HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2021 July 30.

Published in final edited form as:

Clin Cancer Res. 2020 June 15; 26(12): 2783–2788. doi:10.1158/1078-0432.CCR-19-2612.

What is the real impact of estrogen receptor status on the prognosis and treatment of HER2-positive early breast cancer?

Mariana Brandão[1], **Rafael Caparica**[1], **Luca Malorni**[2], **Aleix Prat**[3,4], **Lisa A. Carey**[5], **Martine Piccart-Gebhart**[1]

[1]Institut Jules Bordet and Université Libre de Bruxelles (U.L.B), Boulevard de Waterloo 121, 1000, Brussels, Belgium

[2]"Sandro Pitigliani" Oncology Department and Translational Research Unit, Hospital of Prato, Via Suor Niccolina, 59100 Prato, Italy

[3]Translational Genomics and Targeted Therapeutics in Solid Tumors, IDIBAPS, Barcelona, Spain

[4]Medical Oncology Department, Hospital Clínic of Barcelona, University of Barcelona, 170 Villarroel Street, 08036-Barcelona, Spain

[5]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Abstract

HER2+ early breast cancer is a heterogeneous disease, comprising all the intrinsic breast cancer subtypes. The only biomarker available nowadays for anti-HER2 treatment selection is HER2 status itself, but estrogen receptor (ER) status is emerging as a robust predictive marker within HER2+ disease. In this Perspective, we discuss the biological and clinical differences between patients with HER2+/ER positive (ER+) disease versus those with HER2+/ER negative (ER-neg) tumors, namely short- and long-term (>5 years after diagnosis) prognosis, response to neoadjuvant treatment and benefit from adjuvant anti-HER2 targeted therapies. We also address other possible biomarkers to be used for patient selection in future clinical trials, like gene signatures, PAM50 subtypes, tumor-infiltrating lymphocytes, *PIK3CA* mutations, and changes in Ki67 score during treatment and discuss their limitations. Finally, we suggest new clinical trial designs that can have an impact on clinical practice, aiming to test treatment de-escalation separately for patients with HER2+/ER+ and HER2+/ER-neg tumors. We also propose an integrated classification of HER2+ disease, comprising DNA, RNA, protein expression and microenvironment characteristics, in order to identify those tumors that are truly "HER2-addicted" and may benefit the most from anti-HER2 treatment.

Corresponding author: Martine Piccart-Gebhart, Institut Jules Bordet and Université Libre de Bruxelles (U.L.B), Boulevard de Waterloo, 121, 1000, Brussels, Belgium, martine.piccart@bordet.be, Phone: + 32 (0) 2 541 32 06; Fax: + 32 (0) 2 538 08 58.

Conflict of interest statement

MB: travel grant and speaker honoraria from Roche/GNE. RC: speaker honoraria from Boehringer Ingelheim, AstraZeneca and Janssen; travel grants from AstraZeneca and Pfizer. LM: advisory board for Pfizer and AstraZeneca; research grant from Pfizer. AP: part of an advisory board for NanoString Technologies; research grant from NanoString Technologies. LC: no conflict of interest. MP: consultancy for AstraZeneca, Lilly, MSD, Novartis, Odonate, Pfizer, Roche/GNE, Camel-IDS, Crescendo Biologics, Periphagen, Huya, Debiopharm, PharmaMar, G1 Therapeutics, Menarini, Seattle Genetics, Immunomedics, and Oncoloytics; board member of Radius. MB, RC and MP: research grants to their Institut: from Roche/GNE, Radius, AstraZeneca, Lilly, MSD, GSJ/Novartis, Synthon, Servier, and Pfizer.

Keywords

breast cancer; HER2; Biomarkers; estrogen receptor

Perspective

It is well-known that HER2+ breast cancer is a heterogeneous disease (1,2). Besides HER2 status itself, there are no validated biomarkers to identify patients likely to benefit from anti-HER2 treatments (3). It has been proposed, however, that the expression of the estrogen receptor (ER) drives variable degrees of benefit from existing anti-HER2 treatment strategies. An increasing number of trials are being developed targeting specifically HER2+/ER-positive (ER+) or HER2+/ER-negative (ER-neg) early breast cancer (EBC) and we believe that, in the future, these may be regarded as distinct diseases or we may need additional tools to identify the varying biology within HER2+ disease that is represented by ER status.

Biological differences

Distinct biological characteristics may justify the different clinical behavior observed in HER2+ EBC according to ER status. The ER- and the HER2-pathways drive breast cancer proliferation by a complex interaction of cellular signaling processes (4). Due to the intracellular crosstalk between HER2 and ER, treatments interfering with one of the two pathways can have an effect on the other, with reactivation of ER-signaling being a known mechanism of resistance to anti-HER2 agents in HER2+/ER+ breast cancer (5).

The distribution of intrinsic (PAM50) breast cancer subtypes within HER2+ tumors also differs according to ER status (6): around 75% of HER2+/ER-neg tumors and 30% of HER2+/ER+ are “HER2-Enriched”, which is the subtype associated with HER2/EGFR-pathway activation (2), high proliferation rates, and an immune-activated stroma with elevated tumor-infiltrating lymphocytes (TILs) concentrations (Figure 1). On the other hand, around 70% of HER2+/ER+ tumors are luminal A/B, which are ER-dependent tumors, with low HER2/EGFR-pathway activation and a high rate of *PIK3CA* mutations (1), that are associated with lower response to anti-HER2 treatment (7).

Differences in prognosis between HER2+/ER+ and HER2+/ER-neg EBC in the “trastuzumab era”

In the first 5 years after diagnosis, HER2+/ER-neg patients have worse survival compared to the HER2+/ER+ group. Among 42,887 patients treated between 2010–2015, 5-year overall survival (OS) rates were 88.2% in HER2+/ER+ vs. 83.9% in HER2+/ER-neg subgroup ($p<0.001$) (8). Yet, after 5 years, recurrence risk lowers among HER2+/ER-neg patients, but is maintained among those with HER2+/ER+ tumors (9–11). This leads to similar long-term prognosis: in the HERA trial, 12-year OS in the trastuzumab arms was 81% in the HER2+/ER+ and 78%−79% in the HER2+/ER-neg subgroup (9).

On the other hand, achievement of a pathological complete response (pCR) after neoadjuvant treatment is a prognostic factor in both groups, but it has a stronger impact on event-free survival (EFS) in the HER2+/ER-neg (hazard ratio [HR] 0.25) compared to the HER2+/ER+ subgroup (HR 0.58) (12). However, overall median follow-up for EFS in this meta-analysis was just 5.4 years, thus the prognostic impact of pCR on late recurrences is currently unknown.

Is ER status predictive of treatment benefit?

It is well-documented that HER2+/ER-neg patients treated with chemotherapy and dual anti-HER2 therapy present higher pCR rates (61%−91%) compared to patients with HER2+/ER+ EBC (26%−56%) (13–20); and, compared with HER2+/ER+ tumors, HER2+/ER-neg tumors have consistently demonstrated greater increases in pCR rates with dual anti-HER2 therapy plus chemotherapy compared with chemotherapy/trastuzumab alone (13,18–20). Nonetheless, duration of anti-HER2 treatment seems to matter in HER2+/ER+ EBC: in TBCRC023, increasing treatment length with trastuzumab/lapatinib and letrozole from 12 to 24 weeks led to an increase in pCR rates from 9% to 33%, whereas no significant difference was observed in HER2+/ER-neg tumors (21). This suggests that in HER2+/ER+ tumors, in the absence of chemotherapy, prolonged inhibition of the HER2 and ER pathways may be necessary not only to decrease proliferation, but to induce apoptosis as well. Yet, adding concomitant endocrine therapy (ET) to anti-HER2 therapy and/or chemotherapy did not yield any advantage in the NSABP B-52 or ADAPT HER2+/HR+ studies (22,23). This is intriguing, as one would expect that the ER/HER2 pathways-blockade would suppress their crosstalk and lead to higher tumor response.

On the opposite end of the spectrum, the high chemo-sensitivity of HER2+/ER-neg tumors was demonstrated in the ADAPT HER2+/HR- study, in which the addition of paclitaxel to trastuzumab/pertuzumab increased pCR rates from 36% to 91% (17). Similarly, the KRISTINE trial showed a significantly higher pCR rate in this group with docetaxel/carboplatin plus trastuzumab/pertuzumab compared to T-DM1/pertuzumab (73% vs. 54%, respectively) (16).

In the adjuvant setting, HER2+/ER+ and HER2+/ER-neg subgroups have a similar degree of proportional risk reduction with trastuzumab (9,24,25). Yet, in contrast with the neoadjuvant setting, duration of adjuvant trastuzumab treatment might matter more for HER2+/ER-neg EBC: in a recent meta-analysis, patients receiving 9 weeks to 6 months of trastuzumab had worse EFS compared to patients treated for 12 months (26). Therefore, in HER2+/ER-neg disease, longer trastuzumab treatment is probably more effective than a shorter course. However, the trials included in this meta-analysis had a median follow-up of less than 5 years, so long-term data on HER2+/ER+ patients are needed.

Challenging this idea, the ExteNET trial showed that sequential anti-HER2 blockade (summing two years of treatment) was beneficial for HER2+/ER+ patients, but not for HER2+/ER-neg patients (27). On the other hand, updated survival results from APHINITY show that early dual HER2-blockade with trastuzumab/pertuzumab has an effect both in HER2+/ER-neg and HER2+/ER+ diseases (28). Reasons for this difference may lie in these

drugs' mechanisms of action, timing of administration, and length of follow-up. After stopping adjuvant trastuzumab, HER2+/ER+ patients continue ET, but the single-blocking of the ER-pathway may lead to re-activation of the HER2-pathway on residual trastuzumab-resistant malignant cells (4). As neratinib was administered after trastuzumab, it may have prevented the re-activation of the HER2-pathway and, hence, benefited HER2+/ER+ patients, but not those with HER2+/ER-neg tumors. As neratinib irreversibly inhibits several HER-family members (EGFR, HER2, HER4), it may have prevented this cross-talk in a more effective way than administration of trastuzumab for 2 years (which only inhibits HER2) (9). In APHINITY, the early dual blockade has probably eliminated trastuzumab-resistant cells in part of the patients, but the benefit was seen later in HER2+/ER+ patients, has these tend to have later relapses, as compared to HER2+/ER-neg patients. .

Recently, the KATHERINE trial showed that in patients with residual disease after neoadjuvant treatment, 1 year of adjuvant T-DM1 was superior to trastuzumab, independently of ER status (29). It should be noted that this trial included selected high-risk patients, for whom suboptimal response to neoadjuvant trastuzumab could have influenced the benefit from a salvage treatment with a different anti-HER2 drug, potentially confounding the effect of baseline ER status.

How can we identify patients who benefit more or less from anti-HER2 treatment?

The biggest question nowadays is how to select patients for escalation/de-escalation approaches, maintaining or increasing pCR rates and survival, with minimal toxicity. Therefore, the quest for finding prognostic and predictive biomarkers has been intense (3). One attempt was to quantify gene expression levels of *ESR1* and *ERBB2*, showing that high levels of *ERBB2* (20,30–32) and low levels of *ESR1* (31) are associated with higher pCR rates. Expression levels of genes involved in HER2- and ER-pathways were also combined in a predictive model in an analysis of the NSABP B-31 trial. Patients were classified into 3 groups: i) "high *ESR1*"/"low-intermediate *ERBB2*": no benefit from trastuzumab (HR 1.58); ii) "low *ESR1*"/"low-intermediate *ERBB2*": moderate benefit (HR 0.60); iii) "low-intermediate *ESR1*"/"high *ERBB2*": large benefit (HR 0.28) (33). This 8-gene signature, showing no linear correlation between *ERBB2* and *ESR1* mRNA levels and benefit from adjuvant trastuzumab, was later validated in the N9831 and FB-7 trials (34,35). Nonetheless, these intriguing findings have not yet been tested in prospective studies or applied in the clinic.

Other biomarker studies focused on the correlation between PAM50 subtypes and benefit from anti-HER2 treatment. A consistent finding is that HER2-Enriched tumors present higher pCR rates (between 28%−72%) when treated with anti-HER2 therapies (with/without chemotherapy), compared to other subtypes (20,32,36,37), showing that HER2-Enriched subtype predicts sensitivity to anti-HER2 treatment. In fact, several studies show that ER status loses its association with pCR when subtype is taken into account, indicating that subtype captures most of the information displayed by ER status and also brings additional information (20,32,36,37). One important aspect to take into account when designing de-

escalation trials is that HER2-Enriched subtype is also chemo-sensitive, with overall pCR rates in HER2+ disease of around 60% with vs. 30% without chemotherapy, respectively (20,32,36,37).

It has also been proposed that high scores of a gene expression-signature of loss-of-function of RB1 may identify HER2+ tumors more likely to respond to chemotherapy and this concept has been validated in HER2+/ER+ tumors using a refined 87 gene-signature (RBsig) (38,39). Moreover, higher TILs levels are associated with improved pCR rates and survival both in HER2+/ER-neg and HER2+/ER+ EBC (40,41), and evidence of immune activation by RNA-signatures is independently associated with higher pCR (20,31). It has also been demonstrated that high TIL levels (>75%) predicted benefit from adjuvant trastuzumab/pertuzumab vs. trastuzumab alone (42). Of note, TILs levels tend to be lower in HER2+/ER+ compared to HER2+/ER-neg tumors (40).

A decrease in Ki67 during neoadjuvant treatment is a surrogate for response and prognosis in HER2-negative/ER+ EBC, so its role is being evaluated in HER2+/ER+ disease (43). In ADAPT HER2+/HR+, patients with an early tumor response (Ki67 decrease≥30% or low-cellular tumor at 3 weeks) had a higher pCR rate compared to nonresponders (36% vs. 20%, respectively) (23). In the PerELISA trial, HER2+/ER+ patients with a Ki67 drop after 2 weeks of letrozole (molecular responders) continued on letrozole, and trastuzumab/pertuzumab were added for another 12 weeks. Nonresponders were switched to paclitaxel with trastuzumab/pertuzumab. The pCR rate was 21% among molecular responders, but even more remarkable was the 81% pCR rate among nonresponders (44). Even though the correlation between an early Ki67 drop and long-term survival is not yet validated in patients with HER2+ tumors, it could become a biomarker for selecting patients with HER2+/ER+ who do not respond to ET and would be candidates to chemotherapy, given the impressive pCR rate achieved in this subgroup.

Thus, a dilemma for future clinical trials is how to select patients: should one be guided by HER2/ER immunohistochemistry status, by molecular subtype or by a combination of both? Based on current evidence, tumors with the highest anti-HER2 sensitivity are those HER2+ by immunohistochemistry/ISH and the PAM50 HER2-Enriched. Whether additional biomarkers will help identify higher anti-HER2 sensitivity is currently unknown, although TILs and *PIK3CA* mutations arise as promising candidates (Figure 2). Indeed, tumors with high HER2 amplification and an intact PI3K pathway are especially sensitive to HER2-targeted therapies (30). TILs could also potentially be used to select patients, but there are no standardized cut-points to define “high” vs. “low” TILs infiltration (45). Another question is if an early biopsy to assess Ki67 levels should be performed in HER2+/ER+ patients receiving neoadjuvant treatment. This is limited by Ki67 low reproducibility (46) and absence of validation as a surrogate for long-term survival benefit in HER2+ EBC.

De-escalating strategies: a plea for separate trials according to ER status

Despite distinct biological and clinical characteristics between HER2+/ER-neg and HER2+/ER+ EBC, they are still treated similarly, except for ET. Nevertheless, different de-escalation strategies for HER2+ EBC might be explored according to ER status: a) to

decrease anti-HER2 treatment duration; b) to avoid anthracyclines, and c) to design chemotherapy-free regimens.

As detailed before, a meta-analysis showed a worse outcome with a shorter treatment duration of adjuvant trastuzumab in patients with HER2+/ER-neg disease, but this comparison was non-significant in patients with HER2+/ER+ tumors. Moreover, in the PERSEPHONE trial (the only trial so far proving its non-inferiority hypothesis of 6 months vs. 1 year of trastuzumab), the HR for the comparison of the two strategies was very close to 1 in the HER2+/ER+ subgroup (HR 0.91; 95% confidence interval, 0.68–1.21) (47). Therefore, in patients with HER2+/ER+ tumors, a shorter duration of trastuzumab treatment may be seen as a safe option by some – nonetheless, due to the late relapse profile of these tumors, longer follow-up data are needed before adopting this strategy.

The APT trial (in which patients with ≤3 cm, node-negative tumors received 12 weeks of paclitaxel and 1 year of trastuzumab) showed a 7-year invasive-DFS of 94.6% for HER2+/ER+ disease and of 90.7% for HER2+/ER-neg disease, with just four distant recurrences (1%) (48). Thus, this treatment de-escalation seems very safe for patients with low-burden tumors. Given the high chemo-sensitivity of HER2+/ER-neg tumors, leading to a higher rate of pCR, a possible strategy for avoiding anthracyclines in patients with somewhat larger tumors would be to assess the tumor's sensitivity upfront with neoadjuvant double HER2-blockade plus a taxane. The DeCrescendo trial will test this hypothesis in patients with cT1c-T2N0 HER2+/ER-neg tumors, who will receive 12 weeks of taxanes plus trastuzumab/pertuzumab. Those who achieve pCR will be spared from adjuvant anthracyclines and will only receive double HER2-blockade until completion of 1 year of treatment. The study is powered to test 3-year relapse-free survival (RFS) rate, with a narrow confidence interval, primarily in patients with PAM50 HER2-Enriched tumors and then in the overall population.

The reduced chemo-sensitivity of HER2+/ER+ EBC fuels the interest in alternative, targeted approaches without chemotherapy. One is the use of CDK4/6 inhibitors, which synergize with trastuzumab in HER2+/ER+ tumor models (49). In the small NA-PHER2 study, 20 weeks of palbociclib/ET/trastuzumab/pertuzumab provided a significant reduction in tumor proliferation, but led to a modest pCR rate of 27% (50). Long-term survival results and efficacy according to molecular subtypes are awaited. There are ongoing trials (PALTAN [NCT02907918]; TOUCH [NCT03644186]) exploring this approach. In particular, TOUCH is assessing RBsig (39) as a potential biomarker to identify HER2+/ER+ patients who could be spared from chemotherapy and treated with ET/anti-HER2/palbociclib. On the other hand, a recent joint analysis of neoadjuvant "chemotherapy-free" trials (SOLTI-PAMELA, TBCRC023/TBCRC006, and PerELISA) has shown that the combination of the HER2-Enriched subtype with a high mRNA expression of *ERBB2* leads to the identification of a subgroup of patients exquisitely sensitive to double HER2-blockade – with pCR rates ranging from 44.5%−66.7% (51). Among HER2+/ER+ patients, only 32% were "HER2-Enriched/ERBB2-high", whereas among the HER2+/ER-neg subgroup there were 68% of patients with this profile. Hence, as the HER2+/ER-neg subgroup is clearly enriched with these HER2-addicted tumors, one could envision a trial restricted to HER2+/ER-neg patients: they would be screened upfront and those with a HER2-enriched/ERBB2-high

expression tumor would be proposed to receive neoadjuvant trastuzumab/pertuzumab only. Like in the DeCrescendo trial, patients achieving pCR would be spared of any adjuvant chemotherapy and the primary endpoint would be a high RFS rate with a narrow confidence interval.

Conclusion

Given the predictive value of ER status, it would be reasonable for the next wave of clinical trials to target separately HER2+/ER+ and HER2+/ER-neg patients. This would lead to a better tailoring of de-escalation treatment strategies, and hence to a greater chance of "success". In addition, this could greatly reduce the morbidity and costs associated with the long and intense systemic regimens that patients with HER2+ tumors still receive, despite years of biomarker research. Thus, besides the use of ER status, we feel that an integrated classification of HER2+ tumors, based on their DNA, RNA, protein expression and immune microenvironment would also be useful for further treatment refinement in the future.

Acknowledgments

Funding

MB and RC acknowledge the support of Institut Jules Bordet, which funds their research fellowship.

References

1. Ferrari A, Vincent-Salomon A, Pivot X, Sertier A-S, Thomas E, Tonon L, et al. A whole-genome sequence and transcriptome perspective on HER2-positive breast cancers. Nat Commun 2016;7:12222. [PubMed: 27406316]
2. Prat A, Carey LA, Adamo B, Vidal M, Tabernero J, Cortés J, et al. Molecular features and survival outcomes of the intrinsic subtypes within HER2-positive breast cancer. J Natl Cancer Inst 2014;106.
3. Gingras I, Gebhart G, de Azambuja E, Piccart-Gebhart M. HER2-positive breast cancer is lost in translation: time for patient-centered research. Nat Rev Clin Oncol 2017;14:669–81. [PubMed: 28762384]
4. Giuliano M, Trivedi MV, Schiff R. Bidirectional Crosstalk between the Estrogen Receptor and Human Epidermal Growth Factor Receptor 2 Signaling Pathways in Breast Cancer: Molecular Basis and Clinical Implications. Breast Care 2013;8:256–62. [PubMed: 24415978]
5. Wang Y-C, Morrison G, Gillihan R, Guo J, Ward RM, Fu X, et al. Different mechanisms for resistance to trastuzumab versus lapatinib in HER2- positive breast cancers - role of estrogen receptor and HER2 reactivation. Breast Cancer Res 2011;13:R121. [PubMed: 22123186]
6. Cejalvo JM, Pascual T, Fernández-Martínez A, Adamo B, Chic N, Vidal M, et al. 1727PDistribution of the PAM50 breast cancer subtypes within each pathology-based group: a combined analysis of 15,339 patients across 29 studies. Ann Oncol [Internet]. 2017 [cited 2019 Mar 19];28. Available from: https://academic.oup.com/annonc/article/28/suppl_5/mdx391.026/4109767
7. Loibl S, Majewski I, Guarneri V, Nekljudova V, Holmes E, Bria E, et al. PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol 2016;27:1519–25. [PubMed: 27177864]
8. Hwan K-T, Kim J, Jung J, Chang JH, Chai YJ, Oh SW, et al. Impact of Breast Cancer Subtypes on Prognosis of Women with Operable Invasive Breast Cancer: A Population-based Study Using SEER Database. Clin Cancer Res 2019;25:1970–9. [PubMed: 30559169]
9. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. The Lancet 2017;389:1195–205.

10. Chumsri S, Li Z, Serie DJ, Mashadi-Hossein A, Colon-Otero G, Song N, et al. Incidence of Late Relapses in Patients With HER2-Positive Breast Cancer Receiving Adjuvant Trastuzumab: Combined Analysis of NCCTG N9831 (Alliance) and NRG Oncology/NSABP B-31. J Clin Oncol 2019;37:3425–35. [PubMed: 31622131]
11. Lambertini M, Campbell C, Gelber RD, Viale G, McCullough A, Hilbers F, et al. Dissecting the effect of hormone receptor status in patients with HER2-positive early breast cancer: exploratory analysis from the ALTTO (BIG 2–06) randomized clinical trial. Breast Cancer Res Treat 2019;177:103–14. [PubMed: 31134488]
12. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. The Lancet 2014;384:164–72.
13. Gianni L, Pienkowski T, Im Y-H, Roman L, Tseng L-M, Liu M-C, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:25–32. [PubMed: 22153890]
14. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24:2278–84. [PubMed: 23704196]
15. Loibl S, Jackisch C, Schneeweiss A, Schmatloch S, Aktas B, Denkert C, et al. Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial. Ann Oncol 2017;28:497–504. [PubMed: 27831502]
16. Hurvitz SA, Martin M, Symmans WF, Jung KH, Huang C-S, Thompson AM, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2018;19:115–26. [PubMed: 29175149]
17. Nitz UA, Gluz O, Christgen M, Grischke E-M, Augustin D, Kuemmel S, et al. De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR- phase II trial: efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab ± weekly paclitaxel. Ann Oncol 2017;28:2768–72. [PubMed: 28945833]
18. Baselga J, Bradbury I, Eidtmann H, Di Cosimo S, de Azambuja E, Aura C, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. The Lancet 2012;379:633–40.
19. Robidoux A, Tang G, Rastogi P, Geyer CE, Azar CA, Atkins JN, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. Lancet Oncol 2013;14:1183–92. [PubMed: 24095300]
20. Carey LA, Berry D, T Cirrincione C, T Barry W, Pitcher B, N Harris L, et al. Molecular Heterogeneity and Response to Neoadjuvant Human Epidermal Growth Factor Receptor 2 Targeting in CALGB 40601, a Randomized Phase III Trial of Paclitaxel Plus Trastuzumab With or Without Lapatinib. J Clin Oncol 2015;34.
21. Rimawi MF, Niravath PA, Wang T, Rexer B, Forero A, Wolff AC, et al. Abstract S6–02: TBCRC023: A randomized multicenter phase II neoadjuvant trial of lapatinib plus trastuzumab, with endcorine therapy and without chemotherapy, for 12 vs. 24 weeks in patients with HER2 overexpressing breast cancer. Cancer Res 2015;75:S6–02-S6–02.
22. Rimawi MF, Cecchini RS, Rastogi P, Geyer CE, Fehrenbacher L, Stella PJ, et al. Abstract S3–06: A phase III trial evaluating pCR in patients with HR+, HER2-positive breast cancer treated with neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) +/− estrogen deprivation: NRG Oncology/NSABP B-52. Cancer Res 2017;77:S3–06-S3–06.
23. Harbeck N, Gluz O, Christgen M, Kates RE, Braun M, Küemmel S, et al. De-Escalation Strategies in Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Early Breast Cancer (BC): Final Analysis of the West German Study Group Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response Prediction in Early BC HER2- and Hormone Receptor-Positive Phase II Randomized Trial-Efficacy, Safety, and Predictive

Markers for 12 Weeks of Neoadjuvant Trastuzumab Emtansine With or Without Endocrine Therapy (ET) Versus Trastuzumab Plus ET. J Clin Oncol 2017;35:3046–54. [PubMed: 28682681]

24. Perez EA, Romond EH, Suman VJ, Jeong J-H, Sledge G, Geyer CE, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol 2014;32:3744–52. [PubMed: 25332249]
25. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant Trastuzumab in HER2-Positive Breast Cancer. N Engl J Med 2011;365:1273–83. [PubMed: 21991949]
26. Niraula S, Gyawali B. Optimal duration of adjuvant trastuzumab in treatment of early breast cancer: a meta-analysis of randomized controlled trials. Breast Cancer Res Treat 2019;173:103–9. [PubMed: 30238273]
27. Martin M, Holmes FA, Ejlertsen B, Delaloge S, Moy B, Iwata H, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017;
28. Piccart M, Procter M, Fumagalli D, de Azambuja E, Clark E, Ewer MS, et al. Interim overall survival analysis of APHINITY (BIG 4–11): A randomized multicenter, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer. San Antonio Breast Cancer Symposium; 2019.
29. von Minckwitz G, Huang C-S, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019;380:617–28. [PubMed: 30516102]
30. Veeraraghavan J, Angelis CD, Mao R, Wang T, Herrera S, Pavlick AC, et al. A combinatorial biomarker predicts pathologic complete response to neoadjuvant lapatinib and trastuzumab without chemotherapy in patients with HER2+ breast cancer. Ann Oncol 2019;30:927–33. [PubMed: 30903140]
31. Fumagalli D, Venet D, Ignatiadis M, Azim HA, Maetens M, Rothé F, et al. RNA Sequencing to Predict Response to Neoadjuvant Anti-HER2 Therapy: A Secondary Analysis of the NeoALTTO Randomized Clinical Trial. JAMA Oncol 2016;3:227–34.
32. Llombart-Cussac A, Cortés J, Paré L, Galván P, Bermejo B, Martínez N, et al. HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial. Lancet Oncol 2017;18:545–54. [PubMed: 28238593]
33. Pogue-Geile KL, Kim C, Jeong J-H, Tanaka N, Bandos H, Gavin PG, et al. Predicting degree of benefit from adjuvant trastuzumab in NSABP trial B-31. J Natl Cancer Inst 2013;105:1782–8. [PubMed: 24262440]
34. Pogue-Geile KL, Song N, Serie DJ, Thompson EA. Abstract PD3–18: The NSABP/NRG 8-gene signature accurately predicts degree of benefit from trastuzumab in Alliance/NCCTG N9831: Validation of the 8-gene signature in an independent clinical trial. Cancer Res 2018;78:PD3–18-PD3–18.
35. Pogue-Geile KL, Wang Y, Srinivasan A, Gavin PG, Kim RS, Song N, et al. Abstract P3–10-04: The fully validated NSABP/NRG 8-gene signature which predicted the degree of benefit in the adjuvant setting (B-31 and NCCTG N9831) associates with pCR in the neoadjuvant setting in NSABP clinical trial FB-7. Cancer Res 2019;79:P3–10-04-P3–10–04.
36. Prat A, Angelis CD, Pascual T, Gutierrez C, Wang T, Paré L, et al. Abstract P2–09-12: Independent validation of the HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer. Cancer Res 2018;78:P2–09-12-P2–09–12.
37. Prat A, Slamon D, Hurvitz SA, Press MF, Phillips GL, Valverde VL, et al. Abstract PD3–06: Association of intrinsic subtypes with pathological complete response (pCR) in the KRISTINE neoadjuvant phase 3 clinical trial in HER2-positive early breast cancer (EBC). Cancer Res 2018;78:PD3–06-PD3–06.
38. Witkiewicz AK, Ertel A, McFalls J, Valsecchi ME, Schwartz G, Knudsen ES. RB-pathway disruption is associated with improved response to neoadjuvant chemotherapy in breast cancer. Clin Cancer Res 2012;18:5110–22. [PubMed: 22811582]

39. Risi E, Grilli A, Migliaccio I, Biagioni C, McCartney A, Guarducci C, et al. A gene expression signature of Retinoblastoma loss-of-function predicts resistance to neoadjuvant chemotherapy in ER-positive/HER2-positive breast cancer patients. Breast Cancer Res Treat 2018;170:329–41. [PubMed: 29564743]
40. Salgado R, Denkert C, Campbell C, Savas P, Nuciforo P, Nucifero P, et al. Tumor-Infiltrating Lymphocytes and Associations With Pathological Complete Response and Event-Free Survival in HER2-Positive Early-Stage Breast Cancer Treated With Lapatinib and Trastuzumab: A Secondary Analysis of the NeoALTTO Trial. JAMA Oncol 2015;1:448–54. [PubMed: 26181252]
41. Denkert C, von Minckwitz G, Darb-Esfahani S, Lederer B, Heppner BI, Weber KE, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. Lancet Oncol 2018;19:40–50. [PubMed: 29233559]
42. Krop IE, Paulson J, Campbell C, Kiermaier AC, Andre F, Fumagalli D, et al. Genomic correlates of response to adjuvant trastuzumab (H) and pertuzumab (P) in HER2+ breast cancer (BC): Biomarker analysis of the APHINITY trial. J Clin Oncol 2019;37:1012–1012. [PubMed: 30811295]
43. Dowsett M, Smith IE, Ebbs SR, Dixon JM, Skene A, A'Hern R, et al. Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. J Natl Cancer Inst 2007;99:167–70. [PubMed: 17228000]
44. Guarneri V, Dieci MV, Bisagni G, Frassoldati A, Bianchi GV, De Salvo GL, et al. De-escalated treatment with trastuzumab-pertuzumab-letrozole in patients with HR+/HER2+ operable breast cancer with Ki67 response after 2 weeks letrozole: Final results of the PerELISA neoadjuvant study. J Clin Oncol 2018;36:507–507.
45. Salgado R, Denkert C, Demaria S, Sirtaine N, Klauschen F, Pruneri G, et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann Oncol 2015;26:259–71. [PubMed: 25214542]
46. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J, et al. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst 2011;103:1656–64. [PubMed: 21960707]
47. Earl HM, Hiller L, Vallier A-L, Loi S, Howe D, Higgins HB, et al. PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): Randomised phase 3 non-inferiority trial with definitive 4-year (yr) disease-free survival (DFS) results. J Clin Oncol 2018;36:506–506.
48. Earl HM, Hiller L, Vallier A-L, Loi S, McAdam K, Hughes-Davies L, et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. The Lancet 2019;393:2599–612.
49. Goel S, Wang Q, Watt AC, Tolaney SM, Dillon DA, Li W, et al. Overcoming Therapeutic Resistance in HER2-Positive Breast Cancers with CDK4/6 Inhibitors. Cancer Cell 2016;29:255–69. [PubMed: 26977878]
50. Gianni L, Bisagni G, Colleoni M, Del Mastro L, Zamagni C, Mansutti M, et al. Neoadjuvant treatment with trastuzumab and pertuzumab plus palbociclib and fulvestrant in HER2-positive, ER-positive breast cancer (NA-PHER2): an exploratory, open-label, phase 2 study. Lancet Oncol 2018;19:249–56. [PubMed: 29326029]
51. Prat A, Pascual T, De Angelis C, Gutierrez C, Llombart-Cussac A, Wang T, et al. HER2-enriched subtype and ERBB2 expression in HER2-positive breast cancer treated with dual HER2 blockade. J Natl Cancer Inst 2019;[Epub ahead of print].

Statement of translational relevance

HER2+ early breast cancer is a heterogeneous disease, in which estrogen receptor (ER) status is emerging as a robust predictive marker. This is related to the fact that the ER- and HER2-pathways drive breast cancer proliferation by a complex interaction of cellular signaling processes, including the sharing of intracellular effectors such as MAPK, PI3K and Src3. Thus, due to the crosstalk between HER2 and ER, treatments targeting one pathway can induce the activation of the other. This leads to a different clinical behavior of HER2+/ER+ disease as compared to HER2+/ER-neg early breast cancer. We discuss how the timing and sequencing of treatments, including anti-HER2 targeted therapy, can influence their benefit according to ER status. We also propose different de-escalation trial designs, with potential impact on clinical practice, separately for HER2+/ER+ and HER2+/ER-neg breast cancer, which should be regarded as distinctly different.

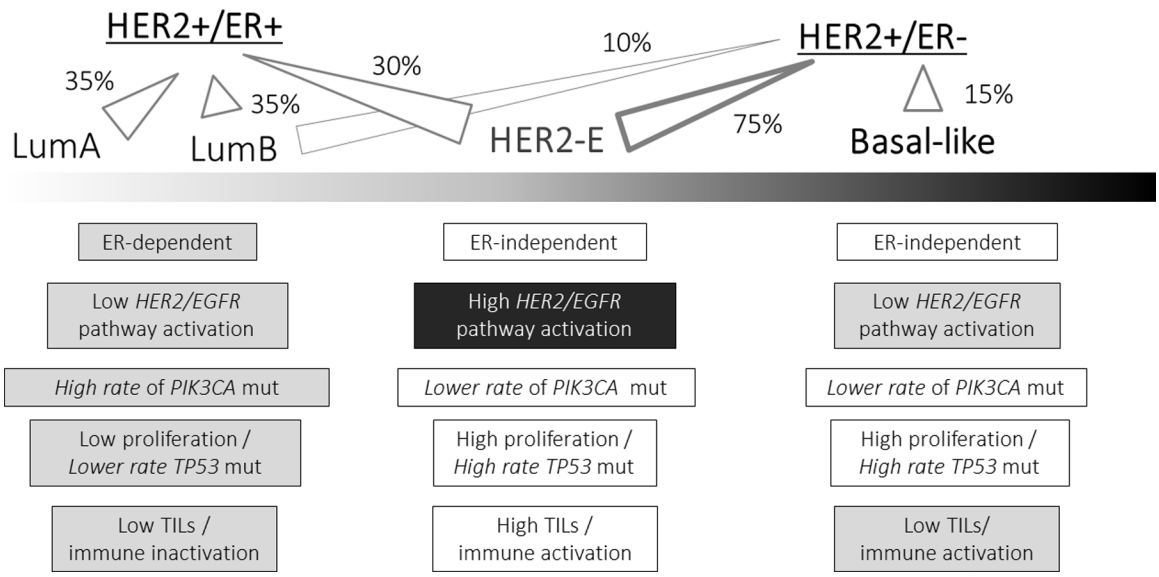

Figure 1 –. Current and future classification of HER2+ disease.

Legend: HER2+ tumors can be divided between estrogen receptor (ER)-positive and ER-negative subgroups, according to the immunohistochemical expression of ER. Yet, at the molecular level, these tumors can be divided into the four molecular subtypes (luminal A, luminal B, HER2-enriched and basal-like), showing different molecular alterations, cell pathways activation and immune microenvironment. This leads to different responses to anti-HER2 treatment, as well to chemotherapy and endocrine therapy.

ER: estrogen receptor; HER2-E: HER2-enriched molecular subtype; LumA: luminal A molecular subtype; LumB: luminal B molecular subtype; mut: mutation; TILs: tumor-infiltrating lymphocytes; WT: wild-type.

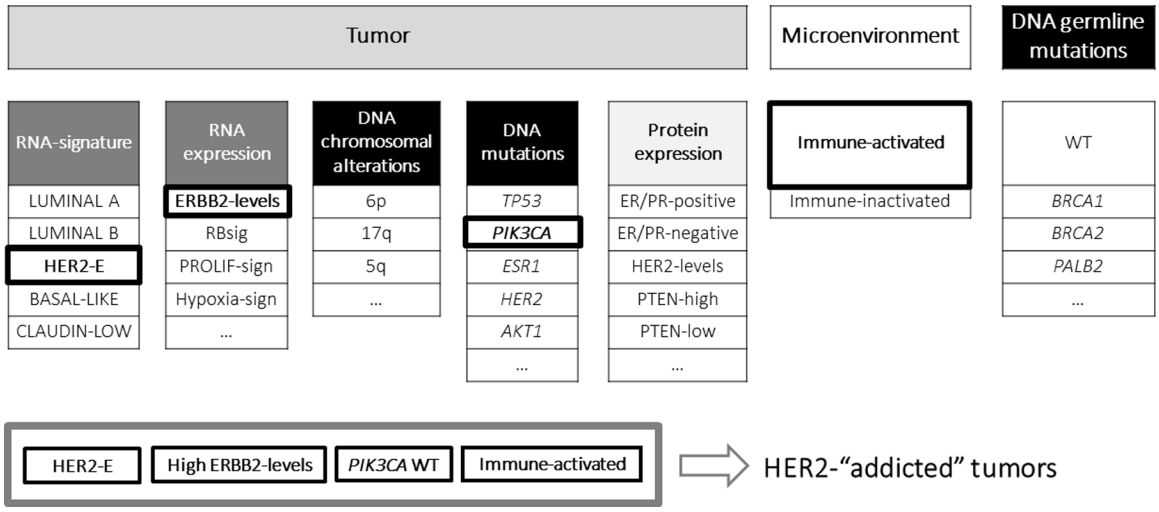

Figure 2 –. Combining biomarkers in HER2+ disease.

Currently, protein expression assessed by immunohistochemistry is the standard method to classify breast cancer into different subtypes, according to tumor's HER2 and estrogen receptors expression. However, an integrated classification of HER2-positive breast tumors, based on their DNA, RNA, protein expression, and microenvironment is needed to implement more precise and guided treatments and to identify those tumors "addicted" to the HER2 cellular pathway. Here, we propose a definition of "HER2-addicted" tumors that can be further refined in the future, as more data become available.

ER: estrogen receptor; HER2-E: HER2-enriched molecular subtype; PR: progesterone receptor; Rbsig: RB loss of function signature; WT: wild-type.