Implications of Neoadjuvant Therapy in Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer

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Breast cancer outcomes have markedly improved in great part because of advances in therapy. These improved outcomes, however, have been accompanied by greater financial costs, toxicities, and overtreatment of a substantial number of patients. We must now focus on studies that leverage our accumulated knowledge and use a more individualized approach for the locoregional[1] and systemic management of this disease.[2-4] De-escalation trials can be harder to perform as a result of the complexities of noninferiority designs, difficulty in funding them, and human nature. Behavioral economists find that people experience negative feelings about losses more strongly than positive feelings about gains of similar size.[5] This makes it harder to conduct trials that are designed to treat breast cancer precisely rather than comprehensively, including studies that aim to de-escalate standard therapy.

The need to better tailor therapy is especially relevant in human epidermal growth factor receptor 2 (HER2)–positive breast cancer. Before HER2 targeting, this subtype had the poorest prognosis, but remarkable improvements in disease-free and overall survival were achieved with adjuvant trastuzumab[6-8] and subsequent reductions in the risk of recurrence were observed with dual or sequential adjuvant anti-HER2 therapy.[9,10] However, ensuring that new standards of care are not simply statistically significant but clinically meaningful has been challenging. For example, full approval by the US Food and Drug Administration in 2017 of the addition of adjuvant pertuzumab to trastuzumab plus chemotherapy was based on improved 3-year invasive disease-free survival (iDFS) from 93% to 94% in the APHINITY trial,[9] a statistically significant but admittedly modest impact in the overall trial population.

Trials that are designed to further tailor therapy in HER2-positive disease will require tools for risk stratification to evaluate de-escalation in patients who are at lower risk for recurrence and to prioritize testing of new therapies for those at higher risk. Using baseline anatomic risk to select patients for therapy de-escalation, the single-arm Adjuvant Trastuzumab Paclitaxel (APT) trial demonstrated impressive outcomes at 7 years with 93% disease-free survival and 95% overall survival for stage I HER2-positive disease.[11] More recently, the KATHERINE trial identified patients who were at high risk of recurrence by enrolling those with residual disease after neoadjuvant trastuzumab—with pertuzumab in some patients—plus combination chemotherapy. This trial demonstrated that an escalation in adjuvant therapy using the antibody–drug conjugate trastuzumab emtansine (T-DM1) in such patients markedly improved 3-year iDFS from 77% to 88%.[12] These findings establish residual disease after neoadjuvant therapy in HER2-positive disease as a definable high risk group and as a useful biomarker for clinical practice and clinical research.[13]

Response to neoadjuvant therapy for HER2-positive breast cancer is a valuable indicator by which to characterize risk. The neoadjuvant approach is increasingly the norm as it downstages local disease and optimizes surgical management,[14] and pathologic complete response (pCR) is an accepted prognostic marker.[15] Given the value of pCR as an intermediate prognostic marker for outcome, neoadjuvant therapy has been endorsed as a research platform with which to assess treatment effects in vivo and as a more efficient strategy to conduct smaller trials that target specific breast cancer subtypes.[16] This platform assumes that shorter-term response will predict longer-term survival, thereby accelerating the transition from smaller neoadjuvant phase II trials to larger and definitive adjuvant phase III randomized trials.[17,18]

The investment in this strategy was exemplified by the 2013 accelerated US Food and Drug Administration approval of pertuzumab in the neoadjuvant setting based in part on the NeoSphere trial in which the addition of pertuzumab to trastuzumab plus docetaxel substantially increased pCR from 29% to 46%.[19] However, this and other neoadjuvant trials of dual anti-HER2 therapy serve as a cautionary tale. Multiple neoadjuvant phase II to III trials that examined either lapatinib or pertuzumab added to trastuzumab plus chemotherapy demonstrated a higher pCR with dual therapy but were less predictive of meaningful outcomes in subsequent adjuvant trials. In that regard,

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Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on April 29, 2019 and published at jco.org on June 3, 2019: DOI https://doi.org/10.1200/JCO.19.01159

the APHINITY trial that investigated the addition of pertuzumab to adjuvant trastuzumab met its statistical objective, whereas the ALTTO trial that tested the addition of lapatinib to adjuvant trastuzumab did not,[20] and in practice the clinical improvement observed in both studies was modest at best. Although this outcome might have been predicted by more sophisticated modeling of the absolute difference in pCR required to produce a meaningful improvement in recurrence for survival,[18] the fact remains that the use of pCR as a surrogate of survival to investigate novel treatments with the hope of eliminating the need for large adjuvant trials has thus far not been realized.

However, neoadjuvant trials have shown that a small but meaningful subgroup of patients with HER2-positive disease can achieve a pCR with all-biologic regimens without chemotherapy. In NeoSphere, 17% of patients who were randomly assigned to just trastuzumab plus pertuzumab achieved pCR, which was considerably lower than when chemotherapy was included. Nevertheless, it is intriguing that some patients seem to benefit from HER2-directed therapy alone, a finding echoed in such trials as TBCRC 006, TBCRC 023, TBCRC 026, and PAMELA, in which 17% to 34% of patients assigned to trastuzumab with either lapatinib or pertuzumab achieved pCR,[21-24] with higher rates observed in patients with estrogen receptor–negative disease than estrogen receptor–positive disease. The challenge now is to determine to what extent pCR itself is associated with favorable outcomes regardless of the treatment used to induce it.

In the article that accompanies this editorial, Hurvitz et al[25] report on the secondary end points from the KRISTINE trial, including 3-year measures of efficacy, safety, and patient-reported outcomes. KRISTINE was a phase III trial that randomly assigned patients with centrally confirmed HER2-positive stage II to III operable breast cancer (tumor size $>$ 2 cm) to either six cycles of a regimen with limited chemotherapy using T-DM1 plus pertuzumab (T-DM1+P) versus docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP). Its primary objective was previously reported[26] and was largely viewed as a negative study for the neoadjuvant T-DM1+P combination as its pCR rate was significantly lower compared with TCHP (44% *v* 56%). Moreover, 7% of patients who received T-DM1+P experienced disease progression during neoadjuvant therapy compared with none on TCHP.

In the article by Hurvitz et al, KRISTINE investigators report on the 3-year event-free survival (EFS; for all enrolled patients) and iDFS (for those who went to surgery after six cycles of study-assigned therapy). Patients who achieved a pCR continued on the same HER2-targeted regimen after surgery (T-DM1+P or trastuzumab and pertuzumab [HP]). Patients in the T-DM1+P arm who had greater than 1 cm of residual disease in the breast, involved lymph nodes, or both were encouraged to undergo chemotherapy, and 24% patients in the T-DM1 arm received postoperative chemotherapy, including 33% (41 of 124) of those patients with residual disease and 9% (nine of 99) of those with pCR.

There are several important findings from this new report. First, more patients experienced disease progression during neoadjuvant T-DM1+P (7%) than during TCHP (0%), and the resulting lower 3-year EFS implies a worse outcome when all patients are considered from study start. Second, there were fewer grade 3 or higher adverse events with T-DM1+P during the neoadjuvant phase; however, in the adjuvant setting, there was more toxicity with T-DM1+P, which is only partially explained by the use of adjuvant chemotherapy and could represent cumulative toxicity with T-DM1 that was also observed in KATHERINE.[12] Compared with HP, adjuvant T-DM1+P in the KRISTINE trial was associated with more grade 3 or higher adverse events (24% *v* 9%) and events leading to treatment discontinuation (18% *v* 4%).

The most intriguing finding, however, was that even though EFS was numerically lower with T-DM1+P compared with TCHP (83% and 94%, respectively), iDFS—which by definition excluded patients with progression during neoadjuvant therapy—was similar with the two regimens (93% and 92%, respectively) but with wide confidence margins (hazard ratio, 1.11; 95% CI, 0.52 to 2.40). In particular, patients who achieved pCR with either regimen had excellent outcomes, with 3-year iDFS of approximately 97% in each arm. Among the 223 patients who achieved pCR in both arms, only five patients experienced disease recurrence, including three in the T-DM1+P arm (two CNS and one distant non-CNS recurrence) and two patients in the TCHP arm (both CNS). Although encouraging, these survival data must be interpreted cautiously as they were secondary descriptive objectives without associated hypothesis testing.

The new results of the KRISTINE trial further reinforce the notion that the neoadjuvant setting can serve as a platform for risk stratification in clinical practice as well as for the development of new treatments for HER2-positive breast cancer. We already knew that pathologic response is a patient-level prognostic marker for long-term outcomes.[15] Just as KATHERINE demonstrated the clinical utility of the neoadjuvant strategy to identify patients with residual disease who derive a survival benefit from an escalation in adjuvant therapy, the secondary outcome results from KRISTINE suggest that patients who achieve pCR with limited chemotherapy exposure, such as T-DM1+P, have a low recurrence risk. If so, pathologic response after neoadjuvant therapy could be used as a functional biomarker with which to identify patients with clinical stage II or III disease who might benefit from less chemotherapy (de-escalation). The challenge then remains to identify patients who have the highest likelihood of achieving pCR with less toxic therapy and who will have excellent long-term outcomes.

Whether on study or in clinical practice, caution is needed and a careful multidisciplinary approach is mandatory. Taken together, KRISTINE, KATHERINE, and similar trials suggest that the neoadjuvant approach in HER2-positive disease holds the potential to allow for a Goldilocks strategy—not too much, nor too little therapy—and it is time to leverage this further. If all pCRs are created equal, no matter how achieved, which is what the KRISTINE trial suggests but has not proven, the goal then should be to achieve pCR with the least toxic therapy. Unfortunately, all-biologic regimens, such as HP, in unselected HER2-positive breast cancers have relatively low pCR rates. Regimens with limited chemotherapy exposure, such as T-DM1+P, result in a higher pCR frequency; however, T-DM1+P also has a relatively high progression rate during the neoadjuvant phase compared with regimens using just a single free chemotherapy drug, such as NeoSphere,[19] NeoALTTO,[28] and CALGB 40601.[27] Therefore, a careful assessment of HER2 status and possibly additional biomarkers will be needed to ensure optimal patient selection for neoadjuvant T-DM1+P.

Today, patients with HER2-positive breast cancer and clinical stage I disease should be referred for surgery and offered adjuvant single-agent paclitaxel and trastuzumab using the APT regimen if pathologic stage is confirmed. On the basis of the results from the KATHERINE trial, patients with clinical stage II and III disease should be offered preoperative combination chemotherapy plus single or dual HER2-targeted therapy, and escalation of adjuvant therapy with T-DM1 for those with residual disease. Finally, although the findings from KRISTINE are promising, it is premature to endorse pCR for de-escalation in routine practice, especially when pCR was obtained using HER2-targeted regimens with limited chemotherapy exposure, such as T-DM1+P. Still, this is clearly a valuable direction of study, and de-escalation trials guided by pCR and other markers must now proceed.

In the future, greater individualization in early-stage HER2-positive disease will be the norm, including the ability to predict which patients are most likely to achieve pCR with less therapy. Factors at presentation, such as intrinsic subtype,[27,29] immune activation markers, and HER2 expression and heterogeneity, as well as factors assessed after therapy is started, such as functional imaging[24] and cell-free DNA, will further refine the assessment of response to therapy by pathologic response categories. The immediate next steps should be to confirm the implications from the KRISTINE trial, namely, that survival outcomes in patients who achieve pCR with HER2-targeted regimens combined with less or no chemotherapy are the same as those achieved with targeted therapy plus combination chemotherapy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.01159.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Giuliano AE, Ballman KV, McCall L, et al: Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The ACOSOG Z0011 (Alliance) randomized clinical trial. JAMA 318:918-926, 2017
2. Wolff AC, Abeloff MD: Adjuvant chemotherapy for postmenopausal lymph node-negative breast cancer: It ain't necessarily so. J Natl Cancer Inst 94:1041-1043, 2002
3. Sparano JA, Gray RJ, Makower DF, et al: Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med 373:2005-2014, 2015
4. Sparano JA, Gray RJ, Makower DF, et al: Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 379:111-121, 2018
5. Thaler RH, Sunstein CR: Nudge. New Haven, CT, Yale University Press, 2008
6. Slamon D, Eiermann W, Robert N, et al: Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365:1273-1283, 2011
7. Perez EA, Romond EH, Suman VJ, 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 32:3744-3752, 2014
8. Cameron D, Piccart-Gebhart MJ, Gelber RD, 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. Lancet 389:1195-1205, 2017
9. von Minckwitz G, Procter M, de Azambuja E, et al: Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med 377:122-131, 2017
10. Martin M, Holmes FA, Ejlertsen B, 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 18:1688-1700, 2017

11. Tolaney SM, Guo H, Pernas S, et al: Seven-year follow-up analysis of adjuvant paclitaxel and trastuzumab trial for node-negative, human epidermal growth factor receptor 2–positive breast cancer. J Clin Oncol 37:1868-1875, 2019
12. von Minckwitz G, Huang C-S, Mano MS, et al: Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 380:617-628, 2019
13. Prowell TM, Beaver JA, Pazdur R: Residual disease after neoadjuvant therapy: Developing drugs for high-risk early breast cancer. N Engl J Med 380:612-615, 2019
14. Morrow M: Management of the node-positive axilla in breast cancer in 2017: Selecting the right option. JAMA Oncol 4:250-251, 2018
15. Cortazar P, Zhang L, Untch M, et al: Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. Lancet 384: 164-172, 2014
16. Wolff AC, Berry D, Carey LA, et al: Research issues affecting preoperative systemic therapy for operable breast cancer. J Clin Oncol 26:806-813, 2008
17. Prowell TM, Pazdur R: Pathological complete response and accelerated drug approval in early breast cancer. N Engl J Med 366:2438-2441, 2012
18. Berry DA, Hudis CA: Neoadjuvant therapy in breast cancer as a basis for drug approval. JAMA Oncol 1:875-876, 2015
19. Gianni L, Pienkowski T, Im Y-H, 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 13:25-32, 2012
20. Piccart-Gebhart M, Holmes E, Baselga J, et al: Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: Results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. J Clin Oncol 34:1034-1042, 2016
21. Rimawi MF, De Angelis C, Contreras A, et al: Low PTEN levels and PIK3CA mutations predict resistance to neoadjuvant lapatinib and trastuzumab without chemotherapy in patients with HER2 over-expressing breast cancer. Breast Cancer Res Treat 167:731-740, 2018
22. Veeraraghavan J, De Angelis C, Mao R, et al: A combinatorial biomarker predicts pathologic complete response to neoadjuvant lapatinib and trastuzumab without chemotherapy in patients with HER2+ breast cancer. Ann Oncol 10.1093/annonc/mdz076 [Epub ahead of print on March 23, 2019]
23. Llombart-Cussac A, Cortés J, Paré L, 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 18: 545-554, 2017
24. Connolly RM, Leal JP, Solnes L, et al: TBCRC026: Phase II trial correlating standardized uptake value with pathologic complete response to pertuzumab and trastuzumab in breast cancer. J Clin Oncol 37:714-722, 2019
25. Hurvitz SA, Martin M, Jung KH, et al: Neoadjuvant trastuzumab emtansine and pertuzumab in patients with human epidermal growth factor receptor 2–positive breast cancer: Three-year outcomes from the phase III KRISTINE study. J Clin Oncol 37:2206-2216, 2019
26. Hurvitz SA, Martin M, Symmans WF, 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 19:115-126, 2018
27. Carey LA, Berry DA, Cirrincione CT, 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 34:542-549, 2016
28. Baselga J, Bradbury I, Eidtmann H, et al: Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): A randomised, open-label, multicentre, phase 3 trial. Lancet 379:633-640, 2012
29. Prat A, Pascual T, De Angelis C, et al: HER2-enriched subtype and ERBB2 expression in HER2-positive breast cancer treated with dual HER2 blockade. J Natl Cancer Inst doi: https://doi.org/10.1093/jnci/djz042

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Research Funding: Myriad Genetics (Inst), Pfizer (Inst), Biomarin (Inst), Celldex (Inst)
Patents, Royalties, Other Intellectual Property: Named as inventor on one or more issued patents or pending patent applications relating to methylation in breast cancer and has assigned his rights to Johns Hopkins University, and participates in a royalty sharing agreement with Johns Hopkins University

Nadine M. Tung
Research Funding: AstraZeneca

Lisa A. Carey
Research Funding: Innocrin Pharma (Inst), Syndax (Inst), Immunomedics (Inst)
Patents, Royalties, Other Intellectual Property: Royalty-sharing agreement, investor interest in licensed intellectual property to startup company, Falcon Therapeutics, that is designing neural stem-cell–based therapy for glioblastoma multiforme (I)

No other potential conflicts of interest were reported.