0.99 (95% CI, 0.85–1.14) (15). The number of patients who died was also equivalent in the 2 groups; 186 in the 1-year group and 196 in the 2-year group (15). More patients in the 2-year group had grade 3–4 adverse events (20.4% *vs.* 16.3%) and reduction in the left ventricular ejection fraction (7.2% *vs.* 4.1%) compared with the 1-year group (15). This information indicates that 2 years of adjuvant trastuzumab should not be proposed as standard treatment because 1 year of treatment is similarly effective, well tolerated, and economical (15). Extending the duration of adjuvant HER2-targeted treatment with trastuzumab from 1 to 2 years did not ameliorate outcomes in the HERA trial, which included relatively low-risk patients (15). Therefore, it is not possible to extend this treatment to all patients with HER2-positive breast cancer based only on anatomy. The toxic effects and cost are too great and only benefit a select few patients.

Short duration of trastuzumab treatment was also evaluated to demonstrate the feasibility of de-escalation. Several

randomized trials have evaluated whether comparable efficacy can be achieved with 1-year adjuvant trastuzumab, but with fewer side effects (19,20). In these studies, trastuzumab was administered concurrently with chemotherapy in the investigational group to manipulate drug synergism [FinHer (19)], or 6 months of trastuzumab treatment was compared with 12 months [the Hellenic trial (20)]. FinHer was the first randomized trial to evaluate adjuvant trastuzumab for <12 months, and as this may be considered the first de-escalation study (19). Patients were allocated to either 21-day cycles of docetaxel or weekly vinorelbine, each group subsequently received 21-day cycles of FEC (fluorouracil, epirubicin, and cyclophosphamide) (19). The 232 patients with HER2-positive breast cancer were randomized for a second time to either weekly trastuzumab, administrated upfront and concurrently with vinorelbine or docetaxel, or to observation alone (19). The patients treated with trastuzumab for 9 weeks plus vinorelbine or docetaxel had an equivalent HR for cancer recurrence (0.42; 95% CI, 0.21–0.83). As similar results were established in the B-31, N9831, and HERA studies after 12-month of trastuzumab treatment, brief administration of trastuzumab with synergistic chemotherapy may be a promising treatment strategy (5,15,19).

It is also important to identify a biomarker that could be used to monitor response to dose escalation (e.g., dual anti-HER targeted therapies or extension of duration) or dose de-escalation (short duration of administration). Previous trials of adjuvant and neoadjuvant therapy have indicated improved outcomes related to immune signatures, which may act as surrogate markers when patients' responses were evaluated (21,22). Tumor-infiltrating lymphocytes (TILs) may be the most relevant biomarkers in the prognosis of HER2-positive breast cancer (21,22). High quantities of TILs in mainly HER2-positive breast cancer lead to improved prognosis and response to treatment (22). CLEOPATRA was a randomized phase 3 study comparing the addition of either pertuzumab or placebo to first-line treatment with trastuzumab plus docetaxel for patients with advanced metastatic HER2-positive breast cancer (21). Tumor samples from 678/808 (84%) patients were evaluated for TILs, including 519 (77%) archival samples, 155 (23%) fresh samples, and 4 samples of unknown archival status (21). High stromal TIL values were significantly associated with longer OS by multivariate analysis (21). Median OS was shorter in patients with TIL values of ≤20% than in patients with TIL values >20% (HR, 0.76; 95% CI, 0.60–0.96; P=0.021) (21). The 3-year Kaplan-Meier estimates of OS by stromal TIL values in the placebo group were 50% (95% CI, 44–57%) in patients with TIL values of ≤20% *vs.* 55% (46–65%) in patients with TIL values >20% (21). In the pertuzumab group, 3-year OS estimates were 64% (58–70%) in patients with TIL values ≤20% *vs.* 78% (69–87%) in patients with TIL values >20% (21). For OS, each 10% increase in stromal TILs was significantly related with durable OS (adjusted HR, 0.89; 95% CI, 0.83–0.96; P=0.0014) (21). Therefore, in patients with metastatic HER2-positive breast cancer treated with pertuzumab or placebo in combination with docetaxel plus trastuzumab, higher TIL values are significantly correlated with improved OS, indicating that the effect of antitumor immunity extends to the metastatic disease situation (21).

The efficaciousness of the immune system to pCR in breast cancer after neoadjuvant docetaxel with either trastuzumab (TH), pertuzumab (TP), or both (THP), or monoclonal antibodies alone (HP) was evaluated in the NeoSphere trial (23). Immune gene mRNA expression, lymphocyte infiltration, and programmed death-ligand 1 (PD-L1) were analyzed in 350 patients (83.8%), 243 patients (58.3%), and 305 patients (73.1%), respectively, and correlated with pCR (23). The authors studied five selected genes—interferon gamma 1 (*IFNG*), programmed cell death protein 1 (*PD-1*), *PD-L1*, programmed cell death 1 ligand 2 (*PDL2*), cytotoxic T-lymphocyte associated protein 4 (*CTLA4*)—and six immune metagenes—plasma cells with immunoglobulin G (*IgG*), T cells with cluster of differentiation 8A (*CD8A*), antigen-presenting cells with major histocompatibility complex 2 (*MHC2*), MHC1 genes (*MHC1*), signal transducer and activator of transcription 1 (*STAT1*) co-expressed genes, and interferon-inducible genes (*IF-I*) (23). Gene expression results from the NOAH trial were evaluated for validation (23,24). TILs as a continuous variable and PD-L1 protein expression were not significantly correlated with pCR (23). There was a trend toward higher expression of all immune factors and lower probability of pCR in the THP group. This trend was significant in the case of *PDL1*, *PD1*, *CTLA4*, and the *MHC1* metagene (23). With THP, higher expression of *PD-1* and *STAT1*, or any of *PD-L1*, *CTLA4*, *MHC1*, and *IF-I* were related with lower pCR (23). In the combined TH/TP/HP therapy groups, higher expression of *PD1*, *MHC2*, and *STAT1* were related with higher pCR, and higher *PD-L1*, *MHC1*, or *IF-I* to lower pCR by multivariate analysis (23). In the NOAH trial, an equivalent relation between high *STAT1* expression and higher pCR, and higher *MHC1* and *IF-I* with lower pCR was observed in patients treated with trastuzumab and chemotherapy but not for those treated with standard chemotherapy alone (24). The extreme advantage from THP is found in cases with

low expression of a few immune markers (i.e., *MHC1*, *CTLA4*) (23). The association with PD-L1 in resistance provides support for evaluating combination of HER2-directed antibodies with immune-checkpoint inhibitors (23).

The prognostic associations of other anti-HER2 agents including lapatinib were also evaluated in the neoadjuvant setting (22). This study aimed to evaluate correlations among the presence of TILs, pCR, and EFS in patients with early breast cancer in treatment with trastuzumab, lapatinib, or both therapies. The NeoALTTO randomization study allocated 455 women with early-stage HER2-positive breast cancer to 1 of 3 neoadjuvant therapy groups: lapatinib, trastuzumab, or both. TILs were evaluated immunohistochemically using hematoxylin and eosin staining of core biopsy sections collected at diagnosis (prior to treatment) in a prospectively defined retrospective examination. TIL abundance was then correlated with efficacy endpoints adjusted for prognostic clinicopathological factors. Of the 455 patients enrolled, 387 (85.1%) tumor samples were used for analysis. For the pCR endpoint, levels of TILs >5% were correlated with higher pCR rates independent of treatment group (adjusted odds ratio, 2.60; 95% CI, 1.26–5.39; P=0.01) (22). With a median follow-up time of 3.77 (3.50–4.22) years, every 1% increase in TILs was correlated with a 3% decrease in the rate of an event (adjusted HR, 0.97; 95% CI, 0.95–0.99; P=0.002) among all treatment groups. The presence of TILs at diagnosis is an independent, positive, and prognostic marker in early HER2-positive breast cancer treated with neoadjuvant chemotherapy and anti-HER2 agents for both pCR and EFS end points (22). Therefore, immune signature could affect patient outcomes more than type of peri-adjuvant targeted therapy.

In conclusion, several new HER2-targeted treatment studies have resulted in a paradigm shift in strategies for breast cancer treatment; the limitations of the present treatment procedures should be understandable.

Tumors not only involve cancer cells, but also an abundance of microenvironment components such as blood vessels, antigen presenting cells (APCs), neutrophils, myeloid-derived suppressor cells, tumor-associated macrophages and fibroblasts, including the extracellular matrix, and soluble factors (such as cytokines and growth factors); all those components may support or inhibit anti-tumor immunological responses (25). This is principally evident from the response to HER2-targeted monoclonal antibodies where the capacity to activate immunological cells in the tumor microenvironment can result in the success or failure of anti-tumor immunological response (25). Future advances will be based on a deeper understanding of microenvironmental interactions, which may help to detect targetable factors for adjuvant treatment in combination with HER2-targeted therapy (25).

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