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Original article

# Insights into biology of luminal HER2 vs. enriched HER2 subtypes: Therapeutic implications

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ABSTRACT

Until recently, due to its aggressive clinical behavior, HER2-positive disease has been considered as a single breast cancer subtype and treated accordingly, particularly in early breast cancer (eBC). Based on the pivotal trial data from the metastatic breast cancer setting, anti-HER2 therapy in eBC has been developed as a one size fits all approach with a chemotherapy backbone independently of tumor endocrine sensitivity. Yet, recent data demonstrated different response rates after neoadjuvant chemotherapy + HER2-targeted therapy for hormone-receptor (HR) negative vs. HR-positive tumors. Pathological complete response seems to have a different impact on patient outcome according to HER2-subtype with the strongest correlation found in HR-negative disease. Moreover, substantial preclinical and emerging clinical data in breast cancer suggest that there is a crosstalk between endocrine and HER2 pathways conferring resistance to agents targeting either pathway and suggesting co-targeted approaches. Early clinical results indicate meaningful pathological response rates by co-targeted approaches against ER and HER2. The big challenge for HER2-positive eBC in the upcoming years will be to individualize anti-HER2 therapy according to endocrine responsiveness as well as relapse risk in order to avoid overtreatment, minimize therapy resistance, and optimally utilize the available treatment options. Taking molecular subtype into account as well as applying early response monitoring by early re-biopsy in the pre-operative setting, dynamic biomarkers, or molecular imaging may help to achieve this goal. New clinical trial concepts such as WSG-ADAPT have already started to consider luminal (ER/PR-positive) vs. HER2-enriched HER2-positive tumors separately.



## Introduction

Until recently, due to its aggressive clinical behavior, HER2-positive disease has been considered as a single breast cancer subtype and treated accordingly, particularly in the early breast cancer setting (eBC). Based on the pivotal trial data from the metastatic breast cancer setting [27], anti-HER2 therapy in eBC has been developed as a one size fits all approach with a chemotherapy backbone independently of tumor endocrine sensitivity.

A Cochrane systemic review of the randomized controlled trials on trastuzumab in early breast cancer considering published evidence up to February 2010 identified eight trials with a total of 11,991 patients. The hazard ratios for disease-free survival (HR 0.60, 95% confidence interval CI 0.50-0.71; $p < 0.00001$) as well as overall survival (HR 0.66, 95% CI 0.57-0.77; $p < 0.00001$) significantly favored trastuzumab containing regimens. Regarding side effects, hematological toxicities did not differ but risk of congestive heart failure (RR 5.11; 90% CI 3.00-8.72; $p < 0.00001$) and that of left ventricular ejection fraction decline (RR 1.83, 90% CI 1.36-2.47; $p = 0.0008$) was significantly increased with trastuzumab [16].

Several studies have looked at optimal trastuzumab duration in the adjuvant setting, but to date no regimen improving upon the one-year standard could be identified. Longer duration as the two years in HERA [7] did not show superior efficacy and shorter duration as the six months in PHARE failed to prove non-inferiority to the established one-year trastuzumab therapy [21].

So far, the standard chemotherapy regimens accompanying trastuzumab in the adjuvant setting have been an anthracycline-taxane sequence based on the US registration trials [18] as well as an anthracycline-free taxane–platinum combination based on BCIRG 006 [28]. Recently, de-escalation of adjuvant chemotherapy (12x paclitaxel weekly) together with adjuvant trastuzumab showed an excellent efficacy with a 3-year disease-free survival rate of 98.7% (95% CI 97.6-99.8) and only 2 distant relapses in 406 patients after a median follow-up of 4 years [30].

Dual blockade in the adjuvant setting has not yet shown superior efficacy regarding patient outcome compared to standard

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trastuzumab therapy: the ALTTO trial evaluating trastuzumab and lapatinib failed to reach its primary endpoint [20]; the APHINITY trial (NCT01358877) exploring dual antibody-based HER2 blockade with trastuzumab and pertuzumab has already finished recruitment but efficacy results are still pending.

Based on the registration trials HERA [7], NSABP-B31/NCCTG N9831 [18], and BCIRG 006 [28], national and international guidelines including the St. Gallen Consensus 2013 now recommend one-year of adjuvant trastuzumab in early stage breast cancer [6]. This recommendation does not differ between hormone-receptor (HR) positive and HR-negative disease.

## Molecular subtypes

Since the groundbreaking work of Drs. Perou, Sorlie, and colleagues about 15 years ago, breast cancer is classified into four major molecular subtypes that impact patient outcome and thus also therapy decision making [19,29]: Luminal A and B, HER2-enriched, and basal-like. In clinical practice, these subtypes can be directly determined by a multigene assay as well as indirectly by immunohistochemistry. Using estrogen (ER) and progesterone receptor (PR) status, HER2 status as well as Ki-67, molecular subtypes can be assessed as follows:

- **Luminal-A-like type** (HR positive, HER2 negative, low proliferation)
- **Luminal-B-like type** (HR-positive, high proliferation, either HER2-positive or HER2-negative),
- **HER2-type non-luminal** (HER2-positive, HR-negative)
- **Basal-like-type** (HR-negative and HER2-negative; *triple negative*).

The St. Gallen consensus 2013 confirmed the immunohistochemical determination of these molecular subytpes as well as their relevance for clinical decision making [6].

Regarding HER2-positivity, only immunohistochemistry and ISH methodology are currently accepted for decision making regarding anti-HER2 therapy in early breast cancer [33]. Consequently, most clinical evidence regarding luminal vs. HER2-enriched subtype is available for HR-positive vs. HR-negative HER2-positive disease and this definition will thus be used throughout this article unless indicated otherwise. It is acknowledged, however, that published evidence looking at molecular subtypes and their impact on therapy efficacy is unfortunately still very heterogeneous regarding the methodology used for subtype determination and that there may well be clinically relevant differences attributable to the determination method used.

The concept of intrinsic subtypes has now provided insights into heterogeneity of HER2-positive disease. Prat et al. [22] have looked at published data sets in order to see how molecular subtypes and clinical HER2 status (according to ASCO CAP guidelines or DNA copy number aberration) overlapped. Clinically HER2-positive breast cancer had a higher frequency of HER2-enriched subtype compared to clinically HER2-negative disease (47% vs. 7.1%) and a lower frequency of luminal A (10.7 vs. 39%) and basal-like subtypes (14.1. vs. 23.4%). The likelihood of clinical HER2-positivity was 64.6% in HER2-enriched, 20% in luminal B, 14.4% in basal-like, and 7.3% in luminal A disease. Interestingly, between clinically HER2-positive and HER2-negative tumors only very few (less than 5%) of genes were found to be expressed differentially within each molecular subtype. In the absence of anti-HER2 therapy, this molecular heterogeneity of HER2-positive disease does not seem to affect patient outcome. Even though clinical HER2 status was associated with poor breast cancer specific survival in this cohort of patients ($n = 1711$) without targeted anti-HER2 therapy (HR 1.53; 95% CI 1.26-1.86; $p < 0.001$), the prognostic effect of clinical HER2 status disappeared within the molecular subgroups [22].

In the adjuvant registration trials, subgroup analysis did not show a substantially different trastuzumab therapy efficacy between HR-positive and HR-negative disease. In the HERA trial, where trastuzumab was given after adjuvant chemotherapy, DFS hazard ratios between 1-year of trastuzumab and control were similar in HR-positive (0.68; 95% CI 0.51-0.89) and HR-negative (0.62; 95% CI 0.50-0.77) cohorts. Nevertheless, the absolute benefits differed between subgroups and a different relapse pattern for HR-negative vs. HR-positive HER2-positive disease was found: In the HR-negative cohort, trastuzumab substantially reduced early relapses whereas in the HR-positive cohort, it offered a modest but constant risk reduction over time [31]. Similar observations with regard to the relapse patterns over time were made in the combined analyses of the B-31/N9831 US trials as shown by Dr. Romond in his SABCS presentation 2012 [26]. Again in the US trials, where trastuzumab was given either after or together with adjuvant chemotherapy, the DFS hazard ratios for HR-positive (0.61; 95% CI 0.51-0.72) and HR-negative tumors (0.62; 95% CI 0.52-0.73) were rather similar [18].

## Crosstalk between endocrine and growth factor pathways

There are several proposed mechanisms of action for trastuzumab including reduction of receptor shedding and p95, inhibition of homo- and heterodimerization, and antibody-dependent cellular cytotoxicity [9]. Very early preclinical data suggest that estrogen (but not progestin) is able to modulate HER2 expression in a dose-dependent manner and that antiestrogens are able to reverse this estrogen-receptor mediated process [23]. In tumor tissue, an inverse relationship between HER2 and ER levels was observed [13]. Substantial preclinical and emerging clinical data in breast cancer suggest that there is a crosstalk between endocrine and HER2 pathways conferring resistance to agents targeting either pathway and suggesting co-targeted approaches [17]. In an in-vivo model, inhibition of EGFR/HER2 improved the antitumor effect of tamoxifen [14].

## Learnings from the neoadjuvant setting

Recent pooled analysis data demonstrated different response rates after neoadjuvant chemotherapy and HER2-targeted therapy in HER2-positive disease for HR-negative vs. HR-positive tumors [4]. Pathological complete response seems to have a different impact on patient outcome according to HER2-subtype with the strongest correlation found in HR-negative disease. In this subgroup, the CTNeoBC pooled analysis showed a HR of 0.15 (95% CI 0.09-0.27) for event-free and 0.08 (0.03-0.22) for overall survival [4]. Similarly, the GBG metaanalysis also showed lower pCR (breast and nodes) rates in luminal B HER2+ tumors (22.2%) than in non-luminal HER2+ tumors (32.9%), both groups treated with chemotherapy and trastuzumab. Moreover, in luminal B HER2+ tumors treated with trastuzumab, pCR did not have a significant impact on survival, neither on disease-free (HR 1.227; 95% CI 0.63-2.37; $p = 0.54$) nor on overall survival (HR 29.72; 95% CI 0.63- >1.000; $p = 0.28$). In contrast, pCR was associated significantly with disease-free (HR 8.74; 95% CI 3.17-24.12; $p < 0.001$) and overall survival (HR 13.80; 95% CI 1.87-102; $p = 0.01$) in non-luminal HER2+ disease [32]. The observed differential response to anti-HER2 therapy between luminal and non-luminal disease is not limited to trastuzumab. In the NeoALTTO trial, higher in-breast pCR rates in were seen in HR-disease with trastuzumab (36.5% vs. 22.7%) and with lapatinib (33.7% vs. 16.1%) as well as with the combination (61.3% vs. 41.6%) [1]. In the NeoSphere trial, in-breast