Editorial Commentary

# De-escalation of neoadjuvant therapy for HER2-positive early breast cancer: an overview

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## Introduction

About 15–20% of invasive breast cancer (BC) patients have overexpression of human epidermal growth factor receptor 2 (HER2) (1). Recently the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) issued a guideline to improve the diagnostic approach to more rigorous interpretation criteria for *in situ* hybridization (ISH) (2). In practice the new guideline resulted in a slight decrease in HER2 positive (HER2$^+$) rate (3). Continuous refinement of HER2 testing is critical for example to identify tumors that display heterogeneity of HER2 expression and which represents a distinct subset of HER2$^+$ BC associated with resistance to anti-HER2 therapies (4).

In the last two decades anti-HER2 targeted agents were developed improving patients' outcomes (5). Adjuvant therapy with trastuzumab (H) significantly improved disease-free and overall survival in early-stage HER$^+$ BC and subsequently the additional anti-HER2 blockade with pertuzumab (P) or sequencing treatment with neratinib showed additional reduction in the recurrence risk. More recently, adjuvant trastuzumab emtansine (TDM1) benefit patients at high risk of recurrence after neoadjuvant therapy that did not achieve pathological complete response (pCR) (6). Anti-HER2 therapies have significantly improved patients' outcomes, nonetheless these advances are associated with increase toxicity, greater costs and clearly an over-treatment for a substantial number of patients.

Adjuvant trials have tried to better tailor therapy in HER2$^+$ BC with less chemotherapy exposure (APT Trial) or "chemo" free regimen (ATEMPT). The APT trial included patients with <3 cm tumors and node negative HER2$^+$ BC to receive reduced chemotherapy regimen and standard H duration in patients demonstrated striking results with a 7-year DFS of 93% and OS of 95% (7). Recently, data presented from ATEMPT trial in the same population now treated with 1-year TDM1 monotherapy showed excellent outcomes with 3-year DFS of 97.7% and similar toxicity compared to APT regimen (8). Several trials evaluated a short duration of adjuvant H, 9 weeks or 6 months *vs.* 12 months with conflicting results nevertheless identifying a sub-group of patients, e.g., T1, N0, estrogen receptor (ER) positive which may benefit of this strategy (9).

These studies highlight the need to an individualized approach for HER2$^+$ treatment and the potential to de-escalate standard therapy. Here we review the data on neoadjuvant trials in HER2$^+$ BC which used a de-escalation design and describe the results and predictive biomarkers to better select patients for these regimens.

## De-escalation neoadjuvant therapy clinical trials

pCR after neoadjuvant therapy for HER2$^+$ BC is a strong prognostic factor showing reduction of 41% in risk to event-free survival (EFS), especially in hormone receptor

**Table 1** Neoadjuvant clinical trials for HER2+ BC using de-escalation design

| Trial | Phase | N | Primary endpoint | Neoadjuvant therapy | pCR |
|---|---|---|---|---|---|
| NEOSPHERE | II | 416 | pCR | Docetaxel HP ×4 | 45.80% |
| | | | | HP ×4 | 11.2% |
| | | | | Docetaxel H ×4 | 29% |
| | | | | Docetaxel P ×4 | 17.7% |
| ADAPT HER2+HR+ | II | 374 | pCR | TDM1 12 w | 40.5% |
| | | | | TDM1 + ET 12 w | 45.8% |
| | | | | H + ET 12 w | 6.7% |
| ADAPT HER2+HR– | II | 134 | pCR in early responders | H + P 12 w | 36.30% |
| | | | | H + P + paclitaxel 12 w | 89.20% |
| TBCRC 023 | II | 33 | pCR | L + H + ET* 12 w | 12% ($ER^+$ 9%/$ER^-$ 20%) |
| | | 64 | | L + H + ET* 24 w | 28% ($ER^+$ 33%/$ER^-$ 18%) |
| TBCRC 026 | II | 88 | Change SUV × pCR | P + T ×4 cycles | 34% |
| TBCRC 006 | II | 64 | pRR | L + H + ET* 12 w | 28% ($HR^+$ 21%/$HR^-$ 42%) |
| PAMELA | II | 151 | pCR in HER2-E** (pCR all patients) | L + H + ET* 18 w | 40%** (30%) |
| KRISTINE | III | 443 | pCR | TDM1 P ×6 | 44.40% |
| | | | | Docetaxel + Carbo HP ×6 | 55.70% |

*, if HR positive; **, HER2-E: HER2 enriched. BC, breast cancer; SUV, standardized uptake value; pCR, ypT0/TisN0; pRR, partial response rate; H, trastuzumab; P, pertuzumab; L, lapatinib; TDM1, trastuzumab emtansine; ET, endocrine therapy.

negative tumors who received H [hazard ratio of 0.15] (10). Neoadjuvant trials without chemotherapy, offering only targeted agents to $HER2^+$ BC, have found a small subgroup of patients that achieves pCR with this strategy and therefore support the concept of de-escalation in this setting. The benefit of anti-HER2 blockade alone were evaluated in four trials, TBCRC 006, TBBCRC 023, BCRC 023 and PAMELA, and resulted in a pCR rate of 17% to 34% either with H + lapatinib (L) or H + P with greater response in ER negative tumors. More recently in KRISTINE trial the anti-body conjugate TDM1 combined with P resulted in 44.5% pCR rate and similar 3-year outcome compared to chemotherapy plus anti-HER2 dual-blockage for those that achieved pCR (11). *Table 1* shows the neoadjuvant clinical trials for $HER2^+$ BC using de-escalation design.

In the Neosphere trial patients randomized to neoadjuvant H + P had a 11.2% pCR rate which was lower than chemotherapy combined to anti-HER2 agents however this result clearly identified patients very sensitive to anti-HER2 dual blockage alone besides having a considerable better safety profile (12). In this study all patients completed the chemotherapy regimens and H after surgery and the 5-year follow-up analysis showed similar outcomes in terms of disease-free survival (DFS) for those patients who had pCR independent of neoadjuvant treatment arm. In addition, patients with pCR had better outcome in terms of progression-free survival (PFS) compared to patients with non-pCR [85% *vs.* 76%; hazard ratio 0.54 (95% CI: 0.29–1.00)] (13). Based on Neosphere results the dual anti-HER2 blockade (H + P) combined with chemotherapy as neoadjuvant treatment for high-risk $HER2^+$ early BC were approved by the regulatory agencies. Following Neosphere trial, other studies have evaluated the de-escalation strategy in neoadjuvant treatment for HER2 positive BC, not all of them with long-term results beyond pCR.

The phase II WSG-ADAPT cohort $HER2^+$/hormonal receptor (HR) positive, randomized women to combination of endocrine therapy (ET) and H *vs.* TDM1 single agent or TDM1 + ET (tamoxifen to pre-menopausal and anastrozole to post-menopausal). In a pre-planned interim analysis pCR rates the arm that received ET + H showed only 6.7% pCR,

 

but to TDM1 alone was 40,5% and the association with ET achieved 45.8%, demonstrating a high activity of regimens without systemic chemotherapy (14). In the cohort of $HER2^+/HR^-$, 90.5% of patients treated with neoadjuvant H + P and weekly paclitaxel had pCR rate compared with 36.3% in the H + P arm (15).

The TBCRC006 was a phase II neoadjuvant $HER2^+$ BC trial without chemotherapy of L and H with ET which included 64 patients with stages II and III disease. In breast pCR was 27% for all patients but greater in ER negative compared to ER positive (36% *vs.* 21%) and the regimen was well tolerated with adverse events mainly grade 1–2 (16).

Another trial, TBCRC023, evaluated the neoadjuvant combination of H + L ± ET for $HR^+$ tumors for 12 *vs.* 24 weeks. The overall pCR was 12% in 12 weeks arm and 28% in 24 weeks arm, it was similar in ER-negative group (20% and 18%) but higher in ER-positive treated for 24 weeks (9% and 33%) (17).

PAMELA phase II study evaluated the combination of H + L ± ET for 18 weeks in 151 patients with stage I–IIIA $HER2^+$ BC which were classified according to intrinsic subtype as HER2-enriched (HER2-E) 67%, luminal A 15%, luminal B 11%, basal-like 6% and normal-like 2% (18). Overall, 30% had pCR in the breast which is quite consistent result in comparison with the same regimen TBCRC006 and 023.

The phase II TBCRC026 study analysed the association of standardized uptake value (SUV) with pCR in patients treated with neoadjuvant combination of P and H in $HER2^+$ BC. After four cycles H + P alone, 34% of patients achieved pCR (95% CI, 24–45%) although 8% of the patients experienced clinical progression during PH treatment phase. In patients with residual disease after 12 weeks or progression which received additional therapy out of study, 54% achieved pCR at time of surgery (19).

Finally, the phase III KRISTINE trial intent to omit standard chemotherapy in neoadjuvant treatment for $HER2^+$ BC. This trial randomized patients to TDM1 + P or docetaxel, carboplatin, H + P (TCHP) resulting in a superior pCR rate with TCHP *vs.* TDM1 + P (55.7 *vs.* 44.5%; P=0.016) (20). About 6.7% of patients in TDM1 + P progressed during neoadjuvant treatment and none in the TCHP arm. Three-year EFS rates were 85.3% with TDM1 + P and 94.2% with TCHP [hazard ratio 2.61 (95% CI: 1.36–4.98)]. After surgery, invasive disease-free survival (iDFS) was similar in the two arms (93% and 92%, hazard ratio 1.11; 95% CI: 0.52–2.40). Interestingly, 3-year iDFS were approximately 97% in both arm for those patients that achieved pCR. The safety profile favors TDM1 + P with more grade 3–4 and serious adverse events in chemotherapy arm, nonetheless more patients discontinued treatment in TDM1 + P arm then TCHP after surgery (18.4% *vs.* 3.8%) (11). KRISTINE trial suggests that patients who achieve pCR with de-escalation regimen have a low recurrence risk. These long-term results support the concept of neoadjuvant setting as a platform for clinical risk stratification and for the development of new agents for $HER2^+$ BC.

Importantly, de-escalation studies with targeted-only regimens in unselected $HER2^+$ BC demonstrated low pCR rates although antibody drug conjugates agents, such as TDM1 in combination with P, resulted in a higher pCR rates with lower toxicity compared to standard chemotherapy regimens. Even so, in KRISTINE study the TDM1 + P had a significant proportion of patients with progressive disease during the neoadjuvant phase compared with studies using chemotherapy combined with anti-HER2 agents. Therefore, it's clear that a portion of patients benefit of targeted agents only however its critical to develop predictive biomarkers to ensure optimal patient selection for neoadjuvant de-escalation studies.

## Predictive biomarkers for pCR in de-escalation regimens

In the clinical trials using de-escalation neoadjuvant strategy there was several biomarkers investigated such as PET/CT uptake, on treatment proliferative markers, BC intrinsic subtypes and stromal tumor-infiltrating lymphocytes (TILs) that could predict pCR and consequently improve long-term outcomes.

In TBCRC 026 trial, early change in SUV corrected for lean body mass (SULmax) on FDG PET/CT identified pCR responders. The SULmax was assessed on day 15 after start of neoadjuvant H + P. Greater median percent reduction in SULmax was observed in patients with pCR compared to non-pCR group (63,8% *vs.* 33.5%, P<0.001). Also, pCR-group showed greater proportion of SULmax 3 or less at C1D15 (93% *vs.* 38%; P<0.001; negative predictive value, 94%; positive predictive value, 55%) (19).

The WGS-ADAPT trials evaluated the concept of early response (defined as proliferation decrease more than 30% or less than 500 invasive tumor cells) in 3-week biopsy to predict pCR. In the $HER2^+/HR^-$ cohort, non-responders (26%) had pCR of 8.3% *vs.* 42.9% in responders of the H + P arm. (20) Whereas in the $HER2^+/HR^+$ cohort, early responders (67%) achieved pCR in 35.7% compared to 19.8% in non-responders (14). These studies showed that biological

 

non-response strongly predicts failure to achieve pCR.

HER2-E subtype was a predictor of pCR following H + L without chemotherapy in early-stage HER2$^+$ BC (PAMELA). Forty-one percent of HER2-E tumors had pCR *vs.* 10% in non-HER2-E (P=0.0004) (18). Another analysis including four clinical trials using dual HER2 blockade, SOLTI-PAMELA, TBCRC023, TBCRC006, PER-ELISA, used the PAM50 assay to classify patients in terms of ERBB2 expression and HER2-E subtype (21). From the total of X patients, 83.8% were classified as HER2-E-high and 44.7% as ERBB2-low tumors. Following L + H, the HER2-E/ERB2 high group showed higher pCR compared to the other profiles (44.5% *vs.* 11.6%; P<0.001), similar results with neoadjuvant P + H was found (66.7% *vs.* 14.7%; P<0.01). A recent meta-analysis including 16 studies confirmed the association of HER2-E subtype in predicting pCR (22). Trials with neoadjuvant regimens without chemotherapy revealed association between HER2-E subtype and pCR in all patients [odds ratio (OR) =5.52, P<0.001] and in HR$^+$ tumors (OR =4.08, P=0.001). The HR negative status had significantly association with pCR, compared to HR$^+$ status, in all patients and within the HER2-E subtype (OR =2.41 and 1.76, respectively; both P<0.001). Phenotypic changes of HER2$^+$ BC during neoadjuvant anti-HER2 dual blockade induced a low-proliferative Luminal A phenotype, more evident in RH$^+$ and appears to increase sensitivity to CDK4/6 inhibition (23).

The association between TILs and pCR was evaluated in patients treated with H + L in PAMELA trial. The presence of TILs on day 15 biopsy was associated with increased pCR and a combined score of tumor cellularity and TILs (CelTIL) measure at day 15 showed no pCR in patients with CelTIL-low and 33% pCR in those considered CelTIL-high (24).

Lastly, in the KRISTINE trial the 15 samples tumors of patients in TDM1 + P neoadjuvant arm who experienced loco-regional progression were evaluated. This analysis revealed higher HER2 heterogeneity and lower HER2 expression compared to samples of the patients without progression in the same setting. Based in this data, patients with molecular profile like this may require more aggressive treatment, like conventional systemic chemotherapy combined with HER2 target therapy.

## Conclusions

In HER2$^+$ BC pCR is a strong prognostic factor for long-term outcome and there is evidence to support the hypothesis that a group of selected HER2$^+$ patients may not need chemotherapy. Therefore, it is critical to identify patients who have the greatest chance of achieving pCR using de-escalation neoadjuvant treatment in future clinical trials.

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*Conflicts of Interest*: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-1035). The authors have no conflicts of interest to declare.

*Ethical Statement*: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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