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Pertuzumab Plus Trastuzumab With or Without Chemotherapy Followed by Emtansine in *ERBB2*-Positive Metastatic Breast Cancer
A Secondary Analysis of a Randomized Clinical Trial

Jens Huober, MD; Patrik Weder, MD; Karin Ribi, PhD; Beat Thürlimann, MD; Jean-Christophe Thery, MD, PhD; Qiyu Li, PhD; Laurence Vanlemmens, MD; Séverine Guiu, MD, PhD; Etienne Brain, MD, PhD; Julien Grenier, MD; Florence Dalenc, MD; Christelle Levy, MD; Aude-Marie Savoye, MD; Andreas Müller, MD; Véronique Membrez-Antonioli, MD; Marie-Aline Gérard, PhD; Jérôme Lemonnier, PhD; Hanne Hawle, MD; Daniel Dietrich, PhD; Epie Boven, MD, PhD; Hervé Bonnefoi, MD; for the Swiss Group for Clinical Cancer Research, Unicancer Breast Group, and Dutch Breast Cancer Research Group

IMPORTANCE In *ERBB2* (formerly *HER2*)-positive metastatic breast cancer (MBC), combining trastuzumab and pertuzumab with taxane-based chemotherapy is the first line of standard care. Given that trastuzumab plus pertuzumab was proven effective in *ERBB2*-positive MBC, even without chemotherapy, whether the optimal first-line strategy could be trastuzumab plus pertuzumab alone instead of with chemotherapy is unresolved.

OBJECTIVE To assess overall survival (OS) at 2 years and progression-free survival (PFS) for patients randomly assigned to receive first-line pertuzumab plus trastuzumab alone or with chemotherapy followed by trastuzumab and emtansine at progression; PFS of second-line trastuzumab and emtansine treatment following trastuzumab plus pertuzumab; and OS and PFS in the *ERBB2*-enriched and *ERBB2*-nonenriched subtypes.

DESIGN, SETTING, AND PARTICIPANTS This was a secondary analysis of a multicenter, open-label, phase 2 randomized clinical trial conducted at 27 sites in France, 20 sites in Switzerland, 9 sites in the Netherlands, and 1 site in Germany. Overall, 210 patients with centrally confirmed *ERBB2*-positive MBC were randomized between May 3, 2013, and January 4, 2016, with termination of the trial May 26, 2020. Data were analyzed from December 18, 2020, to May 10, 2022.

INTERVENTIONS Patients randomly received pertuzumab (840 mg intravenously [IV], then 420 mg IV every 3 weeks) plus trastuzumab (8 mg/kg IV, then 6 mg/kg IV every 3 weeks) without chemotherapy (group A) or pertuzumab plus trastuzumab (same doses) with either paclitaxel (90 mg/m^2 for days 1, 8, and 15, then every 4 weeks for ≥4 months) or vinorelbine tartrate (25 mg/m^2 for first administration followed by 30 mg/m^2 on days 1 and 8 and every 3 weeks for ≥4 months) followed by pertuzumab plus trastuzumab maintenance after chemotherapy discontinuation (group B).

MAIN OUTCOMES AND MEASURES Overall survival at 24 months by treatment group, PFS for first-line treatment, PFS for second-line treatment, and patient-reported quality of life (QOL).

RESULTS A total of 210 patients were included in the analysis, with a median age of 58 (range, 26-85) years. For group A, 24-month OS was 79.0% (90% CI, 71.4%-85.4%); for group B, 78.1% (90% CI, 70.4%-84.5%). Median PFS with first-line treatment was 8.4 (95% CI, 7.9-12.0) months in group A and 23.3 (95% CI, 18.9-33.1) months in group B. Unlike expectations, OS and PFS did not markedly differ between populations with *ERBB2*-enriched and *ERBB2*-nonenriched cancer. Adverse events were less common without chemotherapy, with small QOL improvements from baseline in group A and stable QOL in group B.

CONCLUSIONS AND RELEVANCE The findings of this secondary analysis of a randomized clinical trial suggest that the chemotherapy-free anti-*ERBB2* strategy is feasible without being detrimental in terms of OS. The 50-gene prediction analysis of microarray signature could not help to identify the most appropriate patient population for this approach.

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Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the Swiss Group for Clinical Cancer Research, Unicancer Breast Group, and Dutch Breast Cancer Research Group are listed in Supplement 7.

Corresponding Author: Jens Huober, MD, Professor, Brustzentrum, Kantonsspital St Gallen, Rorschacher Str 95, 9007 St Gallen, Switzerland (jens.huober@kssg.ch).

Metastatic breast cancer (MBC) is considered incurable, with treatments primarily designed to control symptoms and prolong life expectancy while minimizing toxic effects and maintaining quality of life (QOL).[1-3] Combining trastuzumab and pertuzumab without adding chemotherapy was shown to be effective with low levels of toxic effects in *ERBB2* (previously *HER2*)-positive pretreated MBC and in trastuzumab-resistant progressive disease.[4] In patients with *ERBB2*-positive MBC, the CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial[5,6] revealed clinical superiority when adding pertuzumab to standard treatment with a combination of docetaxel and trastuzumab, with significantly increased progression-free survival (PFS) and overall survival (OS). However, docetaxel displays substantial toxic effects. Several trials evaluated pertuzumab plus trastuzumab combined with other chemotherapy agents like paclitaxel or nab-paclitaxel,[7-9] which were highly effective, with acceptable tolerability. Combining pertuzumab plus trastuzumab with taxane-based chemotherapy is the standard for first-line treatment of *ERBB2*-positive MBC. However, dual *ERBB2* receptor blockade by combining trastuzumab with pertuzumab or lapatinib ditosylate may prove effective even without chemotherapy. In *ERBB2*-positive and hormone receptor-positive MBC, combining lapatinib and trastuzumab with an aromatase inhibitor resulted in 11-month PFS, with superior PFS benefits vs trastuzumab and an aromatase inhibitor.[10] In the PERTAIN trial,[11] pertuzumab plus trastuzumab with an aromatase inhibitor exhibited superior PFS vs trastuzumab plus an aromatase inhibitor. In the neoadjuvant NeoSphere trial involving *ERBB2*-positive primary breast cancer, complete response was achieved in 17% patients using trastuzumab plus pertuzumab alone.[12,13] In the neoadjuvant TBCRC 006 trial,[14] pathological complete response rate was 27 of 100 (27%) with anti-*ERBB2* (lapatinib plus trastuzumab) therapy alone. Even with trastuzumab alone followed by chemotherapy at progression vs upfront combination therapy, PFS for trastuzumab plus chemotherapy was similar in these groups with MBC in a randomized phase 3 trial.[15] In second-line *ERBB2*-positive MBC therapy, combined trastuzumab and emtansine was less toxic though superior to lapatinib plus capecitabine.[16-18] Prospective data for trastuzumab plus emtansine following trastuzumab plus pertuzumab therapy are limited, with PFS of 5 months in 29 patients pretreated with trastuzumab plus pertuzumab.[19] Neoadjuvant trials[20] suggested that in *ERBB2*-positive tumors, those with the *ERBB2*-enriched subtype based on intrinsic subtyping according to research-based 50-gene prediction analysis of microarray (PAM50) would better respond to anti-*ERBB2* therapy, especially with dual *ERBB2* blockade.[20]

Anti-*ERBB2* therapy is likely effective even without chemotherapy in *ERBB2*-positive MBC. Herein we tested the following hypotheses: (1) initial chemotherapy-free approach consisting of 2 anti-*ERBB2* agents followed by trastuzumab plus emtansine at progression would not compromise OS, with fewer toxic effects and better QOL vs first-line chemotherapy plus dual anti-*ERBB2* therapy; and (2) patients with *ERBB2*-enriched subtype would better respond to dual *ERBB2* blockade than those without.

Key Points

Question Does a chemotherapy-free approach using an effective first-line anti-*ERBB2* dual treatment regimen consisting of trastuzumab and pertuzumab followed by emtansine result in similar overall survival with fewer toxic effects and better quality of life compared with immediate chemotherapy in combination with trastuzumab and pertuzumab followed by trastuzumab and emtansine in patients with *ERBB2*-positive metastatic breast cancer?

Findings In this secondary analysis of 210 patients from a randomized clinical trial, overall survival was similar for both strategies at 2 years despite a longer progression-free survival observed with the addition of chemotherapy to trastuzumab and pertuzumab.

Meaning These findings suggest that the chemotherapy-free anti-*ERBB2* strategy is an option as first-line treatment in some patients with *ERBB2*-positive metastatic breast cancer.

Methods

Study Design and Patients

In a randomized, open-label phase 2 clinical trial, patients with centrally confirmed *ERBB2*-positive MBC were randomized 1:1 to receive pertuzumab (loading dose of 840 mg intravenously [IV] followed by 420 mg IV every 3 weeks) and trastuzumab (loading dose of 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks) without chemotherapy (group A) or pertuzumab plus trastuzumab (same dosing schedule) combined with paclitaxel (90 mg/m^2 on days 1, 8 and 15, every 4 weeks for ≥4 months) or vinorelbine tartrate (25 mg/m^2 for first administration followed by 30 mg/m^2 on days 1 and 8, then every 3 weeks for ≥4 months) followed by pertuzumab plus trastuzumab maintenance therapy after chemotherapy discontinuation (group B) (eFigure 1 in Supplement 1). The study was approved by respective ethics committees of the participating centers, and patients provided their written informed consent. We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Randomization was conducted centrally via internet. The minimization method used the following stratification factors: hormone receptor status (positive vs negative), prior trastuzumab (never or >12 months vs ≤12 months after last infusion), liver or lung (or both) metastases (present vs absent), and country. Adding endocrine treatment up front to pertuzumab plus trastuzumab was recommended in group A or to pertuzumab plus trastuzumab maintenance therapy after chemotherapy discontinuation in group B. Therapy was given until progression or inacceptable toxic effects. Eligible patients were without prior therapy for inoperable locally advanced breast cancer or MBC. In patients with brain metastases as the only progression site with pertuzumab plus trastuzumab, first-line treatment was maintained, with radiotherapy added. The second-line therapy was trastuzumab plus emtansine (3.6 mg/kg IV) in both treatment groups, with patients eligible if they had received at least 1 dose of first-line

treatment, with proven disease progression. Patients who discontinued first-line therapy due to unacceptable toxic effects without disease progression were ineligible (Supplement 2 and Supplement 3).

The primary efficacy end point was the patient proportion still alive at 24 months, with 90% exact Clopper-Pearson CIs, in each group. Patients lost to follow-up before 24 months were considered to have failed treatment. Secondary end points included PFS, response, and safety in first- and second-line treatments. Progression-free survival was defined as time from randomization until Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1), progression, and disease control was defined as complete response, partial response, or stable disease over 6 months (RECIST). Overall survival was defined as time from randomization until death; time to failure of strategy was defined as time from randomization until RECIST progression or MBC-related death.

We used the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, for adverse events. The National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index (NFBSI-16) was used to assess QOL.

Quality of Life

Patients completed QOL forms at baseline, every 12 weeks up to 24 months or until progression during first-line therapy, before starting second-line therapy, and 12 and 24 weeks thereafter. The NFBSI-16 represents a 16-item self-report measure covering disease- and treatment-related symptoms and/or concerns in advanced breast cancer using a scale from 0 (not at all) to 4 (very much),[21,22] comprising a summary score (range, 0-64), 3 multi-item subscales (disease-related symptoms including physical, treatment adverse effects, and function and/or well-being), and 1 single-item subscale (disease-related symptoms-emotional). Two additional single-item QOL indicators for overall treatment burden and coping effort were linearly transformed into a scale from 0 to 100, with higher scores indicating a better condition.[23,24]

PAM50 Testing

PAM50 testing identifies intrinsic breast cancer subtypes that do not completely overlap with immunohistochemistry results. Gene expression used the NanoString Breast Cancer 360 assay (BC360TM) on NanoString Counter SPRINT Profiler (NanoString Technologies, Inc), covering genes from 33 independent signatures, including PAM50 signature (https://nanostring.com). The NanoString platform measured the relative abundance of each messenger RNA transcript of interest,[25] classified into 4 subtypes: luminal A, luminal B, *ERBB2* enriched, and basallike. Overall and progression-free survival were assessed exploratorily in *ERBB2*-enriched and *ERBB2*-nonenriched subtypes of the overall population and each treatment group.

Statistical Analysis

Data were analyzed from December 18, 2020, to May 10, 2022. The sample size relied on a noncomparative parallel design with a CI approach. Assuming a median 32-month OS in both groups, 104 evaluable patients per group were needed, the width of the 90% Clopper-Pearson CI being 0.166. The independent data monitoring committee reviewed safety reports every 6 months.

Analyses for first-line treatment applied the intention-to-treat principle, and those for second-line treatment included patients who received at least 1 first-line dose and 1 second-line dose. Other efficacy analyses were based on all randomized patients. Safety analyses involved all randomized patients with at least 1 trial dose of the respective treatment line.

All binary end points were expressed as percentages and 90% CIs. Time-to-event end points used Kaplan-Meier methods, with a less restrictive OS estimator at 2 years than the primary end point (where patients lost to follow-up before 24 months were considered to have failed treatment and not censored observations). Overall, 90% CIs for proportions were calculated, and medians estimated with standard 95% CIs (Supplement 4).

For breast cancer molecular subtypes, the Pearson correlation coefficient for the 4 PAM50 centroids was calculated for each sample, the sample being assigned to the subtype of the centroid with the highest correlation (Supplement 5 and Supplement 6). For QOL, indicators were analyzed descriptively during first-line therapy. An exploratory analysis identified the patient proportion reporting clinically relevant symptoms and/or concerns, with the worst score at any time during first-line therapy considered. Analyses were performed using SAS, version 9.4 (SAS Institute Inc), and R, version 3.5.3 (R Project for Statistical Computing).

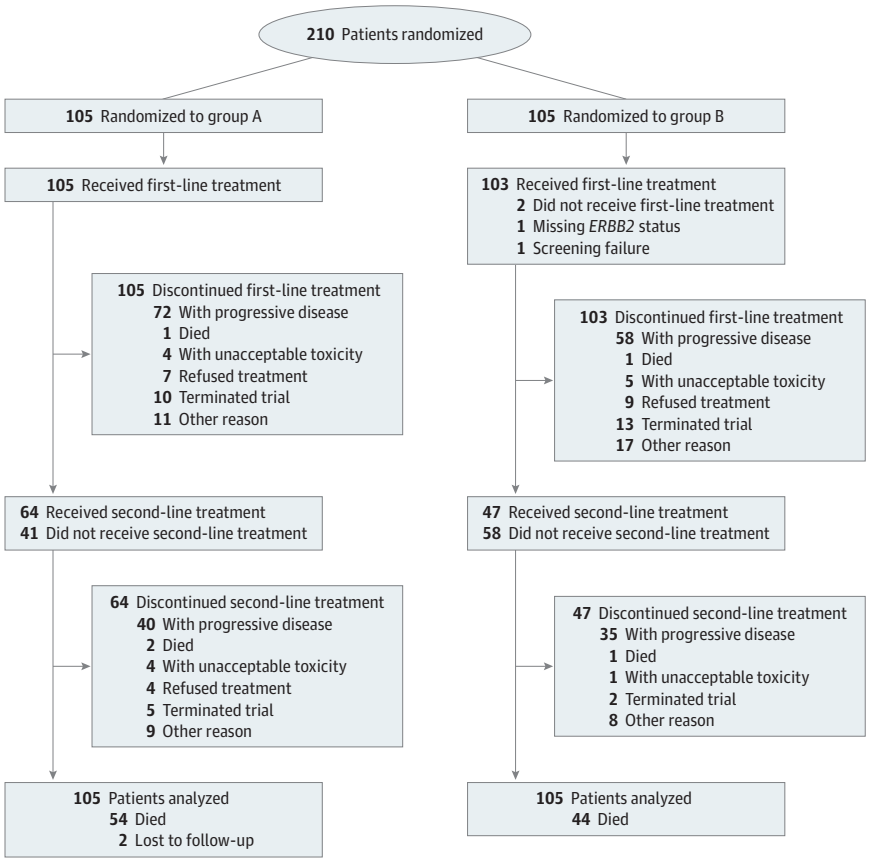
Results

Between May 3, 2013, and January 4, 2016, 210 patients were randomized at 27 sites in France, 20 sites in Switzerland, 9 sites in the Netherlands, and 1 site in Germany. Two patients in group B did not receive any medication. The trial was terminated on May 26, 2020, with 23 patients (10 in group A and 13 in group B) still receiving first-line treatment. Of 111 patients proceeding to second-line treatment, 7 were still under treatment at trial termination. Overall, 98 patients died. The trial flowchart for the intention-to-treat population is provided in **Figure 1**, with analysis data lock on December 18, 2020.

Between-group patient characteristics were well-balanced (eTable 1 in Supplement 1), with a median age of 58 (range, 26-85) years, 134 patients (63.8%) displaying hormone receptor–positive disease, and 202 (96.2%) with a performance status of 0 or 1. Overall, 132 patients (62.9%) exhibited liver or lung metastases, with slightly more patients with liver metastasis in groups A vs B (43 vs 34). In group A, more patients exhibited at least 3 disease sites vs group B (39 vs 28). Bone-only disease was observed in 17 patients (8.1%).

First- and second-line therapy outcomes are summarized in the **Table**. The median follow-up time was 63 (2-83) months. The proportion of patients known to be alive at 2 years was 79.0% (90% CI, 71.4%-85.4%) and 78.1% (90% CI, 70.4%-84.5%) for groups A and B, respectively, with overlapping 90% CIs. This outcome was slightly better in patients with hormone receptor–negative tumors in both groups (Table). The

Figure 1. Study Flowchart



See "Study Design and Patients" section in "Methods" for comprehensive definitions of groups A and B.

Table. Outcomes by Treatment Group

Outcome	Treatment group[a]	
	Group A	Group B
OS at 2 y, % (90% CI)[b]	79.0 (71.4-85.4)	78.1 (70.4-84.5)
ER-positive and/or PgR-positive	76.5 (66.5-84.6)	75.8 (65.5-84.2)
ER-negative and PgR-negative	83.8 (70.5-92.7)	82.1 (68.9-91.3)
First-line PFS, median (95% CI), mo[c]	8.4 (7.9-12.0)	23.3 (18.9-33.1)
ER-positive and/or PgR-positive	8.3 (6.5-13.7)	25.5 (18.9-41.9)
ER-negative and PgR-negative	8.4 (7.9-14.6)	21.0 (11.4-32.6)
TFS, median (95% CI), mo	29.0 (18.9-63.4)	48.6 (35.8-69.5)
OS, median (95% CI), mo	60.5 (42.6-NR)	68.8 (55.3-NR)
Second-line PFS with trastuzumab plus emtansine, median (95% CI), mo	8.9 (4.4-11.7)	6.4 (4.0-12.7)

Abbreviations: OS, overall survival; ER, estrogen receptor; NR, not reached; PFS, progression-free survival; PgR, progesterone receptor; TFS, time to failure of strategy.

[a] See "Study Design and Patients" section in "Methods" for comprehensive definitions of groups A and B.

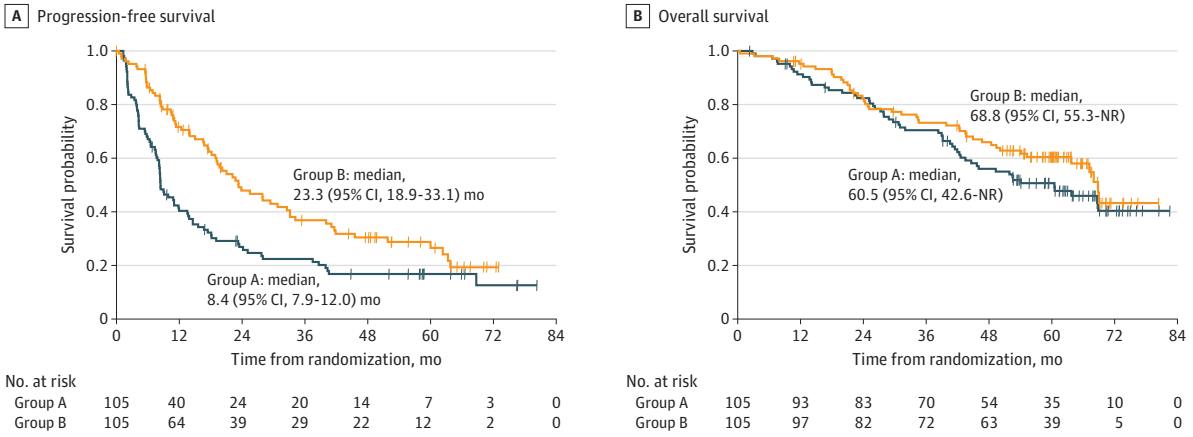
[b] Considered a binary end point.

[c] First central nervous system metastasis was ignored for this end point.

median OS was 60.5 (95% CI, 42.6 to not reached [NR]) months for group A and 68.8 (95% CI, 55.3-NR) months for group B (**Figure 2**). The differences in yearly OS rates (eTable 2 in Supplement 1) between groups A and B (year 1: 91.3% [90% CI, 85.4%-94.9%] vs 95.2% [90% CI, 90.3%-97.7%]; year 2: 82.4% [90% CI, 75.1%-87.7%] vs 82.3% [90% CI, 75.0%-87.6%]; year 3: 70.4% [90% CI, 62.2%-77.2%] vs 73.2% [90% CI, 65.1%-79.7%]; year 4, 56.0% [90% CI, 47.4%-63.8%] vs 66.0% [90% CI, 57.5%-73.1%]; and year 5: 50.7% [90% CI, 42.1%-58.6%] vs 60.4% [90% CI, 51.8%-68.0%]) did not reach the level of significance.

Relevant differences between groups A and B concerned median PFS during first-line treatment (8.4 [95% CI, 7.9-12.0] vs 23.3 [95% CI, 18.9-33.1] months) (Figure 2). The estimated median time to failure of strategy was shorter in group A vs B (29.0 [95% CI, 18.9-63.4] vs 48.6 [95% CI, 35.8-69.5] months). Yearly PFS rates from years 1 to 5 (eTable 2 in Supplement 1) differed between groups A and B, particularly year 1 (40.4% [90% CI, 32.3%-48.2%] vs 71.6% [90% CI, 63.4%-78.4%] months), with differences and CIs getting closer between both groups in years 2 to 5 (year 2: 26.9% [90% CI, 19.9%-34.4%] vs 47.9% [90% CI, 39.%-56.3%]; year 3: 22.4% [90% CI, 15.9%-29.7%] vs 36.9% [90% CI, 28.4%-45.4%]; year 4: 16.8% [90% CI, 11.0%-23.6%] vs 30.5% [90% CI, 22.4%-38.8%]; and year 5: 16.8% [11.0%-23.6%] vs 26.5% [90% CI, 18.6%-35.2%]). Primary progressions during the first 6 months (eTable 3 in

Figure 2. Progression-Free Survival and Overall Survival for First-Line Treatment



The first central nervous system metastasis was ignored for the end point of progression-free survival. See "Study Design and Patients" section in "Methods" for comprehensive definitions of groups A and B. NR indicates not reached.

Supplement 1) during first-line therapy were more frequent in group A (17 [16.2%]) than B (5 [4.8%]), and disease control was high in both groups (65 [61.9%] in group A vs 83 [79.0%] in group B).

Except hematological toxic effects, most adverse events were of grade 1 or 2, almost all being less common in chemotherapy-free patients, except fever and allergic reactions (**Figure 3**). Central nervous system only as the first site of progressive disease was numerically higher in group B during first-line therapy but not with trastuzumab-emtansine (eTable 4 in Supplement 1).

During second-line treatment, median PFS with trastuzumab -emtansine was 6.8 (95% CI, 5.0-11.5) months for all patients, 8.9 (95% CI, 4.4-11.7) months in group A, and 6.4 (95% CI, 4.0-12.7) months in group B (Table). Disease control occurred in 51 of 111 patients (45.9%) and primary progression in 23 (20.7%). Trastuzumab plus emtansine was well tolerated, without new safety concerns (eTable 5 in Supplement 1). First PFS events of second-line treatment including CNS lesions are presented in eTable 6 in Supplement 1. An exploratory analysis revealed that patients with at least 3 sites displayed an unfavorable outcome (eFigures 2 and 3 in Supplement 1).

PAM50 Exploratory Analysis

Our NanoString analysis included 141 breast cancer samples that all passed quality controls, with no samples available for 69 patients. As expected, most *ERBB2*-positive tumors (103 [73.0%]) were of *ERBB2*-enriched subtype by PAM50. Subtype distribution is provided in eFigure 4 in Supplement 1.

The *ERBB2*-enriched subtype did not display increased OS under dual *ERBB2* blockade vs *ERBB2*-nonenriched subtype (**Figure 4**). Considering PFS, the results tended to be slightly better for *ERBB2*-enriched vs *ERBB2*-nonenriched subtypes (Figure 4). Analyses of PFS and OS by PAM50 subtypes and treatment groups (eFigure 5 in Supplement 1) yielded no clear signals except that among participants with the *ERBB2*-enriched subtype, those in group B performed better than those in group A (eFigure 5C in Supplement 1).

Quality of Life

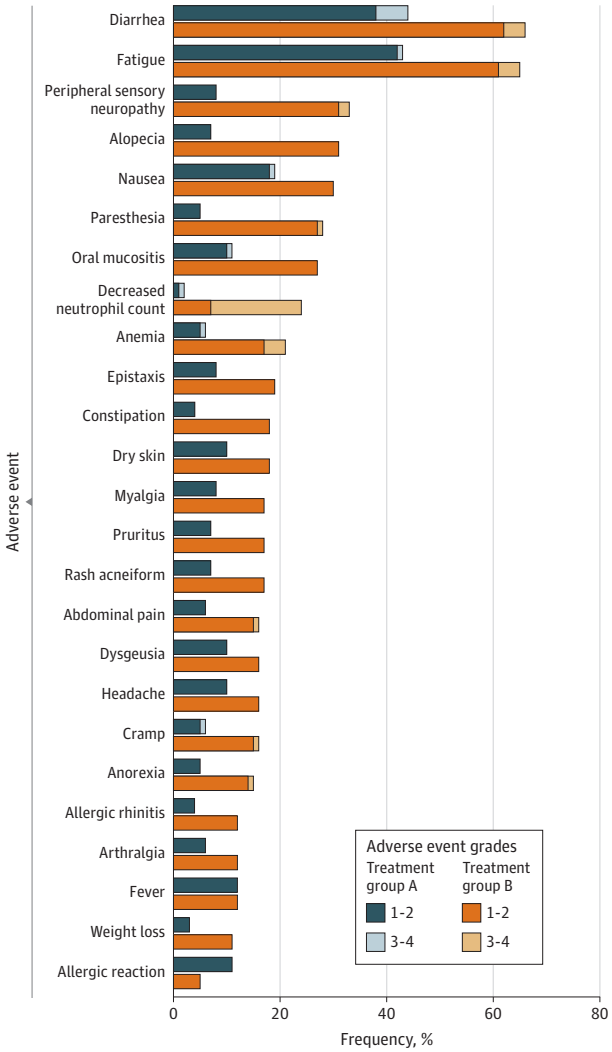
Completion rates for QOL during first-line treatment exceeded 80% at month 3, then gradually declined to less than 50% at month 24 (eTable 7 in Supplement 1) in both groups. The proportion of submitted forms in group A was higher than in group B. eFigure 6 in Supplement 1 provides absolute scores for total NFBSI-16, with the 3 multi-item subscales. Changes from baseline exhibited small initial improvements in NFBSI-16 total scores in group A, which were maintained over the 24-month period (eTable 8 in Supplement 1), with scores remaining stable in group B. The NFBSI-16 subscale scores were similar between both groups, with only small changes over time (eTable 8 in Supplement 1). Scores for treatment burden worsened in both groups, but to a greater extent in chemotherapy-treated patients over the first 3 months, and were worse between months 12 and 18 for patients receiving pertuzumab plus trastuzumab only (eTable 8 in Supplement 1). A substantial improvement in coping effort (eTable 8 in Supplement 1) was reported in both groups.

Analyzing individual NFBSI-16 items (eFigure 7 in Supplement 1) revealed the patient proportion reporting a clinically relevant symptom or concern during first-line treatment tended to be higher in group B. During second-line treatment and in both groups, QOL scores remained stable during the first 6 months (eTable 9 in Supplement 1).

Discussion

We investigated 2 different strategies for newly diagnosed *ERBB2*-positive MBC: an initial chemotherapy-free approach using anti-*ERBB2* therapy with pertuzumab plus trastuzumab alone vs initial chemotherapy combined with pertuzumab plus trastuzumab, both followed by trastuzumab plus emtansine

Figure 3. First-Line Treatment-Related Adverse Events in More Than 10% of Patients



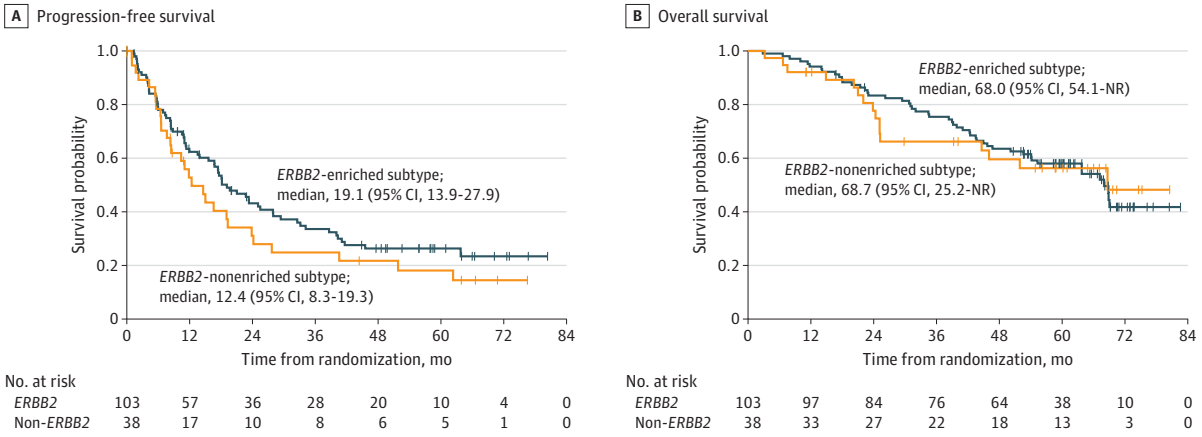
See "Study Design and Patients" section in "Methods" for comprehensive definitions of groups A and B.

at progression. Although 2-year OS did not differ between both strategies, the median PFS was significantly shorter in patients without first-line chemotherapy. Second-line therapy with trastuzumab plus emtansine remained effective following dual pertuzumab plus trastuzumab blockade, with a median PFS of 6.8 months. Patients randomized to dual blockade alone experienced a mean 8-month chemotherapy-free time before embarking on cytostatic therapy, thus a crucial gain for patients displaying restricted lifetime expectations. Chemotherapy was associated with more adverse effects, reflected by a greater proportion of patients reporting symptoms and/or concerns during first-line therapy in group B.

Considering dual anti-*ERBB2* therapy's efficacy without chemotherapy observed in different breast cancer settings,[10-14] this approach has been tested in first-line treatment of *ERBB2*-positive MBC in only 2 trials: the current PERNETTA trial and EORTC 75111-10114 (European Organisation for Research and Treatment of Cancer)[26] trial. The EORTC trial focused on patients older than 60 years[26] who randomly received trastuzumab plus pertuzumab without chemotherapy or trastuzumab plus pertuzumab with oral metronomic cyclophosphamide chemotherapy, PFS being the primary end point. The median PFS was 5.5 months for pertuzumab plus trastuzumab alone vs 12.7 months after adding oral cyclophosphamide. The breast cancer-specific survival cumulative incidence at 1 year was similar between both groups (23.5% vs 16.5%; hazard ratio, 1.10 [95% CI, 0.47-52.8]; $P = .83$), as was OS. Comparison of these data with ours is difficult, as the patient populations differed, with EORTC patients being older (median age, 77 [61-91 vs 58 [26-85] years) and having more severe frailty. Additionally, the end points and chemotherapy backbones differed, with the EORTC trial using metronomic cyclophosphamide, which is not a standard regimen. Additionally, we selected 2-year OS as end point rather than PFS, as we expected a longer PFS when adding chemotherapy to anti-*ERBB2* treatment. As multiple treatment lines are now available for *ERBB2*-positive MBC, we assumed that if omitting upfront chemotherapy would prove unfavorable regarding OS, this would probably occur within the first 2 years. Indeed, exceeding death rates within this time would be attributed to less efficacy of the chemotherapy-free regimen. Given that OS probability at 3, 4, and 5 years was similar between both groups, no evidence suggests that OS results would actually have worsened following a longer observation (eTable 2 in Supplement 1). Yearly PFS rates for first-line therapy revealed the main between-group PFS difference occurred in year 1, while diminishing in years 2 to 5. Despite similar OS, physicians and patients may still worry about PFS differences over the first 2 years. Therefore, a better selection of patients sensitive to anti-*ERBB2* treatment is warranted. Several neoadjuvant studies showed the PAM50 test able to identify *ERBB2*-enriched tumors with increased sensitivity to anti-*ERBB2* treatment.[20,27-29] These patients may be especially suitable for de-escalation. Given this context, a translational PERNETTA project investigated this issue. Using conventional diagnostics, all PERNETTA cohort tumors were centrally confirmed as *ERBB2* positive. PAM50 analysis revealed that, based on gene patterns, there were not only *ERBB2*-enriched subtypes seen, but other subtypes, with possibly different biological behaviors. We assumed that patients with the *ERBB2*-enriched subtype would strongly respond to anti-*ERBB2* therapy alone, rendering chemotherapy unnecessary. However, these expectations were not confirmed by our study data: PFS remained better adding chemotherapy to anti-*ERBB2* treatment for the *ERBB2*-enriched subtype, while PFS was similar between both groups for the *ERBB2*-nonenriched subtype.

In some neoadjuvant trials investigating dual anti-*ERBB2* blockade without chemotherapy, the pathological complete response rate was significantly higher in *ERBB2*-enriched subtypes vs other subtypes. Contrary to our results, this suggested that the *ERBB2*-enriched subgroup consisted of patients particularly sensitive to anti-*ERBB2* therapy alone.[20,30] However, compared with the metastatic setting,

Figure 4. Progression-Free Survival and Overall Survival for *ERBB2*-Enriched and *ERBB2*-Nonenriched Populations During First-Line Therapy



NR indicates not reached.

a pathological complete response is unlikely to be the optimal surrogate for long-term outcome in advanced disease. Indeed, neoadjuvant trial data are recognized to differ from advanced-setting data. Therefore, such data cannot always be extrapolated to the metastatic setting, similar to the different association of programmed cell death ligand 1 status to response to chemoimmunotherapy in metastatic and early triple-negative breast cancer.[31,32]

PAM50 subtyping has proven to estimate benefits from dual *ERBB2* blockade only in 1 retrospective analysis in the MBC setting in overall response, PFS, and OS terms.[30] In this retrospective analysis, the patient population differed from ours, as they were heavily pretreated, with PAM50 subtyping and *ERBB2* messenger RNA combined into 1 assay.[30] Patient characteristics must indeed be considered, as patients who are older and have frailty may be good de-escalation candidates, whereas those with a higher clinical risk or symptomatic disease would still benefit from chemotherapy.

Quality of life is paramount in metastatic disease, and omitting chemotherapy may result in better QOL due to reduced treatment burden. Our patients undergoing chemotherapy reported worse scores for the treatment adverse effect subscale during the first 6 months, with a greater patient proportion reporting several NFBSI-16 individual symptoms and/or concerns as being "quite a bit" or "very much" a problem during first-line treatment, suggesting a patient-reported benefit of the chemotherapy-free approach without translating into a clinically relevant between-group difference in overall QOL (NFBSI-16 total score). A possible explanation would be that QOL assessment intervals had been too large, with relevant differences in QOL changes not assessed, which would have been captured by more frequent assessments.

Limitations

This study has some limitations. The trial consisted of a population with rather good prognostic data, as we included a greater proportion of patients with primary metastatic disease. Patients had fewer prior adjuvant or neoadjuvant pretreatments like anti-*ERBB2* and endocrine therapy.

Conclusions

The findings of this secondary analysis of a randomized clinical trial suggest that selected de-escalation with pertuzumab plus trastuzumab alone without chemotherapy as first-line treatment followed by trastuzumab plus emtansine at progression in *ERBB2*-positive MBC may be a reasonable treatment option for some patients. Overall survival was not compromised by delaying chemotherapy to later treatment lines, despite a much shorter first-line PFS. Selecting these patients with *ERBB2*-enriched tumors according to their PAM50 signature did not enable us to identify the most appropriate population for de-escalation.

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Author Affiliations: Breast Center St Gallen, Cantonal Hospital St Gallen, St Gallen, Switzerland (Huober, Weder, Thürlimann); Swiss Group for Clinical Cancer Research Coordinating Center, Bern, Switzerland (Huober, Weder, Li, Gérard, Hawle, Dietrich); Quality of Life Office, International Breast Cancer Study Group, Bern, Switzerland (Ribi); Department of Medical Oncology, Center Henri Becquerel, Rouen, France (Thery); Department of Medical Oncology, Center Oscar Lambret, Lille, France (Vanlemmens); Department of Medical Oncology, Regional Cancer Institute, Montpellier, France (Guiu); Department of Medical Oncology, Institute Curie, Paris & Saint-Cloud, France (Brain); Department of Medical Oncology, Institute Sainte Catherine, Avignon, France (Grenier); Department of Medical Oncology, Institute Claudius Regaud–Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France (Dalenc); Department of Medical Oncology, Center Francois Baclesse, Caen, France (Levy); Department of Medical Oncology, Institute Jean Godinot, Reims, France (Savoye); Breast Center, Cantonal Hospital of Winterthur, Winterthur, Switzerland (Müller); Department of Medical Oncology, Hospital of Valais, Sion, Switzerland (Membrez-Antonioli); R&D, Unicancer, Paris, France (Lemonnier); Medical Oncology, Amsterdam UMC, Vrije Universiteit Amsterdam/Cancer Center Amsterdam, Amsterdam, the Netherlands (Boven); Department of Medical Oncology, Institut Bergonié Unicancer, Universitaire Bordeaux, Institut National de la Santé et de la Recherche Médicale U1218, Bordeaux, France (Bonnefoi).

Author Contributions: Mrs Li and Dr Dietrich had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Huober, Ribi, Thürlimann, Li, Müller, Gérard, Lemonnier, Boven, Bonnefoi.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Huober, Ribi, Thürlimann, Li, Brain, Savoye, Membrez-Antonioli, Gérard, Boven, Bonnefoi.
Critical review of the manuscript for important intellectual content: Huober, Weder, Ribi, Thürlimann, Théry, Li, Vanlemmens, Guiu, Brain, Grenier, Dalenc, Levy, Müller, Lemonnier, Hawle, Dietrich, Boven, Bonnefoi.
Statistical analysis: Li, Dietrich.
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REFERENCES

1. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). *Ann Oncol*. 2018;29(8):1634-1657. doi:10.1093/annonc/mdy192

2. Liedtke C, Jackisch C, Thill M, Thomssen C, Müller V, Janni W; AGO Breast Committee. AGO recommendations for the diagnosis and treatment of patients with early breast cancer: update 2018. *Breast Care (Basel)*. 2018;13(3):196-208. doi:10.1159/000489329

3. Ghislain I, Zikos E, Coens C, et al; European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group; Breast Cancer Group; EORTC Headquarters. Health-related quality of life in locally advanced and metastatic breast cancer: methodological and clinical issues in randomised controlled trials. *Lancet Oncol*. 2016;17(7):e294-e304. doi:10.1016/S1470-2045(16)30099-7

4. Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. *J Clin Oncol*. 2010;28(7):1138-1144. doi:10.1200/JCO.2009.24.2024

5. Baselga J, Cortés J, Kim SB, et al; CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366(2):109-119. doi:10.1056/NEJMoa1113216

6. Swain SM, Baselga J, Kim S-B, et al; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in *HER2*-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724-734. doi:10.1056/NEJMoa1413513

7. Bachelot T, Ciruelos E, Schneeweiss A, et al; PERUSE investigators. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for *HER2*-positive locally recurrent or metastatic breast cancer (PERUSE). *Ann Oncol*. 2019;30(5):766-773. doi:10.1093/annonc/mdz061

8. Perez EA, López-Vega JM, Petit T, et al. Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with *HER2*-positive locally advanced or metastatic breast cancer: VELVET cohort 1 final results. *Breast Cancer Res*. 2016;18(1):126. doi:10.1186/s13058-016-0773-6

9. Andersson M, López-Vega JM, Petit T, et al. Efficacy and safety of pertuzumab and trastuzumab administered in a single infusion bag, followed by vinorelbine: VELVET cohort 2 final results. *Oncologist*. 2017;22(10):1160-1168. doi:10.1634/theoncologist.2017-0079

10. Johnston SRD, Hegg R, Im SA, et al. Phase III, randomized study of dual human epidermal growth factor receptor 2 (*HER2*) blockade with lapatinib plus trastuzumab in combination with an aromatase inhibitor in postmenopausal women with *HER2*-positive, hormone receptor-positive metastatic breast cancer: ALTERNATIVE. *J Clin Oncol*. 2018;36(8):741-748. doi:10.1200/JCO.2017.74.7824

11. Rimawi M, Ferrero JM, de la Haba-Rodriguez J, et al; PERTAIN Study Group. First-line trastuzumab plus an aromatase inhibitor, with or without pertuzumab, in human epidermal growth factor receptor 2–positive and hormone receptor–positive metastatic or locally advanced breast cancer (PERTAIN): a randomized open label phase 2 trial. *J Clin Oncol*. 2018;36(28):2826-2835. doi:10.1200/JCO.2017.76.7863

12. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early-stage *HER2* positive breast cancer (NeoSphere): a multicenter, open label, phase 2 randomized trial. *Lancet Oncol*. 2012;13(1):25-32. doi:10.1016/S1470-2045(11)70336-9

13. Gianni L, Pienkowski T, Im YH, et al. 5-Year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage *HER2*-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol*. 2016;17(6):791-800. doi:10.1016/S1470-2045(16)00163-7

14. Rimawi MF, Mayer IA, Forero A, et al. Multicenter phase II study of neoadjuvant lapatinib and trastuzumab with hormonal therapy and without chemotherapy in patients with human epidermal growth factor receptor 2-overexpressing breast cancer: TBCRC 006. *J Clin Oncol*. 2013;31(14):1726-1731. doi:10.1200/JCO.2012.44.8027

15. Pagani O, Klingbiel D, Ruhstaller T, et al; Swiss Group for Clinical Cancer Research (SAKK). Do all patients with advanced *HER2* positive breast cancer need upfront-chemo when receiving trastuzumab? randomized phase III trial SAKK 22/99. *Ann Oncol*. 2017;28(2):305-312. doi:10.1093/annonc/mdw622

16. Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated *HER2*-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncol*. 2017;18(6):743-754. doi:10.1016/S1470-2045(17)30313-3

17. Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated *HER2*-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(6):732-742. doi:10.1016/S1470-2045(17)30312-1

18. Verma S, Miles D, Gianni L, et al; EMILIA Study Group. Trastuzumab emtansine for *HER2*-positive advanced breast cancer. *N Engl J Med*. 2012;367(19):1783-1791. doi:10.1056/NEJMoa1209124

19. Dzimitrowicz H, Berger M, Vargo C, et al. T-DM1 activity in metastatic human epidermal growth factor receptor 2-positive breast cancers that received prior therapy with trastuzumab and pertuzumab. *J Clin Oncol*. 2016;34(29):3511-3517. doi:10.1200/JCO.2016.67.3624

20. 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*. 2017;18(4):545-554. doi:10.1016/S1470-2045(17)30021-9

21. Cella D, Rosenbloom SK, Beaumont JL, et al. Development and validation of 11 symptom indexes to evaluate response to chemotherapy for advanced cancer. *J Natl Compr Canc Netw*. 2011;9(3):268-278. doi:10.6004/jnccn.2011.0026

22. Garcia SF, Rosenbloom SK, Beaumont JL, et al. Priority symptoms in advanced breast cancer: development and initial validation of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy–Breast Cancer Symptom Index (NFBSI-16). *Value Health*. 2012;15(1):183-190. doi:10.1016/j.jval.2011.08.1739

23. Bernhard J, Maibach R, Thürlimann B, Sessa C, Aapro MS; Swiss Group for Clinical Cancer Research. Patients' estimation of overall treatment burden: why not ask the obvious? *J Clin Oncol*. 2002;20(1):65-72.

24. Hürny C, Bernhard J, Bacchi M, et al; Swiss Group for Clinical Cancer Research (SAKK) and the International Breast Cancer Study Group (IBCSG). The Perceived Adjustment to Chronic Illness Scale (PACIS): a global indicator of coping for operable breast cancer patients in clinical trials. *Support Care Cancer*. 1993;1(4):200-208. doi:10.1007/BF00366447

25. Geiss GK, Bumgarner RE, Birditt B, et al. Direct multiplexed measurement of gene expression with color-coded probe pairs. *Nat Biotechnol*. 2008;26(3):317-325. doi:10.1038/nbt1385

26. Wildiers H, Tryfonidis K, Dal Lago L, et al. Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with *HER2*-positive metastatic breast cancer (EORTC 75111-10114): an open-label, randomised, phase 2 trial from the Elderly Task Force/Breast Cancer Group. *Lancet Oncol*. 2018;19(3):323-336. doi:10.1016/S1470-2045(18)30083-4

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*. 2016;34(6):542-549. doi:10.1200/JCO.2015.62.1268

28. Dieci MV, Prat A, Tagliafico E, et al. Integrated evaluation of PAM50 subtypes and immune modulation of pCR in *HER2*-positive breast cancer patients treated with chemotherapy and *HER2*-targeted agents in the CherLOB trial. *Ann Oncol*. 2016;27(10):1867-1873. doi:10.1093/annonc/mdw262

29. Guarneri V, Dieci MV, Bisagni G, et al. De-escalated therapy for HR+/*HER2*+ breast cancer patients with Ki67 response after 2-week letrozole: results of the PerELISA neoadjuvant study. *Ann Oncol*. 2019;30(6):921-926. doi:10.1093/annonc/mdz055

30. 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*. 2020;112(1):46-54. doi:10.1093/jnci/djz042

31. Schmid P, Cortes J, Pusztai L, et al; KEYNOTE-522 Investigators. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382(9):810-821. doi:10.1056/NEJMoa1910549

32. Cortes J, Rugo HS, Cescon DW, et al; KEYNOTE-355 Investigators. Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. *N Engl J Med*. 2022;387(3):217-226. doi:10.1056/NEJMoa2202809