In the 1980s, HER2 overexpressing tumors were recognized as a distinct subset of breast cancer, with greater likelihood of nodal involvement, younger age of onset, higher grade pathology features (high proliferative rate, metastatic potential and neoangiogenesis), and poor survival (median about 3 years vs 6-7 years for HER2- negative tumors). About 20-30% of breast cancer diagnosed at any stage shows HER2-receptor over-expression or gene amplification. Trastuzumab is a humanized monoclonal antibody against HER2 receptor that has change the biological history of the HER2-positive breast cancer subtype. The linkage of trastuzumab with the receptor blocks its activation, which in turn induces an arrest in the downstream intracellular transduction pathway and prevents the transcription of related genes. In vitro, trastuzumab demonstrated synergism with several cytotoxics (in particular anthracyclines and taxanes), with increased apoptosis and decreased cell proliferation. The cytotoxic synergism of combined trastuzumab and chemotherapy is also supported by clinical data in metastatic and neoadjuvant settings. In HER2+ advanced disease, the combination of trastuzumab and chemotherapy resulted in 25% survival increase (from 20 to 25 months median survival); the two pivotal studies with paclitaxel and docetaxel respectively have also demonstrated that patients with advanced disease receiving the trastuzumab and chemotherapy combination upfront had a better outcome than those who received trastuzumab delayed at disease progression. Similarly, in the neoadjuvant experience of MDACC, patients with HER2 positive operable breast cancer who received upfront chemotherapy (4 courses of paclitaxel followed by 4 courses of FEC) with concomitant trastuzumab achieved a significantly higher rate of pathological complete response (pCR = 66.7% with vs. 26.3% without trastuzumab respectively).

A large benefit in disease free and overall survival has been reported from 5 different randomized studies with trastuzumab in the adjuvant setting that have included more than 10,000 women with HER2 positive breast cancer. In these trials, one year of trastuzumab reduced by ~50% the risk of relapse (HR 0.52 in the combined analysis of the NSABP-B31 e NCCTG N9831 studies; 0.76 in the HERA study; 0.64 in the AC-TH arm and 0.75 in the TCH arm of the BCIRG006 trial). Moreover, at an interim analysis of N9831 trial, an advantage for the combination of chemotherapy and trastuzumab over the sequence has been reported (HR 0.77; 99.9% CI, 0.53 to 1.1) even if the p value (0.02) didn’t cross the pre-specified O’Brien-Fleming boundary. In conclusion, both biological and clinical data strongly support the synergistic cytotoxic effects of trastuzumab and chemotherapy on HER2 positive breast cancer cells, while the sequential administration of trastuzumab after chemotherapy seems to induce mainly a cytostatic effect that might require longer treatment to achieve maximum clinical benefit. Unfortunately, the only study prospectively designed to test different durations of trastuzumab administration is the HERA trial; at present however, the results of the comparison of one versus two years of treatment are still pending. However, in a small adjuvant study from Finland, trastuzumab has been given upfront for 3 months in combination with docetaxel or vinorelbine followed by 3 FEC courses without trastuzumab: the risk of relapse revealed similar to that observed in a previous studies with 1 year of trastuzumab, suggesting that shorter treatment durations might produce comparable efficacy but with significant lower toxicities and costs. By now, one year of treatment with trastuzumab must be still considered the gold standard but the optimum adjuvant trastuzumab duration remains to be established.

With regard to cardiac toxicity, it is well known that trastuzumab by itself is not directly cardiotoxic but, by inhibiting the survival pathway activated through HER2 receptors, can impair the reparative mechanisms activated by myocardial cells following oxidative stress induced by cytotoxics (in particular anthracyclines). Cardiac safety has been closely evaluated and monitored in trastuzumab adjuvant studies. Despite the selection of the optimal patient population and different definitions of cardiac event: in NSABP-B31, 6.7% of the patients never started trastuzumab due to a LVEF drop greater than 16% after anthracyclines while, among the 1159 patients who started it, 31.4% stopped the treatment before the 52 planned weeks for an asymptomatic or symptomatic
decline in the LVEF. In the N9831 trial, the cumulative incidence of CHF was 3.5% and 2.6% in patients respectively randomized to concomitant or sequential trastuzumab, versus 0.2% in the control arm. In the HERA trial, trastuzumab was stopped in 5% of the patients due to cardiac problems; a symptomatic CHF was recorded in 2% of the patients who received trastuzumab, versus 0% in the control arm. An asymptomatic decline in LVEF was observed in 4% of the patients treated with trastuzumab, versus 1% of the controls. In the BCIRG 006 trial, the incidence of grade III-IV cardiac events was 2% among patients treated with AC-TH, 0.4% among patients who received H without anthracyclines, and 0.7% in the control arm. The decline of LVEF >10% was 18.6%, 9.4% and 11.2% in the three arms, respectively. In the FinHer study no severe cardiac toxicity has been reported, while 3.5% of the patients showed a transient decline of EF >15%.

To test the hypothesis that a shorter duration of adjuvant trastuzumab concomitant with chemotherapy might be effective but less toxic, we have designed a phase III multicentre, randomized trial (ShortHer) in order to evaluate if short (9 weekly administrations) versus long (18 three-weekly administrations) adjuvant trastuzumab combined with chemotherapy is equally effective in terms of DFS, and less toxic from a cardiac viewpoint: the enrolment is running. Other European trials are addressing the same questions (PHARE trial, SOLD trial, PERSEPHONE trial), but in addition our trial will explore less intensive adjuvant trastuzumab regimens in the node negative pT1a,b HER2 positive breast cancer population so poorly represented in most clinical trials.

In fact the previous mentioned trials of adjuvant trastuzumab have included patients with node-positive tumors, or node-negative tumors larger than 1cm in size; only BCIRG006 randomized patients with tumors <1cm only if N+ or N- with ER/PgR negative and/or G2-3 and/or age <35 years. As a consequence, there are no reliable information on whether women with infracentimetric, node-negative cancers might benefit from trastuzumab. Several published experiences reported that HER2 positive T1a,bN0 tumors carry a risk greater than that in comparably staged, HER2 negative cancers: the risk of recurrence without trastuzumab (10 to 20%) suggests that there would be clinically meaningful benefit from adding adjuvant chemotherapy plus trastuzumab. Current guidelines from the National Comprehensive Cancer Network recommend to consider a trastuzumab-based chemotherapy for women with node-positive breast cancer or with node-negative tumors that are at least 0.6 cm in diameter.

Another area of controversy in the management of HER2 positive early breast cancer are represented by the possibility to avoid anthracyclines, at least in patients with small tumours, low risks or relative contraindication to anthracycline-based regimens, and to identify which patients judged to be low risk by routine clinico-pathological/molecular assessment (such a hormone receptor positive) might not require chemotherapy if trastuzumab is given. Finally, especially for patients at substantial recurrence risk despite trastuzumab and chemotherapy, novel agents beyond trastuzumab are estimated to improve important clinical outcomes: lapatinib is being examined in the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial, aimed to understand which anti-HER2 agent is more effective and which is the best schedule of administration (sequentially or concurrently with trastuzumab). At the meantime, the TEACH trial designed to determine whether adjuvant therapy with lapatinib for 1 year improve DFS, has very recently demonstrated to prolong DFS only in ER/PgR negative or <1 year from diagnosis. In summary, many questions related to trastuzumab use in the adjuvant setting still remain unanswered.


Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. J Clin Oncol. 2009 Dec 1;27(34):5685-92
