Review Article

Risk-Based Therapeutic Strategies for HER2-Positive Early Breast Cancer: A Consensus Paper

Mattia Garutti,[1] Linda Cucciniello,[1,9] Grazia Arpino,[2] Alessandra Fabi,[3] Lorenzo Livi,[4] Elisabetta Munzone,[5] Nicoletta Staropoli,[6] Claudio Zamagni,[7] Alberto Zambelli,[8] Fabio Puglisi[1,9]

Abstract

Breast cancer represents the most commonly diagnosed neoplasm worldwide and the HER2-positive subtype accounts for nearly 1 in 5 breast cancers. The majority of patients with breast cancer present with an early-stage disease upon diagnosis, which is thus susceptible to virtually curative treatment strategies. For a stage, I T1a/b N0 HER2-positive disease, upfront surgery followed by adjuvant therapy is the preferred approach. However, there is some uncertainty regarding the appropriate management of stage cT1c cN0, as both the neoadjuvant approach and upfront surgery have been proven to be feasible therapeutic options. The aim of this Delphi consensus was to define the best strategies for the treatment of early HER2-positive breast cancer. This work may help clinicians in the management of early HER2-positive breast cancer.

Clinical Breast Cancer, Vol. 23, No. 7, e458–e469 © 2023 Published by Elsevier Inc.
Keywords: Adjuvant, Neoadjuvant, Pertuzumab, Trastuzumab, Trastuzumab Emtansine

Introduction

With more than 2 million new cases registered every year, breast cancer (BC) represents the most commonly diagnosed neoplasm worldwide.[1]

Up to 90% of BC patients present with an early-stage disease (confined to the mammary gland and/or the locoregional lymph nodes), which is susceptible to more effective treatment strategies. HER2-positive (HER2+) BC accounts for 15% to 20% of the diagnoses.[2,3] The hyperexpression and/or amplification of HER2 has historically represented a negative prognostic factor,[4] until the introduction to the clinical practice of anti-HER2 target therapy. Trastuzumab was the first anti-HER2 agent that demonstrated significant improvement in survival with HER2+ metastatic BC when used in combination with chemotherapy, compared with chemotherapy alone.[5]

Later, trastuzumab also demonstrated efficacy in the management of early-stage HER2+ BC.[6,7] Patients with stage II or III HER2+ BC are generally offered a neoadjuvant therapy, followed by surgery and adjuvant therapy.[8] For stage I T1a/bN0 HER2+ disease, upfront surgery followed by adjuvant therapy is the preferred approach, according to the results of the APT trial.[9] However, appropriate management of stage I cT1c cN0 HER2+ BC remains uncertain, as both the neoadjuvant approach and upfront surgery have proven to be feasible therapeutic options.[9,10]

The aim of this work was to revise the literature concerning the type and duration of (neo)adjuvant anti-HER2 therapy for early

List of abbreviation: BC, breast cancer; DFS, disease-free survival; EFS, event-free survival; IDFS, invasive disease-free survival; HER2+, HER2-positive; HR, hazard ratio; HR+, hormone receptor-positive; N−, node-negative; N+, node-positive; OS, overall survival; pCR, pathologic complete response; RFI, recurrence-free interval; RT, radiotherapy; TNBC, triple-negative breast cancer;
List of regimens: AC(-T), doxorubicin + cyclophosphamide (followed by a taxane); AC(-TH), doxorubicin + cyclophosphamide (followed by a taxane + trastuzumab); EC, epirubicin + cyclophosphamide; FEC, 5-fluorouracil + epirubicin + cyclophosphamide; T, taxane; TC, docetaxel + carboplatin; TCH, docetaxel + carboplatin + trastuzumab; TCHP, docetaxel + carboplatin + trastuzumab + pertuzumab; TDM1, trastuzumab emtansine; TH, taxane + trastuzumab; wP, weekly paclitaxel.

[1]CRO Aviano, National Cancer Institute, IRCCS, Aviano, Italy
[2]Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy
[3]Precision Medicine in Breast Cancer Unit, Department of Woman and Child Health and Public Health, IRCCS, Scientific Directorate, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy
[4]Radiation Oncology Unit, Azienda Ospedaliero Universitaria Careggi, Florence, Italy
[5]Division of Medical Senology, European Institute of Oncology, IRCCS, Milan, Italy
[6]Medical Oncology and Translational Medical Oncology Units, Department of Experimental and Clinical Medicine, Magna Graecia University, AOU Materdomini Catanzaro, Campus Salvatore Venuta, Catanzaro, Italy
[7]Medical Oncology Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[8]Department of Biomedical Sciences Humanitas University and IRCCS Istituto Clinico Humanitas, Rozzano, Milan, Italy
[9]Department of Medicine, University of Udine, Udine, Italy

Submitted: May 12, 2023; Revised: Jul 11, 2023; Accepted: Jul 24, 2023; Epub: 26 July 2023

Address for correspondence: Mattia Garutti, MD, CRO Aviano, National Cancer Institute, IRCCS, 33081, Aviano, Italy.
E-mail contact: mattia.garutti@cro.it

1526-8209/$ - see front matter © 2023 Published by Elsevier Inc.
https://doi.org/10.1016/j.clbc.2023.07.006

Table 1 Preliminary List of Clinical Decisional Nodes for Early HER2+ Breast Cancer to be Discussed in Delphi Consensus

Neoadjuvant Therapy vs. Upfront Surgery
1. Indications for neoadjuvant treatment
2. Features to consider when choosing a neoadjuvant treatment in cT1c
3. Neoadjuvant regimen options
Postneoadjuvant Setting
4. Features to consider when choosing the postneoadjuvant regimen
5. Management of HER2-discrepancy among pre- and postoperative settings
6. How to manage patients achieving a pCR
7. How to manage patients not achieving a pCR
8. How to manage patients not achieving a pCR but with minimal disease burden
9. Concomitant radiotherapy with TDM1
Adjuvant Setting
10. Therapeutic options for pT1 pN0 stage
11. Features to consider when choosing an adjuvant regimen in pT1 pN0 stage
12. Therapeutic options for pT2–3 and/or pN+ stage
13. Indications for double HER2-blockade
14. Anti-HER2 duration

Abbreviations: c = clinical staging system, p = pathological staging system, pCR = pathologic complete response, TDM1 = trastuzumab emtansine.

HER2+ BC. In addition, we tried to define the different clinical scenarios in which neoadjuvant therapy can be preferred to upfront surgery for patients with cT1cN0 disease.

Material and Methods

A panel of 10 BC experts held 2 preparatory meetings, 2 Delphi rounds, and a final consensus conference between June 2022 and January 2023. The panel comprises nationally and internationally renowned breast oncologists who work at tertiary centers. In the preparatory meetings, decisions were made on the final scope and structure of the project, methods, and topics, including relevant clinical questions that the consensus should address. Fourteen clinical questions were identified (Table 1) in 3 areas of interest: neoadjuvant therapy vs. upfront surgery, postneoadjuvant setting, and adjuvant setting.

Two experts reviewed the literature to answer the clinical questions identified and proposed a draft of statements with supporting evidence for each clinical question. Quality of evidence was graded as very low, low, moderate, and high, according to GRADE.[11]

PubMed was used for the literature search, and reference lists of the included articles were searched for additional articles of interest. Articles included original papers, randomized controlled trials, systematic reviews or meta-analyses, guidelines, and consensus papers; those not in English were excluded.

The first draft of the proposed statements was discussed at a second meeting in October 2022, after which a survey with all the statements was submitted and completed by all the experts. The Delphi survey took place online, anonymously, and a Likert scale was used to collect agreement or disagreement with each statement (1 "complete disagreement"; 2-3 "poor agreement"; 4-6 "moderate agreement"; and 7-9 "agreement"). The median score was used to classify agreement with the statements, and the 30th to 70th interpercentile range corrected for asymmetry was used to assess agreement/disagreement between panelists. After viewing the results of the first round, in which their responses were highlighted, panel members were asked to review their choices in a second Delphi round.

The final consensus meeting took place on January 20. The goal was to reach final consensus on the statements. The Likert scale was replaced with a binary scale (agree/disagree); consensus was defined as reaching a level of agreement ≥66.6% (ie, two-thirds) between all participants (Table 2).

Results

Each statement that reached a final consensus is further characterized by evidence from the literature (Table 2).

Indications for Neoadjuvant Treatment

Consensus Statements.

- *Neoadjuvant and adjuvant therapies are associated with similar survival outcomes when the same therapeutic regimen is administered in the neoadjuvant or adjuvant setting*
- *Patients with clinical stage II and III HER2+ BC should be candidates for a neoadjuvant anti-HER2 treatment*
- *Patients with cT1a/b cN0 HER2+ BC can be candidates for upfront surgery and then adjuvant therapy with paclitaxel-trastuzumab*
- *In patients with cT1c cN0 HER2+ BC, upfront surgery could represent a treatment option, although neoadjuvant therapy could be considered in selected cases*

Sources of Evidence. Neoadjuvant and adjuvant therapies for early BC are associated with similar survival outcomes when the same therapeutic regimen is administered in the neoadjuvant or adjuvant setting.[13,14] Neoadjuvant therapy has been traditionally employed for the management of locally advanced or inflammatory BC, but it has recently also become the standard approach for patients with clinical stage II disease, especially in those with a HER2+ molecular profile.[8]

Patients with node-positive (N+) or high-risk node-negative (N−) HER2+ disease (ie, T≥2 cm) should be offered neoadjuvant chemotherapy combined with trastuzumab. In the NOAH trial, 235 patients with locally advanced HER2+ BC receiving neoadjuvant chemotherapy were randomly allocated to receive or not receive 1 year of treatment with trastuzumab (administered in both the neoadjuvant and adjuvant setting). The 3-year event-free survival (EFS) rate significantly increased in patients receiving trastuzumab (71% in patients treated with trastuzumab vs. 56% without trastuzumab; HR 0.59, 95% CI 0.38-0.90; $P = .013$).[15]

The importance of neoadjuvant therapy is mainly related to whether pathologic complete response (pCR) can be achieved and to define, accordingly, the most appropriate postoperative therapeutic strategy (TDM1 if no pCR and trastuzumab with pCR).[10]

The most appropriate management of patients with HER2+ T1c (1<T<2 cm) N0 HER2+ BC is still a matter for debate, and this subgroup has been considered in both the KATHERINE and APT trials.[10,16]

Table 2 List of Consensus Statements

Statement	QoE	Recommendation	Consensus
Neoadjuvant Therapy vs. Upfront Surgery			
1.1 Neoadjuvant and adjuvant therapies are associated with similar survival outcomes when the same therapeutic regimen is administered in the neoadjuvant or adjuvant setting	High	Statement of fact	90%
1.2 Patients with clinical stage II and III HER2+ BC should be candidates for a neoadjuvant anti-HER2 treatment	High	Strong for	100%
1.3 Patients with cT1a/b cN0 HER2+ BC can be candidates for upfront surgery and then adjuvant therapy with paclitaxel-trastuzumab	High	Weak for	90%
1.4 In patients with cT1c cN0 HER2+ BC, upfront surgery could represent a treatment option, although neoadjuvant therapy could be considered in selected cases	Low	Weak for	100%
2.1 In the presence of N+ HER2+ BC, neoadjuvant rather than adjuvant therapy should be preferred	High	Strong for	100%
2.2 Ki-67 and hormone receptor status might be considered to determine the probability of benefitting from neoadjuvant therapy	Low	Weak for	100%
2.3 Patients' age and comorbidities should be adequately considered when defining the appropriate treatment options	Low	Strong for	100%
3.1 EC/ACx4–wPx12 + trastuzumab is one of the preferred therapeutic regimens in the neoadjuvant setting. Whenever possible, pertuzumab should also be used	High	Strong for	100%
3.2 Dose-dense schedule could be an option in the neoadjuvant setting, based on clinical and tumor characteristics	Low	Weak for	90%
3.3 The addition of pertuzumab in the neoadjuvant setting increases the chance of achieving a pCR and might improve outcomes	Mod	Statement of fact	100%
3.4 TCH x 6 could be a suboptimal neoadjuvant approach	Low	Weak for	100%
3.5 TCHP x 6 might be considered an alternative to the anthracycline-containing regimen in the neoadjuvant setting, especially in patients with cardiovascular risk factors/comorbidities	Mod	Weak for	100%
3.6 In cT1N0 patients, wPx12 + trastuzumab may be considered as a preoperative approach in selected cases	Low	Weak for	100%
3.7 In selected cT1N0 patients wPx12 + trastuzumab + pertuzumab might be an adequate de-escalation strategy, but the actual evidence is still inadequate to propose this regimen without anthracycline use after surgery	Low	Weak for	90%
Postneoadjuvant Setting			
4.1 pCR is the major determinant of the best therapeutic strategy to adopt in patients who have completed a neoadjuvant therapy	High	Statement of fact	100%
5.1 After neoadjuvant therapy, adjuvant anti-HER2 therapy should be continued in case of HER2-negative residual disease	Low	Strong for	100%
6.1 Patients obtaining a pCR to a neoadjuvant anti-HER2 therapy should receive adjuvant trastuzumab for the remainder of the 1 y of total anti-HER2 therapy	High	Strong for	100%
6.2 Neratinib should not be considered within 1 y from the end of trastuzumab in patients with HR+ HER2+ early BC who have obtained pCR	Low	Strong against	100%
7.1 Patients with residual disease after neoadjuvant anti-HER2 therapy should receive adjuvant TDM1 to complete 1 y of total anti-HER2 therapy	High	Strong for	100%
7.2 1 year of adjuvant therapy with neratinib might be offered to selected patients with HR+ HER2+ early BC within 1 y from the end of anti-HER2 therapy who have not reached pCR, according to the individual risk of disease recurrence defined by the initial clinical and/or pathologic stage	Low	Weak for	90%
8.1 ypT1mic and ypT1a with ypN0 appear to benefit from an escalation strategy in the adjuvant setting with TDM1	Mod	Weak for	100%
8.2 ypN1mi might benefit from an escalation strategy in adjuvant therapy	Low	Weak for	100%
8.3 ypTis in the absence of residual nodal disease has a good prognosis and adjuvant escalation should not be offered	Mod	Strong against	100%
9.1 Although a higher toxicity from the concomitant use of TDM1 and radiotherapy cannot be excluded, this approach can be used, especially in the adjuvant setting	Mod	Weak for	100%

(*continued on next page*)

Table 2 (*continued*)

Statement	QoE	Recommendation	Consensus
Adjuvant Setting			
10.1 wPx12 + trastuzumab is the gold standard in pT1pN0 HER2+ BC with a diameter <2 cm	Mod	Strong for	100%
10.2 In stage I HER2+ BC, TCx6 + trastuzumab might offer a low absolute benefit in terms of OS with significant toxicity, and is therefore not recommended	Low	Strong against	100%
10.3 In stage I HER2+ BC, ECx4–wPx12 + trastuzumab + pertuzumab should not be offered	High	Strong against	100%
11.1 Patients' age and hormone receptor status could be considered when choosing between anthracycline- or nonanthracycline-based adjuvant therapy in patients with pT≤2 pN0 HER2+ BC	Mod	Weak for	100%
12.1 In pT>2 N0 HER2+ BC, EC/ACx4–wPx12 + trastuzumab is one of the preferred regimens in the adjuvant setting In pT>2 N+ HER2-positive BC, pertuzumab is also recommended	High	Strong for	100%
12.2 Dose-dense schedule could be considered in the adjuvant setting in HER2+ BC >2 cm or N+	Low	Weak for	90%
12.3 The addition of pertuzumab in the adjuvant setting in N+ HER2+ BC appears to increase long-term outcomes	High	Statement of fact	100%
12.4 TCH x 6 could be a suboptimal adjuvant approach in HER2+ BC >2 cm or N+	Low	Weak for	100%
12.5 TCHP x 6 might be considered an alternative to anthracycline-containing regimens in the adjuvant setting in HER2+ BC >2 cm or N+, especially in patients with cardiovascular risk factors/comorbidities	Mod	Weak for	100%
12.6 One year's adjuvant therapy with neratinib might be offered to patients with pN+ HR+ HER2+ high-risk BC after optimal adjuvant treatment with anthracycline-/taxane-based CT and trastuzumab	Low	Weak for	90%
12.7 1 year's adjuvant therapy with neratinib might be considered for carefully selected HR+ HER2+ early BC >2 cm without lymph node involvement after optimal adjuvant treatment with CT and trastuzumab	Low	Weak for	90%
13.1 The addition of pertuzumab to adjuvant trastuzumab-containing CT should be offered in N+ HER2+ BC	High	Strong for	100%
13.2 The addition of pertuzumab to adjuvant trastuzumab-containing CT should not be offered in N− HER2+ BC <2 cm	High	Strong against	100%
13.3 The addition of pertuzumab to adjuvant trastuzumab-containing CT might be offered in select cases with N− HER2+ BC >2 cm	Low	Weak for	100%
14.1 Patients with HER2+ early BC should receive anti-HER2 therapy for a total of 12 months	High	Strong for	100%
14.2 In selected cases (ie, low risk of BC recurrence or reduced tolerance to anti-HER2 therapy) early interruption of the anti-HER2 therapy (after 6 mo) could be considered	Low	Weak for	100%

Abbreviations: BC = breast cancer; CT = chemotherapy; HR = hormone receptor; mod = moderate, QoE = quality of evidence. Recommendations have been made in accordance with the GRADE guidelines.[12]

The KATHERINE trial established the importance of using neoadjuvant therapy in patients with early HER2+ BC (including patients with clinical stage T1c N0). In this trial, 1486 patients with residual disease after neoadjuvant anti-HER2 therapy, were randomized to either TDM1 or trastuzumab. Of these, 72.3% had hormone receptor-positive (HR+) HER2+ BC. At 3-year follow-up, patients receiving TDM1 had a greater invasive disease-free survival (IDFS) rate than those receiving trastuzumab (3-year disease-free survival [DFS] rate 88.3% vs. 77%).[10]

The APT trial was a single-arm, multicenter trial evaluating the efficacy of a de-escalated (anthracycline-free) therapeutic approach in 406 patients with early-stage (pT ≤3 cm, pN0/N1mic) HER2+ BC, which demonstrated that adjuvant treatment with paclitaxel (administered every week for 12 weeks) and trastuzumab (administered every week alongside paclitaxel for 12 weeks, then continued alone every 3 weeks for another 9 months) could provide a 10-year recurrence-free interval of 96.3%, with a limited toxicity profile.[9] In this subgroup, a clear consensus strategy has not been reached. According to the most recent ASCO guidelines, neoadjuvant therapy could represent a feasible option in patients with clinical T1cN0 HER2+ BC.[8] However, in view of the positive results of the APT trial, upfront surgery, if feasible, seems to represent an appropriate therapeutic strategy in this setting. Nevertheless, neoadjuvant therapy might be considered, in selected cases (for example, a tumor that measures approximately 2 cm in size).

Finally, patients with clinical T1a/T1bN0 disease can be safely managed with upfront surgery, then considered for adjuvant therapy with paclitaxel and trastuzumab according to the results of the APT trial.[9]

Features to Consider When Choosing a Neoadjuvant Treatment in cT1c

Consensus Statements.

- In the presence of N+ HER2+ BC, neoadjuvant rather than adjuvant therapy should be preferred
- Ki-67 and hormone receptor status might be considered to determine the probability of benefitting from neoadjuvant therapy
- Patients' age and comorbidities should be adequately considered when defining appropriate treatment options

Sources of Evidence. Different clinical and molecular variables correlate with the efficacy of a neoadjuvant treatment. Anthracycline-based chemotherapy with trastuzumab (and eventually pertuzumab) should be considered in patients with high-risk (ie, T≥2 cm) N− or N+ HER2+ BC.

Ki-67 is a cell proliferation marker and could be indicative of the aggressiveness of a tumor. It has been postulated that tumors with a high expression of Ki-67 might respond better to neoadjuvant chemotherapy containing anthracyclines and/or taxanes.[17] Such a benefit has been reported using different Ki-67 thresholds. Therefore, a cut-off of 30% (according to international recommendations) may be considered as a possible threshold for patients with a poor prognosis when selecting the appropriate therapeutic strategy.[18]

BC patients can respond differently to neoadjuvant therapy depending on their molecular subtype. HER2+ and triple-negative BC (TNBC), being aggressive phenotypes, tend to respond better to neoadjuvant treatment, whereas lower response rates (in terms of obtained pCR) are observed in both the luminal A and luminal B molecular subtypes.[19,20]

Younger BC patients (ie, aged <40 years) typically present with more aggressive disease, but also tend to respond better to neoadjuvant therapy.[21] In a pooled analysis of 8 randomized clinical trials of neoadjuvant therapy (N = 8949 women evaluated), higher pCR rates were observed in patients <40 years old than those aged 40-49 and >50 years (20.9%, 17.7%, and 13.7%, respectively). However, from this pooled analysis, young patients with luminal-like BC seemed to gain greater benefit from neoadjuvant therapy, whereas age was not a major prognostic factor in patients with HER2+ or TNBC.[22]

Age and comorbidities should be considered when defining the appropriate therapeutic strategy for patients with early BC, in view of the reported toxicity profiles of both chemotherapeutic and anti-HER2 agents.

Neoadjuvant Regimens Options

Consensus Statements.

- EC/ACx4–wPx12 + trastuzumab is one of the preferred therapeutic regimens in the neoadjuvant setting. Whenever possible, pertuzumab should also be used.
- Dose-dense schedule could be an option in the neoadjuvant setting, based on clinical and tumor characteristics.
- The addition of pertuzumab in the neoadjuvant setting increases the chance of achieving pCR and might improve outcomes.
- TCHx6 could be a suboptimal neoadjuvant approach.
- TCHPx6 might be considered an alternative to the anthracycline-containing regimen in the neoadjuvant setting, especially in patients with cardiovascular risk factors/comorbidities.
- In cT1N0 patients, wPx12 + trastuzumab may be considered as a preoperative approach in selected cases.
- In selected cT1N0 patients, wPx12 + trastuzumab + pertuzumab might be an adequate de-escalation strategy, but the actual evidence is still inadequate to propose this regimen without anthracycline use after surgery.

Sources of Evidence. Neoadjuvant therapy is a well-consolidated approach to treating HER2+ BC, especially for tumors >2 cm or with lymph node involvement.[23,24] Several different regimens demonstrated activity in this setting and many studies have shown substantial equivalence in long-term outcomes comparing preoperative vs. adjuvant chemotherapy.[25,26]

One of the most studied regimens is the sequential schedule of an anthracycline + cyclophosphamide (AC/EC) followed by a taxane (T), generally weekly paclitaxel (wP). In the NSABP B41 study, 177 patients with HER2+ BC were treated with 4 cycles of doxorubicin + cyclophosphamide every 3 weeks followed by 12 weekly paclitaxel administrations (wPx12) + trastuzumab. The pCR rate (ypT0 and ypN0) was 49% in the whole population, 45% in the HR+ group, and 58% in the HR− group; the 5-year recurrence-free interval (RFI) was 84% and the 5-year overall survival (OS) was 94%.[27,28] In the GeparQuinto study, 307 patients with HER2+ BC were treated with 4 cycles of epirubicin plus cyclophosphamide followed by 4 cycles of docetaxel and trastuzumab every 3 weeks. The pCR rate was 45% (with a higher proportion among HR-negative BC patients compared with those with HR-positive disease); the 3-year DFS was 84% and the 3-year OS was 91%.[29,30] These data, combined with those from the adjuvant setting,[31] define EC/AC-wP/D as a solid treatment option in the neoadjuvant setting.

Although the "original" anthracycline-taxane-based schedule includes the use of trastuzumab, the recent availability of pertuzumab raises some questions about its inclusion. Several neoadjuvant trials have shown a benefit in pCR and virtual long-term outcomes when pertuzumab is included. In the NeoSphere phase II trial, 417 patients with HER2+ BC were randomized into 4 arms to receive in the neoadjuvant setting docetaxel + trastuzumab ± pertuzumab, or trastuzumab + pertuzumab without docetaxel. All patients received an anthracycline-based regimen in the adjuvant setting and those who were not exposed to docetaxel received it in the adjuvant phase; all patients completed a year of treatment with trastuzumab. Triple therapy (docetaxel + trastuzumab + pertuzumab) showed a better pCR rate than docetaxel + trastuzumab (46% vs. 29%).[32] The 5-year relapse-free survival rate was not improved with triple therapy, although the study was not powered to highlight this outcome.[33] In the phase II TRYPHAENA study in the neoadjuvant setting, the arm that included an anthracycline-taxane regimen with trastuzumab + pertuzumab showed a pCR rate of 55%, higher than a historical cohort of patients treated with a single anti-HER2 therapy, with a 3-year DFS rate of 88%.[34,35] Similar results were shown in the GeparSepto trial, in which 400 patients with

HER2+ BC were treated with a sequential anthracycline-taxane regimen with the addition of trastuzumab + pertuzumab, achieving a pCR rate of 58%.[36] Results from the adjuvant APHINITY trial underline the benefit of adding pertuzumab. In this trial, 4804 patients with HER2+ BC were randomized to receive chemotherapy + trastuzumab or chemotherapy + trastuzumab + pertuzumab. The dual anti-HER2 blockade did not significantly improve OS at the 8.4-year follow-up (hazard ratio [HR] 0.83, 95% CI 0.68-1.02; $P = .078$). However, an OS benefit was reported in the N+ subpopulation (8-year IDFS: HR 0.72, 95% CI 0.60-0.87), suggesting that treatment escalation should be proposed in this group of patients.[37]

Concerning the schedule of chemotherapy administration, the EBCTCG meta-analysis has shown a better efficacy in terms of 10-year recurrence risk (28% vs. 31%) and 10-year BC-specific survival (18.9% vs. 21.3%) with the dose-dense regimens (eg, EC every 14 days) compared with standard schedule of administration (eg, EC every 21 days) without increasing mortality for other causes.[38] However, although the dose-dense regimen seems to provide a survival advantage in HR+ BC and TNBC, in HER2+ BC it appears somewhat less clear. Only 50% of patients included in this meta-analysis had a known HER2 status and the use of anti-HER2 therapies was not routine in several trials. Therefore, although dose-dense regimens seem to provide a benefit in HER2+ BC (HR 0.83, 95% CI 0.67-1.02), no definitive conclusion can be drawn from this study. In an exploratory analysis of the GIM2 trial in HER2+ BC patients treated with trastuzumab + FECx4 (5-fluorouracil + epirubicin + cyclophosphamide) followed by Px4 every 2 or 3 weeks, the dose-dense regimen appeared to provide a little-to-null benefit of DFS and OS compared with the standard schedule.[39] However, the use of a noncontemporary regimen and the initiation of trastuzumab after chemotherapy completion in some patients, limit the applicability of these data. A secondary analysis of the PANTHER trial, in which 342 HER2+ patients received a dose-dense anthracycline-taxane-based regimen vs. the standard schedule, showed a numerical benefit of 32% with dose-dense therapy, in BC-specific relapse-free survival; this was not statistically significant. Similar to the GIM2 trial, in the PANTHER trial some patients begun trastuzumab after chemotherapy completion and 29 patients discontinued anti-HER2 therapy prematurely. The rates of cardiac toxicity did not differ between the 2 groups after 6 years' follow-up.[40] In a retrospective study including a contemporary cohort of patients with HER2+ BC treated with EC x 4 every 2 or 3 weeks followed by paclitaxel every 1 or 2 weeks, the dose-dense schedule increased the pCR rate (38% vs. 29%; $P = .052$) and, after a follow-up of 55 months, the distant DFS (HR 0.49), the EFS (HR 0.54), and BC-specific survival (HR 0.41), although without statistical significance. However, the subgroup of younger women (<40 years) seemed to derive a particular benefit from dose-dense therapy (5-year distant DFS 100% vs. 75.3%; $P = .017$; 5-year EFS 96.9% vs. 78.3%; $P = .022$). Moreover, dose-dense treatment did not appear to increase cardiologic toxicity.[41]

Whether anthracyclines could be omitted in favor of platinum salts is a highly controversial topic. Although anthracyclines have been shown to be highly effective in the management of HER2+ BC, they expose patients to several long-term toxicities, including heart failure and acute myeloid leukemia. A putative alternative to the EC-T regimen emerged from the BICRG-006 study in which adjuvant therapy with carboplatin + docetaxel + trastuzumab (TCH) showed a nonsignificant lower difference in 5-year DFS rate compared with AC-docetaxel + trastuzumab (81% vs. 84%) with a similar 5-year OS (91% vs. 92%). However, the study was not powered to show differences between these arms, therefore these results should be taken with caution.[42] In the neoadjuvant setting, the TRAIN-2 study compared the FEC x 3 regimen followed by TCHP x 6 (docetaxel + carboplatin + trastuzumab + pertuzumab) with TCHP x 9. At 3 years of follow-up, no difference was reported between the FEC + TCHP and TCHP-only regimens in terms of pCR (67% vs. 68%), EFS (94% vs. 93%), and OS (98% vs. 98%). Patients who received anthracyclines experienced more frequent febrile neutropenia (10% vs. 1%) and a reduction in the left ventricle ejection fraction (36% vs. 22%).[43] However, both regimens are noncanonical, precluding a direct translation of this evidence into clinical practice.[34,35,44,45] Nevertheless, these results seem consistent with those of other trials in which TCH ± P appears to perform similarly to the anthracycline-containing scheme, even though these trials were not powered or performed to demonstrate an equivalence of the 2 regimens. Some indirect evidence, such as network meta-analysis, seems to underline the putative equivalence between anthracycline-containing and anthracycline-free regimens.[46]

The use of wP (or docetaxel) + trastuzumab ± pertuzumab has been evaluated in the neoadjuvant setting, although the vast majority of trials also planned a postneoadjuvant phase with anthracyclines, limiting the conclusions that can be drawn.[32,47,48] Based on the data obtained in the adjuvant phase, wP + trastuzumab may be recommended in the neoadjuvant phase in very selected cases (eg, advanced age, comorbidities).[49] Instead, treatment with wP + trastuzumab + pertuzumab has been evaluated in the ADAPT trial. In the HR− HER2+ BC cohort of this umbrella trial, 42 patients received wP + trastuzumab + pertuzumab for 12 weeks with a pCR rate (ypT0 ypN0) of 79%. Among those patients who achieved pCR, 79% were exposed in the postsurgical phase only to radiotherapy (RT) and trastuzumab without any further chemotherapy.[50] Intriguingly, in this group the 5-year IDFS rate was 100%, suggesting that in some patients a de-escalation should be explored with a phase III clinical trial.

Features to Consider When Choosing the Postneoadjuvant Regimen

Consensus Statement.

- pCR is the major determinant of the best therapeutic strategy to adopt in patients who have completed a neoadjuvant therapy

Sources of Evidence. pCR can have different definitions, but it is commonly referred to as the absence of invasive residual disease in both mammary glands and locoregional lymph nodes after neoadjuvant therapy. It has an established positive prognostic role, particularly represented in patients with aggressive BC molecular subtypes, including HER2+ and TNBC, in which an improved long-term clinical benefit is observed after achieving pCR to neoadjuvant therapy.[20]

Whether pCR is achieved with a neoadjuvant therapy, is used to guide the choice of the optimal adjuvant treatment. Patients with

pCR after anti-HER2 neoadjuvant therapy will receive trastuzumab in the adjuvant setting until they have completed 1 full year of anti-HER2 therapy. This is based on the results of the HERA trial, discussed in section 3.6.2.[51]

Patients with residual disease after anti-HER2 neoadjuvant therapy should receive TDM1 until they have completed 1 full year of anti-HER2 therapy, based on the results of the KATHERINE trial.[10]

Management of HER2-Discrepancy Among Pre- and Postoperative Settings

Consensus Statement.

- After neoadjuvant therapy, adjuvant anti-HER2 therapy should be continued in case of HER2-negative residual disease

Sources of Evidence. From 10% to 20% of HER2+ BC patients who received an anti-HER2 neoadjuvant treatment, experienced the loss of HER2 expression after surgery.[52-54] However, the biological meaning of the HER2 loss and the implications regarding adjuvant therapy selection is still unknown.

Several retrospective studies suggest a putative worst prognosis for patients with a discordant HER2 status before and after neoadjuvant therapy,[52] even though less biased studies have not confirmed these data.[54] Therefore, the prognostic effect of HER2 loss is still controversial.

In the KATHERINE trial, nearly 8.3% of patients experienced the loss of HER2-positivity after neoadjuvant treatment.[55] None of the patients who received TDM1 experienced disease relapse (0/28) vs. 11 events observed in those who received trastuzumab (11/42; 26%).[55,56] Therefore, although current evidence is limited, anti-HER2 therapy should be continued in the adjuvant setting in case of loss of HER2 expression.

How to Manage Patients Achieving a pCR

Consensus Statements.

- Patients obtaining pCR with neoadjuvant anti-HER2 therapy should receive adjuvant trastuzumab for the remainder of the 1 year of total anti-HER2 therapy.
- Neratinib should not be considered within 1 year from the end of trastuzumab in patients with HR+ HER2+ early BC who have obtained pCR.

Sources of Evidence. In the HERA trial, 5099 patients with early HER2+ BC were randomized to receive trastuzumab for 1 or 2 years or to observation. After a median follow-up of 11 years, patients who had received 1 year of trastuzumab had a significantly lower risk of DFS and mortality compared with the observation group (HR for DFS 0.76, 95% CI 0.68–0.86; HR for mortality 0.74, 95% CI 0.64-0.86). Furthermore, extending the duration of therapy to a total of 2 years did not significantly improve DFS compared with 1 year of therapy (HR 1.02; 95% CI 0.89-1.17).[51]

In the ExteNET phase III clinical trials, 2840 patients with locally advanced HER2+ BC who had completed 1 year of trastuzumab-based therapy, were randomized to receive or not receive adjuvant neratinib for 1 year.[57] After 5 years, a greater IDFS was observed among patients who received neratinib (90.2% with neratinib vs. 87.7% with placebo).[57] However, in the subgroup analysis, the benefit was exclusive for the HR+ population and those who had begun neratinib within 1 year from the end of trastuzumab. This improvement in IDFS was consistent in both the pCR and no pCR subgroups (5-year IDFS 84.0% vs. 74.2% with pCR and 85.0% vs. 77.6% with no pCR); it was also maintained for OS (5-year OS rate 91.3% vs. 82.2% with pCR and 93.3% vs. 73.7% with no pCR). However, few patients were in the subgroup with pCR after neoadjuvant therapy (n = 38).[58]

Achieving pCR after neoadjuvant therapy represents a consolidated positive prognostic factor.[20] Therefore, patients with early HER2+ BC who obtain pCR can be safely managed with trastuzumab in the adjuvant setting to complete 1 full year of total anti-HER2 therapy and do not benefit from an escalated treatment with TDM1 or neratinib.[10,51]

How to Manage Patients Not Achieving pCR

Consensus Statements.

- Patients with residual disease after neoadjuvant anti-HER2 therapy should receive adjuvant TDM1 to complete 1 year of total anti-HER2 therapy.
- One year of adjuvant therapy with neratinib might be offered to selected patients with HR+ HER2+ early BC within 1 year from the end of anti-HER2 therapy who have not reached pCR, according to the individual risk of disease recurrence defined by the initial clinical and/or pathologic stage.

Sources of Evidence. In the KATHERINE trial, 1486 patients with residual disease after neoadjuvant anti-HER2 therapy, were randomly allocated to receive either TDM1 or trastuzumab for 14 cycles. At 3-year follow-up, patients receiving TDM1 had a greater IDFS rate than those receiving trastuzumab (88.3% vs. 77%).[10]

Patients with BC who do not reach pCR have an increased risk of disease relapse.[20] For this reason, they are candidates for escalated therapy with TDM1 in the adjuvant setting. In addition, HR+ HER2+ BC patients may be offered 1 year of adjuvant neratinib therapy based on the survival benefit reported in the ExteNET trial.[10]

How to Manage Patients Not Achieving pCR But With a Minimal Disease Burden

Consensus Statements.

- ypT1mic and ypT1a with ypN0 appear to benefit from an escalation strategy in the adjuvant setting with TDM1.
- ypN1mi might benefit from an escalation strategy in adjuvant therapy.
- ypTis in the absence of residual nodal disease has a good prognosis and adjuvant escalation should not be offered.

Sources of Evidence. pCR is the complete histologic clearance of invasive cancer after neoadjuvant therapy and is defined by the TNM staging system as ypT0/ypTis and ypN0.[20] Patients achieving pCR have a better prognosis compared with those with residual disease.[20] However, a low burden of residual disease (hypothetically,

ypT1 ≤5 mm or ypN1mic) might identify patients with an intermediate prognosis.[59] Overall, pCR allows stratification of patients based on their risk, and several risk-adapted approaches are being developed.

As previously mentioned, after 3 years follow-up in the KATHERINE trial, patients treated with TDM1 achieved a better IDFS (88% vs. 77%), and a trend in OS benefit was reported (HR 0.70, 95% CI 0.47-1.05; $P = .08$).[10] In the subgroup analysis, patients with a low burden of residual disease (ypT0, ypT1a, ypT1b, ypT1mic, ypTis) also appeared to derive a benefit from the adjuvant escalation strategy (3-year IDFS 88.3% vs. 83.6%; HR 0.66). Of note, ypT1a/ypT1b/ypT1mic and ypN0 represented nearly one-fifth of the population; patients with both ypTis and ypN0 were not recruited in the study.[10] Regarding nodal status, a benefit in IDFS rate was reported in patients with ypN1 residual disease with the escalation strategy with TDM1 (3-year IDFS 88.9% vs. 75.8%; HR 0.49).[10]

Concomitant Radiotherapy With TDM1

Consensus Statement.

- Although a higher toxicity from the concomitant use of TDM1 and RT cannot be excluded, this approach can be used, especially in the adjuvant setting.

Sources of Evidence. To date, the largest available clinical experience of concomitant use of TDM1 with RT originates from the KATHERINE trial. In this study, patients received RT concomitantly with adjuvant treatment with either TDM1 or trastuzumab. In a subgroup analysis, the combination of RT + TDM1 compared with only TDM1 caused more grade ≥3 toxicities (27.4% vs. 16.2%) and serious adverse events (13.2% vs. 10.3%). However, there were no new safety signals and overall pulmonary and skin toxicities were not significantly different between TDM1 and trastuzumab therapy (1.5% vs. 0.7% for radiation pneumonitis, 25.4% vs. 27.6% for radiation-related skin injury, and 1.4% vs. 1% for grade 3 skin injury).[10,56]

Another phase II trial using adjuvant TDM1 found no clear increase in cardiologic or pulmonary toxicities. Sequential or concomitant RT did not affect patients' ability to complete prespecified RT programs. However, although grade ≥3 toxicities were similar between concomitant and sequential groups, grade 2 adverse events were more common in the concomitant cohort (7.7% vs. 2.6%).[60] Similarly, in 2 other case series, concomitant use of TDM1 and RT showed an acceptable toxicity profile.[61,62]

Although the use of concomitant TDM1 with breast locoregional irradiation has shown substantial safety, its use during brain RT is somewhat less clear. Some case series have highlighted a putative increased risk for radionecrosis,[63,64] although other trials have not confirmed this.[65]

Therapeutic Options for pT1pN0 Stage

Consensus Statements.

- wPx12 + trastuzumab is the gold standard in pT1pN0 HER2+ BC with a diameter <2 cm.
- In stage I, HER2+ BC, TCx6 + trastuzumab might offer a low absolute benefit in terms of OS with significant toxicity and is therefore not recommended.
- In stage I, HER2+ BC, ECx4–wPx12 + trastuzumab + pertuzumab should not be offered.

Sources of Evidence. pT1pN0 BC is characterized by a more favorable prognosis compared with other stages,[66] limiting the absolute benefit of adjuvant treatments.

In the single-arm phase II APT trial, 410 patients with HER+ pN0 BC with a ≤3 cm diameter, were treated with weekly paclitaxel for 12 weeks + 1 year of trastuzumab; 91% of patients had a pT1 tumor and 67% were HR+. After 10 years' follow-up, 96.3% were recurrence-free, BC-specific survival was 98.8%, and OS 94.3%, highlighting the overall good prognosis of this cancer stage. The 7-year DFS was greater than 90% for both HR+ and HR− subgroups (91.6% and 90.6%, respectively).[9]

A limited number of patients with stage I HER2+ BC were included in clinical trials involving anthracycline- or platinum-based regimens.[67] Moreover, the absolute benefit of AC-TH/TCH regimens in stage I is low, making the interpretation of risk/benefit ratio more difficult.[9] In the BICRG-006 study, 3222 women with HER2+ BC were randomized to AC-T, AC-TH, and TCH. Nearly 40% had a pT1 tumor and nearly 30% had node-negative disease. Despite both trastuzumab-containing regimens achieving better outcomes than chemotherapy-alone regimens, no differences in DFS and OS were found between the 2 trastuzumab arms (note that the study was not powered to detect any differences between these 2 cohorts), and 5-year rates were 92% and 91%, respectively. In the pT1c subgroup, 5-year DFS rates for AC-TH and TCH were 87% and 86%, respectively, and for pT1a-b they were 93% and 90%. Although these data confirm the efficacy of these 2 regimens, the absence of a statistical analysis centered on pT1pN0 patients limits further considerations.[42] Notably, the cardiologic adverse events were not negligible, with a congestive heart failure rate of 2.0% and 0.4% in the AC-TH and TCH groups, and a reduction in left ventricular ejection fraction >10% in 18.6% and 9.4%, respectively.[42]

Finally, in the randomized phase III APHINITY trial, 4804 HER+ BC patients with a tumor diameter of ≥1 cm, were randomized to AC-TH or TCH + pertuzumab or placebo.[37] With a follow-up of 8.4 years, fewer deaths were observed with pertuzumab, despite the data not being statistically significant. However, the benefit was apparent only in the N+ subgroup (IDFS HR 0.72 in pN+ vs. 1.01 in pN−).[68] Therefore, treatment escalation with the addition of pertuzumab should be offered only to patients with high-risk tumors.

Features to Consider When Choosing an Adjuvant Regimen in pT pN0 Stage

Consensus Statement.

- Patients' age and hormone receptor status could be considered when choosing between anthracycline- or nonanthracycline-based adjuvant therapy in patients with pT≤2 pN0 HER2+ BC.

Sources of Evidence. The phase II APT trial was a single-arm multicenter trial evaluating efficacy and safety of a de-escalated (anthracycline-free) therapeutic approach in 406 patients with early-stage (pT≤3 cm, pN0/N1mic) HER2+ BC. The study demonstrated that adjuvant treatment with a taxane (paclitaxel in 76% of patients, administered every week for 12 weeks) and trastuzumab (administered every week alongside paclitaxel for 12 weeks, then continued alone every 3 weeks for 9 months) could provide a 7-year DFS rate of 93%, with a limited toxicity profile. Notably, approximately 50% of patients had a pT≤1 cm, 67% of patients had HR+ disease and 56% had a grade 3 tumor.[16]

At the 7-year follow-up analysis, results of the exploratory analysis regarding intrinsic subtyping by PAM50 (performed in 278 patients) were revealed. Most cases (66%) were HER2-enriched, and a high percentage of both hormone receptor-negative and -positive tumors were HER2-enriched (84% and 58%, respectively). Intrinsic molecular subtypes are known to predict the response to anti-HER2 therapies[69,70]; however, given the low number of events reported in this study, a clear correlation between molecular subtype and survival outcomes cannot be established.[16] In terms of toxicity profile, 6% of patients receiving paclitaxel-trastuzumab developed an asymptomatic reduction of the left ventricle ejection fraction and 1% developed symptomatic cardiac failure.[16]

Young age at BC diagnosis has been proposed as a poor prognostic factor.[71] The prognostic and predictive role of young age in patients with HER2+ BC has been evaluated in several trials. In the HERA trial, for example, young age (<40 vs. >40 years) was not found to be associated with poor prognosis and it was not predictive of the efficacy of an anti-HER2 therapy.[72]

In the phase III randomized clinical APHINITY trial, 4804 patients with HER2+ N+ or high-risk N− early BC were randomized to receive adjuvant chemotherapy + trastuzumab in addition to either placebo or pertuzumab. This study demonstrated how the addition of pertuzumab can lead to a significant improvement in IDFS, especially in patients with N+ disease.[73] Young age at diagnosis was not found to have a prognostic or predictive role.[74]

Therapeutic Options for pT2-3 and/or pN+ Stage

Consensus Statements.

- In pT>2 N0 HER2+ BC, EC/ACx4–wPx12 + trastuzumab is one of the preferred regimens in the adjuvant setting. In pT>2 N+ HER2-positive BC, pertuzumab is also recommended.
- Dose-dense schedule could be considered in the adjuvant setting in HER2+ BC >2 cm or N+.
- The addition of pertuzumab in the adjuvant setting in N+ HER2+ BC appears to increase long-term outcomes.
- TCHx6 could be a suboptimal adjuvant approach in HER2+ BC >2 cm or N+.
- TCHPx6 might be considered an alternative to anthracycline-containing regimens in the adjuvant setting in HER2+ BC >2 cm or N+, especially in patients with cardiovascular risk factors/comorbidities.
- One year's adjuvant therapy with neratinib might be offered to patients with pN+ HR+ HER2+ high-risk BC after optimal adjuvant treatment with anthracycline/taxane-based chemotherapy and trastuzumab.
- One year's adjuvant therapy with neratinib might be considered for carefully selected HR+ HER2+ early BC >2 cm without lymph node involvement after optimal adjuvant treatment with chemotherapy and trastuzumab.

Sources of Evidence. T2 or N+ BC are characterized by a worse prognosis than earlier stages.[66] Several different regimens are effective in this setting, which has already been discussed (Section 3.3).

Indications for Double HER2-Blockade

Consensus Statements.

- The addition of pertuzumab to adjuvant trastuzumab-containing chemotherapy should be offered in N+ HER2+ BC.
- The addition of pertuzumab to the adjuvant trastuzumab-containing chemotherapy should not be offered in N− HER2+ BC <2 cm.
- The addition of pertuzumab to adjuvant trastuzumab-containing chemotherapy might be offered in select cases of N− HER2+ BC >2 cm.

Sources of Evidence. As discussed in section 3.10.2, in the APHINITY trial a treatment escalation with pertuzumab showed a benefit only in the N+ subgroup.[68] This result could reflect the excellent prognosis of the N− subgroup, which is characterized by a 6-year IDFS >91%.[75] Therefore, treatment escalation with the addition of pertuzumab seems to have a clinical utility, especially in patients with nodal involvement.

Anti-HER2 Duration

Consensus Statements.

- Patients with HER2+ early BC should receive anti-HER2 therapy for a total of 12 months.
- In selected cases (ie, low risk for BC recurrence or reduced tolerance to anti-HER2 therapy) early interruption of anti-HER2 therapy (after 6 months) could be considered.

Sources of Evidence. In the previously discussed HERA trial (see 3.6.2), extending the duration of trastuzumab therapy to a total of 2 years did not significantly improve DFS compared with 1 year's therapy.[51]

In the FinHer trial, 1010 patients with either N+ or high-risk N− early BC were randomized to receive 3 cycles of adjuvant chemotherapy with either docetaxel or vinorelbine, followed by 3 cycles of chemotherapy with FEC. Furthermore, patients with HER2+ BC, which accounted for approximately 20% of randomized patients, were further randomized to receive or not receive trastuzumab for 9 weeks with either docetaxel or vinorelbine. After a median follow-up of 62 months, a better distant DFS was reported in patients with HER2+ disease who had received trastuzumab (HR 0.65, 95% CI 0.38-1.12; $P = .12$).[76]

In phase III, noninferiority, randomized clinical trial PHARE, 3384 patients with HER2+ early BC were randomized to receive either 6 or 12 months' adjuvant trastuzumab. After a median follow-up of approximately 7 years, a total of 704 DFS events were observed; 345 (20.4%) were in patients receiving trastuzumab for

12 months and 359 (21.2%) in those receiving trastuzumab for 6 months (HR 1.08, 95% CI 0.93-1.25; $P = .39$). Therefore, the PHARE trial failed to demonstrate noninferiority of 6 months' adjuvant therapy with trastuzumab compared with 12 months.[77]

In the Short-HER trial, 1254 patients with N+ or high-risk N− HER2+ early BC were randomized to receive adjuvant chemotherapy with anthracyclines and taxanes with trastuzumab for either 12 months or 9 weeks. After a median follow-up of 5 years, the DFS rate was 88% with 1 year's trastuzumab vs. 85% with 9 weeks' trastuzumab (HR 1.13, 90% CI 0.89-1.42). The 5-year OS rate was 95.2% with 1 year's trastuzumab vs. 95% with 9 weeks' trastuzumab (HR 1.07, 90% CI 0.74-1.56). Although this trial did not demonstrate noninferiority of the shorter treatment duration, a significantly lower incidence of cardiac events was reported with 9 weeks' therapy (RR 0.33, 95% CI 0.22-0.50; $P = .0001$).[78]

In the SOLD trial, 2174 patients with HER2+ early BC were randomized. They all receive adjuvant therapy consisting of 3 cycles of docetaxel + trastuzumab for 9 weeks, followed by 3 cycles of FEC. Treatment was then stopped in 1 group, whereas the other group continued trastuzumab until completing 1 year of anti-HER2 therapy. After a median follow-up of approximately 5 years, no significant difference was reported between the 2 treatment arms (5-year DFS 88% in the 9-week arm vs. 90.5% in the 1-year arm; HR 1.39, 95% CI 1.12-1.72). Therefore, this trial failed to demonstrate the noninferiority of reduced duration of anti-HER2 therapy.[79]

Different results were observed with the PERSEPHONE trial, in which 4089 patients were randomized to either 6 or 12 months' adjuvant therapy with trastuzumab (administered with chemotherapy, either concomitantly or sequentially). The 4-year DFS was 89.4% vs. 89.9% in the short- and long-duration groups, respectively (HR 1.07, 90% CI 0.93-1.24; $P = .011$), thus demonstrating the noninferiority of a shorter anti-HER2 regimen.[80] Therefore, 12 months' anti-HER2 therapy represents the standard of care for patients with HER2+ early BC. However, in selected cases, such as low risk for disease recurrence or intolerance to treatment, an early interruption (after 6 months' therapy) can be considered.

Conclusions

Anti-HER2 therapy represents the cornerstone of the management of early and metastatic HER2+ BC. Patients with stage I cT1a/bN0 disease should be candidates for upfront surgery followed by adjuvant therapy with paclitaxel and trastuzumab. The management of stage I cT1cN0 BC is still uncertain; both surgery and the neoadjuvant approach may represent viable options, although, in young patients with estrogen receptor-negative HER2-positive disease, the neoadjuvant approach might be preferred. Instead, stage II-III BC patients should be preferential candidates for neoadjuvant therapy, followed by surgery and adjuvant systemic therapy, defined according to whether pCR is achieved. Patients with high-risk HER2-positive estrogen receptor-positive disease could be offered an additional year of adjuvant therapy with neratinib.

Finally, new biomarkers are urgently needed to better identify patients who might benefit from a neoadjuvant approach and those who might require treatment escalation.

Disclosure

This work was supported by an unrestricted grant from Roche Italia S.p.A. AF receives honoraria from Roche, Novartis, Eli Lilly, Daiichi Sankyo, Seagen, AstraZeneca, Pfizer, Dompé Biotech, Exact Science, and Gilead; GA received medical writing and article processing charges and Institutional Grants from Astra Zeneca, Consulting fees from Astra Zeneca, Daiichi Sankyo, Novartis, Roche, Pfizer, Eli Lilly, Gilead, and Seagen, honoraria from Exact Sciences, Gilead, Novartis, Roche, Seagen, and Viatris, support for attending meetings from Daiichi Sankyo, Roche, and Novartis, participation in AB meetings for Astra Zeneca, Daiichi Sankyo, Eisai, Eli Lilly, Gilead, Novartis, Roche, and Seagen. NS has no conflict of interest to disclose; MG received honoraria or consultation fees from Novartis, Eli Lilly, PierreFabre, Roche, and Organon and travel fees from Daichii Sankyo, all outside the submitted work. FP received honoraria for advisory boards and activities as a speaker from Amgen - Astrazeneca - Daichii Sankyo - Celgene - Eisai - Eli Lilly - Exact Sciences- Gilead - Ipsen – Menarini - MSD - Novartis - Pierre Fabre - Pfizer - Roche - Seagen - Takeda – Viatris. FP received research grants from Astrazeneca – Eisai – Roche; AZ, LC, CZ, LL, EM have no conflict of interest to disclose related to the submitted work.

CRediT authorship contribution statement

Mattia Garutti: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Linda Cucciniello:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Grazia Arpino:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Alessandra Fabi:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Lorenzo Livi:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Elisabetta Munzone:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Nicoletta Staropoli:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Claudio Zamagni:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Alberto Zambelli:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Fabio Puglisi:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 Cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209–249. doi:10.3322/caac.21660.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7–34. doi:10.3322/caac.21551.
3. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thürlimann B, Senn H-J. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. *Ann Oncol*. 2007;18:1133–1144. doi:10.1093/annonc/mdm271.
4. Bonotto M, Gerratana L, Poletto E, et al. Measures of outcome in metastatic breast cancer: insights from a real-world scenario. *Oncologist*. 2014;19:608–615. doi:10.1634/theoncologist.2014-0002.
5. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344:783–792. doi:10.1056/NEJM200103153441101.
6. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353:1673–1684. doi:10.1056/NEJMoa052122.

7. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353:1659–1672. doi:10.1056/NEJMoa052306.
8. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO Guideline. *J Clin Oncol*. 2021;39:1485–1505. doi:10.1200/JCO.20.03399.
9. Tolaney SM, Tarantino P, Graham N, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial. *Lancet Oncol*. 2023;24:273–285. doi:10.1016/S1470-2045(23)00051-7.
10. von Minckwitz G, Huang C-S, Mano MS, et al. Trastuzumab Emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. 2019;380:617–628. doi:10.1056/NEJMoa1814017.
11. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64:401–406. doi:10.1016/j.jclinepi.2010.07.015.
12. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol*. 2013;66:719–725. doi:10.1016/j.jclinepi.2012.03.013.
13. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from national surgical adjuvant breast and bowel project B-18. *JNCI Monogr*. 2001;2001:96–102. doi:10.1093/oxfordjournals.jncimonographs.a003469.
14. Mamounas EP. NSABP Protocol B-27. Preoperative doxorubicin plus cyclophosphamide followed by preoperative or postoperative docetaxel. *Oncology (Williston Park)*. 1997;11:37–40.
15. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER. *Lancet*. 2010;375:377–384. doi:10.1016/S0140-6736(09)61964-4.
16. 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*. 2019;37:1868–1875. doi:10.1200/JCO.19.00066.
17. Chen X, He C, Han D, et al. The predictive value of Ki-67 before neoadjuvant chemotherapy for breast cancer: a systematic review and meta-analysis. *Futur Oncol*. 2017;13:843–857. doi:10.2217/fon-2016-0420.
18. Burstein HJ, Curigliano G, Thürlimann B, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. *Ann Oncol*. 2021;32:1216–1235. doi:10.1016/j.annonc.2021.06.023.
19. Yoo C, Ahn J-H, Jung KH, et al. Impact of immunohistochemistry-based molecular subtype on chemosensitivity and survival in patients with breast cancer following neoadjuvant chemotherapy. *J Breast Cancer*. 2012;15:203. doi:10.4048/jbc.2012.15.2.203.
20. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384:164–172. doi:10.1016/S0140-6736(13)62422-8.
21. Huober J, von Minckwitz G, Denkert C, et al. Effect of neoadjuvant anthracycline–taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. *Breast Cancer Res Treat*. 2010;124:133–140. doi:10.1007/s10549-010-1103-9.
22. Loibl S, Jackisch C, Lederer B, et al. Outcome after neoadjuvant chemotherapy in young breast cancer patients: a pooled analysis of individual patient data from eight prospectively randomized controlled trials. *Breast Cancer Res Treat*. 2015;152:377–387. doi:10.1007/s10549-015-3479-z.
23. Rashmi Kumar N, Berardi R, Abraham J, et al. NCCN Guidelines Version 4.2022. *Breast Cancer*. 2022;1.
24. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30:1194–1220. doi:10.1093/annonc/mdz173.
25. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. *J Clin Oncol*. 2008;26:778–785. doi:10.1200/JCO.2007.15.0235.
26. Mauri D, Pavlidis N, Ioannidis JPA. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst*. 2005;97:188–194. doi:10.1093/jnci/dji021.
27. Robidoux A, Tang G, Rastogi P, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomized phase 3 trial. *Lancet Oncol*. 2013;14:1183–1192. doi:10.1016/S1470-2045(13)70411-X.
28. Guarneri V, Griguolo G, Miglietta F, Conte PF, Dieci MV, Girardi F. Survival after neoadjuvant therapy with trastuzumab–lapatinib and chemotherapy in patients with HER2-positive early breast cancer: a meta-analysis of randomized trials. *ESMO Open*. 2022;7. doi:10.1016/j.esmoop.2022.100433.
29. Untch M, Loibl S, Bischoff J, et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomized phase 3 trial. *Lancet Oncol*. 2012;13:135–144. doi:10.1016/S1470-2045(11)70397-7.
30. Untch M, von Minckwitz G, Gerber B, et al. Survival analysis after neoadjuvant chemotherapy with Trastuzumab or Lapatinib in patients with human epidermal growth factor receptor 2–positive breast cancer in the GeparQuinto (G5) study (GBG 44). *J Clin Oncol*. 2018;36:1308–1316. doi:10.1200/JCO.2017.75.9175.
31. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol*. 2011;29:3366–3373. doi:10.1200/JCO.2011.35.0868.
32. 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 randomized multicenter, open-label, phase 2 trial. *Lancet Oncol*. 2012;13:25–32. doi:10.1016/S1470-2045(11)70336-9.
33. Gianni L, Pienkowski T, Im Y-H, 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 multicenter, open-label, phase 2 randomized trial. *Lancet Oncol*. 2016;17:791–800. doi:10.1016/S1470-2045(16)00163-7.
34. Schneeweiss A, Chia S, Hickish T, et al. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive ea. *Eur J Cancer*. 2018;89:27–35. doi:10.1016/j.ejca.2017.10.021.
35. Schneeweiss A, Chia S, Hickish T, 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;24:2278–2284. doi:10.1093/annonc/mdt182.
36. Loibl S, Jackisch C, Schneeweiss A, 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. doi:10.1093/annonc/mdw610.
37. Piccart M, Procter M, Fumagalli D, et al. Adjuvant Pertuzumab and Trastuzumab in early HER2-positive breast cancer in the APHINITY trial: 6 Years' follow-up. *J Clin Oncol*. 2021;39:1448–1457. doi:10.1200/JCO.20.01204.
38. Gray R, Bradley R, Braybrooke J, et al. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomized trials. *Lancet*. 2019;393:1440–1452. doi:10.1016/S0140-6736(18)33137-4.
39. Lambertini M, Poggio F, Bruzzone M, et al. Dose-dense adjuvant chemotherapy in HER2-positive early breast cancer patients before and after the introduction of trastuzumab: exploratory analysis of the GIM2 trial. *Int J Cancer*. 2020;147:160–169. doi:10.1002/ijc.32789.
40. Papakonstantinou A, Matikas A, Bengtsson NO, et al. Efficacy and safety of tailored and dose-dense adjuvant chemotherapy and trastuzumab for resected HER2-positive breast cancer: results from the phase 3 PANTHER trial. *Cancer*. 2020;126:1175–1182. doi:10.1002/cncr.32653.
41. Wang L, Zhang Y, He Y, et al. Impact of dose-dense neoadjuvant chemotherapy on pathologic response and survival for HER2-positive breast cancer patients who receive trastuzumab. *Npj Breast Cancer*. 2021;7:1–7. doi:10.1038/s41523-021-00284-y.
42. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365:1273–1283. doi:10.1056/NEJMOA0910383.
43. van Ramshorst MS, van der Voort A, van Werkhoven ED, et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicenter, open-label, randomized, phase 3 trial. *Lancet Oncol*. 2018;19:1630–1640. doi:10.1016/S1470-2045(18)30570-9.
44. Yu K-D, Liu G-Y, Chen C-M, et al. Weekly Paclitaxel/Carboplatin/Trastuzumab therapy improves pathologic complete remission in aggressive HER2-positive breast cancers, especially in luminal-b subtype, compared with a once-every-3-weeks schedule. *Oncologist*. 2013;18:511–517. doi:10.1634/theoncologist.2012-0057.
45. Coudert BP, Largillier R, Arnould L, et al. Multicenter phase II trial of neoadjuvant therapy with trastuzumab, docetaxel, and carboplatin for human epidermal growth factor receptor-2-overexpressing stage II or III breast cancer: results of the GETN(A)-1 trial. *J Clin Oncol*. 2007;25:2678–2684. doi:10.1200/JCO.2006.09.9994.
46. Zhang J, Yu Y, Lin Y, et al. Efficacy and safety of neoadjuvant therapy for HER2-positive early breast cancer: a network meta-analysis. *Ther Adv Med Oncol*. 2021;13 17588359211006948. doi:10.1177/17588359211006948.
47. Shao Z, Pang D, Yang H, et al. Efficacy, safety, and tolerability of Pertuzumab, Trastuzumab, and Docetaxel for patients with early or locally advanced ERBB2-positive breast cancer in Asia: the PEONY phase 3 randomized clinical trial. *JAMA Oncol*. 2020;6. doi:10.1001/jamaoncol.2019.3692.
48. Horiguchi J, Oyama T, Koibuchi Y, et al. Neoadjuvant weekly paclitaxel with and without trastuzumab in locally advanced or metastatic breast cancer. *Anticancer Res*. 2009;29:517–524.
49. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer. *N Engl J Med*. 2015;372:134–141. doi:10.1056/nejmoa1406281.
50. Nitz U, Gluz O, Graeser M, et al. De-escalated neoadjuvant pertuzumab plus trastuzumab therapy with or without weekly paclitaxel in HER2-positive, hormone receptor-negative, early breast cancer (WSG-ADAPT-HER2+/HR–): survival outcomes from a multicenter, open-label, randomised, phase 2 treatment. *Lancet Oncol*. 2022;23:625–635. doi:10.1016/S1470-2045(22)00159-0.

51. 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*. 2017;389:1195–1205. doi:10.1016/S0140-6736(16)32616-2.
52. Branco FP, Machado D, Silva FF, et al. Loss of HER2 and disease prognosis after neoadjuvant treatment of HER2+ breast cancer. *Am J Transl Res*. 2019;11:6110–6116.
53. Niikura N, Tomotaki A, Miyata H, et al. Changes in tumor expression of HER2 and hormone receptors status after neoadjuvant chemotherapy in 21 755 patients from the Japanese breast cancer registry. *Ann Oncol*. 2016;27:480–487. doi:10.1093/annonc/mdv611.
54. Wetzel CL, Sutton TL, Gardiner S, Farinola M, Johnson N, Garreau JR. Loss of HER2-positivity following neoadjuvant targeted therapy for breast cancer is not associated with inferior oncologic outcomes. *J Surg Oncol*. 2021;124:1224–1234. doi:10.1002/jso.26646.
55. Mamounas EP. Characteristics of residual invasive breast cancer after neoadjuvant therapy in the KATHERINE study. *Ann Oncol*. 2021;32:1191–1192. doi:10.1016/j.annonc.2021.05.802.
56. Loibl S, Huang C-S, Mano MS, et al. 96O Adjuvant trastuzumab emtansine (T-DM1) vs trastuzumab (T) in patients (pts) with residual invasive disease after neoadjuvant therapy for HER2+ breast cancer: subgroup analysis from KATHERINE. *Ann Oncol*. 2020;31:S48. doi:10.1016/j.annonc.2020.03.036.
57. 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*. 2017;18:1688–1700. doi:10.1016/S1470-2045(17)30717-9.
58. Chan A, Moy B, Mansi J, et al. Final efficacy results of Neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET trial. *Clin Breast Cancer*. 2021;21:80–91.e7. doi:10.1016/j.clbc.2020.09.014.
59. Symmans WF, Wei C, Gould R, et al. Long-term prognostic risk after neoadjuvant chemotherapy associated with residual cancer burden and breast cancer subtype. *J Clin Oncol*. 2017;35:1049–1060. doi:10.1200/JCO.2015.63.1010.
60. Krop IE, Suter TM, Dang CT, et al. Feasibility and cardiac safety of trastuzumab emtansine after anthracycline-based chemotherapy as (neo)adjuvant therapy for human epidermal growth factor receptor 2-positive early-stage breast cancer. *J Clin Oncol*. 2015;33:1136–1142. doi:10.1200/JCO.2014.58.7782.
61. Zolcsák Z, Loirat D, Fourquet A, Kirova YM. Adjuvant Trastuzumab Emtansine (T-DM1) and concurrent radiotherapy for residual invasive HER2-positive Breast Cancer: single-center preliminary results. *Am J Clin Oncol Cancer Clin Trials*. 2020;43:895–901. doi:10.1097/COC.0000000000000769.
62. Becherini C, Stocchi G, Visani L, et al. Safety of concurrent TDM-1 and radiotherapy for patients with residual HER2-positive breast cancer. *ESTRO PO-1096*. 2021;1.
63. Stumpf PK, DiM Cittelly, Robin TP, et al. Combination of trastuzumab emtansine and stereotactic radiosurgery results in high rates of clinically significant radionecrosis and dysregulation of aquaporin-4. *Clin Cancer Res*. 2019;25:3946–3953. doi:10.1158/1078-0432.CCR-18-2851.
64. Geraud A, Xu HP, Beuzeboc P, Kirova YM. Preliminary experience of the concurrent use of radiosurgery and T-DM1 for brain metastases in HER2-positive metastatic breast cancer. *J Neurooncol*. 2017;131:69–72. doi:10.1007/s11060-016-2265-z.
65. Mills MN, Walker C, Thawani C, et al. Trastuzumab Emtansine (T-DM1) and stereotactic radiation in the management of HER2+ breast cancer brain metastases. *BMC Cancer*. 2021;21:223. doi:10.1186/s12885-021-07971-w.
66. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. 2017;67:93–99. doi:10.3322/caac.21388.
67. Romond E, Suman V, Jeong J-H, et al. Abstract S5-5: Trastuzumab plus adjuvant chemotherapy for HER2-positive breast cancer: final planned joint analysis of overall survival (OS) from NSABP B-31 and NCCTG N9831. American Association for Cancer Research (AACR); 2012, p. S5-5-S5-5. https://doi.org/10.1158/0008-5472.sabcs12-s5-5.
68. Loibl S, Jassem J, Sonnenblick A, et al. VP6-2022: adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up. *Ann Oncol*. 2022;0. doi:10.1016/J.ANNONC.2022.06.009.
69. 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. *JNCI J Natl Cancer Inst*. 2014;106(8):dju152. doi:10.1093/jnci/dju152.
70. Pernas S, Barroso-Sousa R, Tolaney SM. Optimal treatment of early stage HER2-positive breast cancer. *Cancer*. 2018;124:4455–4466. doi:10.1002/cncr.31657.
71. Azim HA, Partridge AH. Biology of breast cancer in young women. *Breast Cancer Res*. 2014;16:427. doi:10.1186/s13058-014-0427-5.
72. Partridge AH, Gelber S, Piccart-Gebhart MJ, et al. Effect of age on breast cancer outcomes in women with human epidermal growth factor receptor 2–positive breast cancer: results from a Herceptin adjuvant trial. *J Clin Oncol*. 2013;31:2692–2698. doi:10.1200/JCO.2012.44.1956.
73. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377:122–131. doi:10.1056/NEJMoa1703643.
74. Lambertini M, Fielding S, Loibl S, et al. Impact of age on Clinical outcomes and efficacy of adjuvant dual anti-HER2 targeted therapy. *JNCI J Natl Cancer Inst*. 2022;114:1117–1126. doi:10.1093/jnci/djac096.
75. Gelber RD, Wang XV, Cole BF, et al. Six-year absolute invasive disease-free survival benefit of adding adjuvant Pertuzumab to Trastuzumab and chemotherapy for patients with early HER2-positive breast cancer: a subpopulation treatment effect pattern plot (STEPP) analysis of the APHINITY (BIG 4-11) trial. *Eur J Cancer*. 2022;166:219–228. doi:10.1016/j.ejca.2022.01.031.
76. Joensuu H, Bono P, Kataja V, et al. Fluorouracil, Epirubicin, and Cyclophosphamide with either Docetaxel or Vinorelbine, with or without Trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer trial. *J Clin Oncol*. 2009;27:5685–5692. doi:10.1200/JCO.2008.21.4577.
77. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab in early breast cancer (PHARE): final analysis of a multicenter, open-label, phase 3 randomized trial. *Lancet*. 2019;393:2591–2598. doi:10.1016/S0140-6736(19)30653-1.
78. Conte P, Frassoldati A, Bisagni G, et al. Nine weeks versus 1 year adjuvant trastuzumab in combination with chemotherapy: final results of the phase III randomized Short-HER study. *Ann Oncol*. 2018;29:2328–2333. doi:10.1093/annonc/mdy414.
79. Joensuu H, Fraser J, Wildiers H, et al. Effect of adjuvant Trastuzumab for a duration of 9 weeks vs 1 year with concomitant chemotherapy for early human epidermal growth factor receptor 2–positive breast cancer. *JAMA Oncol*. 2018;4:1199. doi:10.1001/jamaoncol.2018.1380.
80. Earl HM, Hiller L, Vallier A-L, et al. Six 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. *Lancet*. 2019;393:2599–2612. doi:10.1016/S0140-6736(19)30650-6.