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CONSENSUS STATEMENT

Tailoring neoadjuvant systemic therapy in breast cancer: "The advent of a personalized approach"—The Breast-Gynecological and Immuno-Oncology International Cancer Conference (BGICC) consensus and recommendations

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Abstract

Background: The management of early breast cancer (BC) has witnessed an uprise in the use of neoadjuvant therapy and a remarkable reshaping of the systemic therapy postneoadjuvant treatment in the last few years, with the evolution of many controversial clinical situations that require consensus.

Methods: During the 14th Breast-Gynecological and Immuno-Oncology International Cancer Conference held in Egypt in 2022, a panel of 44 BC experts from 13 countries voted on statements concerning debatable challenges in the neo/adjuvant

treatment setting. The recommendations were subsequently updated based on the most recent data emerging. A modified Delphi approach was used to develop this consensus. A consensus was achieved when ≥75% of voters selected an answer.

Results and Conclusions: The consensus recommendations addressed different escalation and de-escalation strategies in the setting of neoadjuvant therapy for early BC. The recommendations recapitulate the available clinical evidence and expert opinion to individualize patient management and optimize therapy outcomes. Consensus was reached in 63% of the statements (52/83), and the rationale behind each statement was clarified.

KEYWORDS
adjuvant therapy, breast cancer, HER2-positive breast cancer, hormone receptor-positive breast cancer, neoadjuvant therapy, triple-negative breast cancer

INTRODUCTION

Neoadjuvant chemotherapy (NCT) has been historically introduced as the treatment of choice for patients with unresectable locally advanced or inflammatory breast cancer (BC) whose disease may be rendered resectable with neoadjuvant therapy. Subsequently, NCT was used to increase breast conservation rates and to potentially de-escalate axillary surgery, both leading to improved quality of life. This was supported by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis,[1] which indicated that preoperative chemotherapy provides increased breast conservation rates (65% vs. 49%), similar distant recurrence rates, and mortality as postoperative adjuvant systemic therapy for BC unselected by subtype. More recently, neoadjuvant therapy for triple-negative BC (TNBC) and human epidermal growth factor receptor 2 (HER2)-positive BC have been employed to allow early assessment of in-vivo response to systemic therapy. Response to neoadjuvant therapy provides a better categorization of prognosis by using the pathologic complete response (pCR) as a surrogate for survival.[2–4] Also, the extent of residual disease at the time of surgery then provides a unique opportunity for better optimization of subsequent adjuvant therapy at the patient level, individualized to the tumor response (response-adapted therapy) in both TNBC and HER2-positive BC.

The main aim of these consensus recommendations is to provide a roadmap with supportive evidence and expert opinion for controversial clinical questions faced by most breast oncologists in real-world multidisciplinary teams. More time was provided for discussion to refine the neo/adjuvant therapy plans to optimize outcomes. Finally, panelists collaborated to formulate clinically and biologically based treatment algorithms, which would then guide approaches to tailor systemic therapy in the postoperative setting, based on response to neoadjuvant therapy.

METHODS

The voting questions and statements were developed by the steering committee after reviewing the literature and defining current gaps of knowledge (which warranted an expert opinion-based consensus) in the clinical management of resectable BC in the preoperative and postoperative settings. The recommendation statements were evaluated through a modified Delphi approach.[5] The whole panel reviewed and edited the statements through several consecutive rounds until a final version was reached and approved by all the panelists before the conference. Then, they were finalized during the consensus session at the 14th Breast-Gynecological and Immuno-Oncology International Cancer Conference held in January 2022 in Cairo, Egypt; during which a panel of 44 international experts specialized in BC management attended physically or virtually. The panelists represented 13 countries, comprising 16 medical oncologists, 13 clinical oncologists, four radiologists, four pathologists, two radiation oncologists, and five surgeons. The panelists voted anonymously on the statements, whereas the discussions and comments were recorded for further consideration. The panelists were instructed to abstain if they had either insufficient expertise with a specific statement or a conflict of interest that could influence their decision. A consensus was defined as ≥75% of votes for a specific answer, and the consensus agreement percentage was calculated without including the abstaining votes in the denominator. Later after this meeting, updated data for some trials were presented at international conferences, where relevant results were considered in the current article. Clinical practical algorithms were developed to guide the management in each clinical setting. The consensus article was drafted and revised, after which the final version was circulated to all panel members for critical revision of important intellectual content. The results of the panelists' voting and supporting evidence are presented for the consensus statements.

RESULTS AND DISCUSSION

Consensus was reached on 52 of the 83 statements (63%). The 83 questions were divided in the following five sections.

Evaluation and work-up

The panel unanimously agreed (100%) that it is essential to discuss all patients with early and locally advanced, nonmetastatic BC within multidisciplinary teams, including BC specialists in medical, surgical, and radiation oncology, radiology, and pathology.

The combination of mammography and ultrasound is the gold standard for diagnostic imaging before neoadjuvant therapies, whereas additional imaging modalities may be indicated in specific situations.[6] For cases in which the mammogram shows Breast Imaging Reporting and Data System density *category A* according to the American College of Radiology[7] (i.e., primarily fatty breast in approximately 15%–30% of cases and mainly postmenopausal[8,9]), 70% of the panel believed that no further breast imaging is recommended to assess tumor extent before neoadjuvant therapy, whereas 30% favored that further imaging with a contrast-enhanced modality, such as magnetic resonance imaging (MRI) or contrast-enhanced mammography (CEM), may be warranted for defining the tumor extent or identifying occult lesions in specific situations.[10–12] In contrast, if breast-conservative surgery (BCS) is planned for patients with breast density category B, C, or D, 90% of the panelists strongly agreed that a contrast-enhanced imaging modality is warranted to assess the tumor extent before neoadjuvant therapy. The panel recommended breast MRI and CEM (75% and 70%, respectively) as the preferred imaging modalities for these cases. It is important to note that the use of preoperative MRI has not been associated with reductions in local or distant recurrence rates.[13] A few small to moderately sized studies suggest that CEM has efficacy comparable to that of MRI for diagnostic imaging (with the potential for lower cost and more accessibility), with both being superior to mammogram. However, those studies did not specifically evaluate the utility of imaging in the neoadjuvant setting or determine the most appropriate extent of surgery.[14–17] Recognizing the specific diagnostic challenges in the detection of lobular cancer (atypical mammographic features, multifocality, and occult contralateral carcinomas),[18] the panel unanimously recommended (97%) further contrast-enhanced breast imaging (MRI or CEM) for patients with lobular carcinoma who are planned for neoadjuvant therapy.[19]

In addition, the vast majority of panel members (84%) recommended a mandatory biopsy of sonographically detected, suspicious axillary lymph nodes to allow both accurate local staging and clip placement if needed.[20–22] In the case of biopsy-proven carcinoma in axillary nodes, clipping may be preferred to improve targeted resection, which has been shown to reduce false-negative rates of sentinel lymph node biopsy (SLNB) after neoadjuvant therapy.[22] It was underscored that, after neoadjuvant treatment, the surgical specimen and lymph nodes should be examined extensively by the pathologist, in accordance with international recommendations,[23] because the results may drive treatment changes.

Neoadjuvant systemic therapy

Hormone receptor-positive/HER2-negative breast cancer

This subset of patients accounts for approximately 70% and 75% of premenopausal and postmenopausal women, respectively. Estrogen receptor (ER) stimulation induced tumor cell growth and proliferation stands as a key biologic feature of these tumors, hence the universal use of endocrinal therapy (ET) can be extremely effective in many patients, although it is less effective and even ineffective in others. Conversely, most of these tumors do not respond well to chemotherapy in the neoadjuvant setting, with modest pCR rates that rarely exceed 10%.[24]

Indications and rationale: Preoperative rather than postoperative systemic therapy

Eighty percent of panel members confirmed that the primary goal of neoadjuvant therapy for nonmetastatic hormone receptor (HR)-positive/HER2-negative BC is to increase the chance of breast conservation and/or axillary surgery de-escalation, provided that the same therapy would also be indicated in the adjuvant setting. Reviewing the literature, the panel noted that it was possible to achieve breast conservation in 24%–55% of patients who received NCT and in 33%–56% of patients who received neoadjuvant endocrine treatment (NET) among those who were otherwise planned to undergo mastectomy.[25–28]

Moreover, 73% of the panel elected neoadjuvant therapy instead of upfront surgery for patients with clinically positive lymph nodes (cN1) because of the potential opportunity to de-escalate axillary surgery in special situations.[29]

The panel agreed that using pathologic surrogates to dissect the HR-positive/HER2-negative BC into luminal A and luminal B subtypes plays a role in assigning the planned treatment modality (discussed below). Most of panel members were inclined to adopt upfront surgery as the preferred treatment modality for nonmetastatic, resectable luminal A BC (clinical T2 [cT2]–cT3N0), regardless of the planned surgery type, as voted by 75% and 80% of the panel for premenopausal and postmenopausal females, respectively. However, as mentioned above, if downsizing of the tumor is warranted to allow breast conservation, neoadjuvant therapy would still be the appropriate modality, in case the same therapy would also be indicated in the adjuvant setting, to lower the risk of distant recurrence and cancer-related mortality.

In contrast, for resectable luminal B BC (cT2-cT3 N0), the panel preferred preoperative systemic therapy (regardless of the planned surgery type), as voted by 70% and 65% of the panel for premenopausal and postmenopausal females, respectively. This was extrapolated from the results of the landmark Collaborative Trials in

Neoadjuvant Breast Cancer pooled analysis,[3] which showed that pCR rates were more than doubled in the grade 3, HR-positive/HER2-negative subgroup compared with the subgroup that had grade 1 and 2 tumors (16.2% vs. 7.5%). Moreover, a pCR was positively associated with event-free survival (EFS) and overall survival (OS); for EFS: hazard ratio, 0.27; 95% confidence interval [CI], 0.14–0.50; for OS: hazard ratio, 0.29; 95% CI, 0.13–0.65) in grade 3 tumors but not in grade 1 or 2 tumors. Conversely, collated data from different trials indicated that outcomes for a residual cancer burden (RCB) of 0, (RCB 0; i.e., pCR) were the same as outcomes for the RCB 1 group who had HR-positive/HER2-negative BC compared with the RCB 2 and 3 groups, who clearly had a worse prognosis.[30] Furthermore, the receipt of preoperative systemic therapy may allow for the individualization of postoperative systemic therapy, particularly considering the recent approval of olaparib for patients with germline *BRCA* (g*BRCA*) mutations in case of residual invasive disease with clinical and pathologic stage (CPS) and ER status and histologic grade (CPS + EG) scores ≥3, according to the OlympiA trial (ClinicalTrials.gov identifier NCT02032823).[31,32]

Neoadjuvant therapy regimen

Dissecting the heterogeneity of HR-positive/HER2-negative BC. HR-positive/HER2-negative BCs widely vary in terms of quantitative levels of ER and PR expression, histologic grade, rate of proliferation (determined according to the Ki67 proliferation index), and gene expression profiles. Low-grade tumors often have higher ER and PR expression, with lower rates of proliferation and a favorable (low-risk) gene expression profile, whereas high-grade tumors usually express lower levels of ER, may lack PR expression, have higher rates of cell proliferation, and have an unfavorable (high-risk) gene expression profile. These characteristics are typically related to intrinsic subtypes (luminal A and B according to PAM50 gene expression subtype) and may provide a reliable prediction of sensitivity to systemic neoadjuvant therapies, in which luminal A-like tumors are anticipated to respond better to NET, whereas luminal B-like tumors to respond better to NCT.[33]

The role of BC multigene signatures in deciding the optimal neoadjuvant systemic therapy. Formerly, BC multigene signatures (BCMS) were developed and validated as prognostic tools in the adjuvant setting, which also provided their ability to predict the potential benefit of adjuvant chemotherapy in patients with early stage luminal BC.[34] Although the clinical utility of BCMS has not been conclusively established in the neoadjuvant setting, several small studies have strongly suggested their potential role in predicting the benefit of NCT versus NET in patients with HR-positive/HER2-negative BC.[35] A recent meta-analysis[36] demonstrated that tumors with a high Oncotype DX (Exact Sciences Corporation) recurrence score (RS) had a higher pCR rate with NCT compared with tumors that had a low-to-intermediate RS (10.9% vs. 1.1%. respectively; risk ratio, 4.47; 95% CI, 2.76–7.21; $p < .001$). Moreover, 68.5% of patients with a high RS achieved a disease down-staging (pCR or partial response) with NCT compared with 35.7% of patients with a low-to-intermediate RS (risk ratio, 1.79; 95% CI, 1.16–2.76; $p = .03$), which would be particularly relevant to increase the proportion of patients undergoing post-neoadjuvant BCS. On the same note, another meta-analysis[37] confirmed the significantly higher response rate with NET in patients who had a low-to-intermediate RS (<25) compared with those who had a high-risk RS (odds ratio, 4.60; 95% CI, 2.53–8.37; $p < .001$).

The panel was split on the role of BCMS (whenever accessible) to decide on the type of neoadjuvant therapy (NCT vs. NET). Fifty percent of the panelists endorsed their use for premenopausal/postmenopausal patients (N0 disease) and for postmenopausal patients with N1 disease, as applied in the adjuvant setting, whereas 21% recommended their application exclusively in postmenopausal patients with N0 and N1 disease. Interestingly, 29% of the panelists did not consider the use of BCMS to select the type of neoadjuvant therapy, highlighting the inadequate evidence to support their clinical utility in this context, which is in line with current American Society of Clinical Oncology (ASCO) guidelines.[38] However, it is important to acknowledge that few studies have evaluated the use of biopsy samples instead of surgical specimens for genomic tests (i.e., MammaPrint [Netherlands Cancer Institute], Oncotype DX) and established their feasibility, thus allowing for their use in the neoadjuvant setting.[39,40] Those authors note that trials evaluating genomic tests in the neoadjuvant setting assess more short-term end points (pCR, clinical response, the BCS rate) rather than the real long-term benefit of chemotherapy (EFS/disease-free survival [DFS] or OS).

The role of immunohistochemistry in deciding the optimal neoadjuvant systemic therapy. Although all panelists generally acknowledged the superiority of molecular subtypes identified with BCMS to classify the tumor biology and make treatment decisions versus establishing surrogate subtypes by immunohistochemistry (IHC), nevertheless, they opted to refer to St Gallen's definition of luminal subtypes based on the typical four IHC parameters as a more realistic approach.[41] Accordingly, all panelists agreed that "luminal A-like" disease is defined as tumors with strong ER/PR expression, lower histologic grade, and a low Ki67 proliferation index, whereas tumors designated as "luminal B-like" disease have low levels of ER/PR expression, higher grade, and a high Ki67 proliferation index. The panel also acknowledged the inherent limitations of individual biomarkers, especially Ki67 status, given intratumor and interobserver variations as well as the subjective human interpretation of IHC results. Hence they strongly advocated compliance with the technical methodologies as recommended by the updated Ki67 in the Breast Cancer Working Group[42] to improve the reliability of results (quality-assurance programs are essential for all laboratories reporting on Ki67).

The panel was asked about the "clinically preferred" Ki67 cutoff values to guide the selection of appropriate primary systemic therapy regimens. More than 75% of panelists favored ≤5% as a cutoff to define low Ki67 (indicating NET), and ≥30% as a cutoff to define high Ki67 (indicating NCT) based on the latest Ki67 working group recommendations.[42] Also, the panel highlighted that the Ki67 value should not be used alone as the sole criterion to select patients for

NCT, although it plays a role in the surrogate markers used to define the intrinsic subtype in combination with the other prognostic makers. Moreover, evidence for the use of Ki67/IHC4 in decisions about NCT is extrapolated from the adjuvant setting.

Unfortunately, most patients with HR-positive/HER2-negative tumors (>75%) have Ki67 values that range between >5% and <30%, which would limit its clinical utility to support decisions in such a large proportion of patients with biologically heterogeneous luminal disease, reinforcing the importance of further individualized treatment decisions.

Individualized neoadjuvant therapy in HR-positive/HER2-negative breast cancer. The choice of neoadjuvant treatment in HR-positive/HER2-negative BC is largely extrapolated from large phase 3 studies in the adjuvant setting, which reported invasive DFS (iDFS) and OS as the key efficacy end points. This is in addition to smaller—often phase 2—studies in the neoadjuvant setting that have assessed clinical response and pCR rates in addition to the BCS rates as the outcomes of interest (for details, see below). In view of this, the panel discussed the preferred options for the different scenarios encountered in the neoadjuvant setting according to disease stage, biology, and menopausal status in the HR-positive/HER2-negative BC population.

If we limit consideration to low-proliferative, HR-positive, early stage BC, both NET and NCT have demonstrated comparable clinical and pathologic response rates and breast-conservation rates, although NET is associated with lower toxicity.[25,43–46] Yet the role of NET in postmenopausal women was assessed in phase 3 studies[25,47] and had response rates and breast-conservation rates similar to those of chemotherapy in luminal-like disease, so it may be an option for these patients, keeping individual tumor biology in mind. Importantly, in a meta-analysis of three studies[25] that prospectively compared NCT versus NET using an aromatase inhibitor (AI) in postmenopausal women (with strongly HR-positive tumors, ie: ≥10%), there was no superiority of either treatment approach in terms of clinical response, radiologic response, or BCS rates.

Few phase 2/3 trials (with a limited number of patients)[26,27,48] have studied NET in premenopausal women and reported generally lower response rates compared with chemotherapy. This is likely because of variations in biology, with higher rates of luminal B and basal-like intrinsic subtypes, which are more chemotherapy-sensitive in premenopausal women. Hence chemotherapy is still the standard of care for neoadjuvant therapy in most premenopausal females with HR-positive/HER-negative, early stage disease in the absence of genomic assay testing.[49]

Early stage (cT2–cT3N0) luminal A-like and luminal B-like BC. To individualize neoadjuvant therapy even further, the panel discussed the preferred options according to tumor biology, stage, and menopausal status in the HR-positive/HER2-negative BC population. Most of the panel (76%) preferred NET versus 24% who preferred NCT (14% and 8% adopted conventional and dose-dense schedules, respectively), for postmenopausal patients with early stage (cT2–cT3N0), luminal A BC.

Conversely, for premenopausal patients with early stage (cT2–cT3N0) luminal A BC, 78% of the panel preferred NCT (53% and 25% adopted conventional and dose-dense schedules, respectively), whereas 22% favored NET. This chemotherapy preference was influenced by the results of the landmark TAILORx trial (ClinicalTrials.gov identifier NCT00310180)[50] in the adjuvant setting, in which a significant, iDFS benefit from chemotherapy was seen in young women (aged 50 years or younger) with negative nodes and a midrange[16–25] RS (approximately 46% of this cohort). This is in addition to patients with a high RS (≥26), who represented 13.4% of the study population and are already known to need chemotherapy. Similar data of the preferential benefit of chemotherapy versus ET in premenopausal women was also reported in an exploratory analysis of the MINDACT study for patients with high clinical risk/low MammaPrint risk BC.[51] Moreover, in the neoadjuvant setting, a prior meta-analysis[52] of eight German studies (8949 patients who received chemotherapy), a subgroup analysis according to age (younger than 50 years vs. 50 years and older), younger patients who had luminal-like BC seemed to achieve a significantly higher pCR rate from NAC compared with older women. However, the most appropriate chemotherapy regimen for premenopausal patients with HR-positive/HER2-negative disease in the low-to-moderate risk setting remains uncertain.

For patients who have luminal B BC with early stage (cT2–cT3N0) BC, the preferred neoadjuvant regimen (if planned) was chemotherapy for all patients (premenopausal and postmenopausal), as agreed by 81% of the panel (52% and 29% adopted conventional and dose-dense schedules, respectively) compared with only 19% of the panel who opted to customize the neoadjuvant therapy according to menopausal status, i.e., chemotherapy for premenopausal patients and ET for postmenopausal patients. Importantly, if neoadjuvant therapy is planned for HR-positive/HER2-negative BC in elderly patients and/or those with comorbidities, 90% of the panel accepted ET as the preferred choice.

In contrast, if neoadjuvant therapy is planned for HR-positive/HER2-negative BC in patients who have ER-low disease (1%–9%), chemotherapy was the preferred regimen by 100% of the panelists (57% and 43% adopted conventional and dose-dense schedules, respectively). Although the panel recommended treating such patients as though they have TNBC, this tumor biology was not typically included in TNBC trials. Therefore, the panelists recommended adopting neoadjuvant regimens that incorporate adding carboplatin with or without pembrolizumab in patients with ER-low disease, as in patients with TNBC; however, enrollment in dedicated clinical studies should be encouraged.

Advanced stage (cT2–cT4N1–N3), luminal A-like and luminal B-like BC. In addition, 85% of the panel recommended chemotherapy as the preferred neoadjuvant therapy regimen for premenopausal women with HR-positive/HER2-negative BC and positive axillary nodes (N1), irrespective of the biologic subtype. This was based on a

Korean study[27] that randomized 174 premenopausal women with lymph node-positive (N+) disease to receive either eight cycles of the standard anthracycline/cyclophosphamide-taxane or 24 weeks of ovarian function suppression (OFS) and tamoxifen. Those authors reported significantly higher clinical responses with NCT compared with NET (83.9% vs. 71.3%; $p = .046$). Nonetheless, the conversion rate to BCS in patients who were planned to undergo total mastectomy was 13.8% and 11.5% ($p = .531$) in the NCT and NET groups, respectively.

In the adjuvant setting, the results from the RxPONDER trial[53] could further confirm the significant iDFS benefit (hazard ratio, 0.60; 95% CI, 0.43–0.83; $p = .002$) and the distant relapse-free survival (RFS) benefit (hazard ratio, 0.58, 95% CI, 0.39–0.87; $p = .009$) from adding chemotherapy to ET among premenopausal women with positive nodes (N1) and low or intermediate risk (RS, ≤25) in approximately 33% of the cohort. This would leave practically no room for omitting chemotherapy in such patients, with no need to consider genomic assays. Certainly controversy exists about whether suppressing ovarian function rather than the cytotoxic effect of chemotherapy drove the benefit in this group of patients.[54,55] Indeed, only 6% of premenopausal women enrolled in RxPONDER received OFS as part of their ET in the chemotherapy arm, although data from the SOFT and TEXT trials[56] have indicated s clear long-term benefit from this approach. This particular debate is subject of the ongoing NRG-BR009 phase 3 study (ClinicalTrials.gov NCT05879926), which is evaluating the addition of chemotherapy to OFS plus ET in premenopausal patients with pathologic N0–N1, ER-positive/HER2-negative, early BC and an Oncotype RS ≤25.

Conversely, the preferred neoadjuvant regimen for postmenopausal patients with N+, HR-positive/HER2-negative BC was chemotherapy according to 75% of the panel, whereas 25% voted for ET in the absence of genomic signatures.[57]

Lobular carcinoma. Molecularly, the vast majority of classic invasive lobular carcinoma (ILC) belongs to the luminal-A intrinsic subtype (78%) and the luminal-B subtype (11%),[58] hence ET plays a main role in the management of these tumors. In current clinical practice, patients with ILC are usually treated no differently than patients with luminal invasive ductal carcinoma (IDC) based on the lack of definite prospective specific data in patients who have this histologic type.

In the neoadjuvant setting, ILC has been known for chemoresistance compared with luminal IDC, with significantly lower pCR rates, although the prognosis was significantly better among patients who had ILC,[58,59] with the notable exception of pleomorphic or triple-negative lobular cancers.

In a more recent report[60] including approximately 116,000 patients who had early BC from the National Cancer Database, ILC histology (15,763 patients) was associated with a lower percentage of high Oncotype RS compared with IDC histology (6.6% vs. 16.0%; $p < .0001$). These data would at least partially explain the lower benefit of chemotherapy in ILC. Interestingly, the RS has been shown to have prognostic as well as predictive value in ILC, with an association between OS benefit and chemotherapy receipt in patients who have ILC with a high RS, especially if they have N+ disease. It is crucial to mention that genomic tests (Oncotype, MammaPrint, and others) were developed and validated mainly for ductal BC, not lobular BC, in which it is still being investigated.

Accordingly, when neoadjuvant therapy is planned for patients who have HR-positive/HER2-negative BC (cT2–cT3N0) with non-pleomorphic ILC, 46% of the panel favored NET, 19% favored chemotherapy,[61] and 35% preferred tailoring neoadjuvant therapy according to menopausal status (chemotherapy for premenopausal patients and ET for postmenopausal patients). In a large, retrospective study,[62] postmenopausal patients with ILC who received adjuvant ET alone were compared with those who received chemotherapy and ET, and no additional survival benefit was observed from the addition of chemotherapy in contrast to patients who had IDC. AIs appear to be significantly superior to tamoxifen at a higher magnitude of benefit in patients who have ILC compared with those who have IDC.[63]

Type and duration of neoadjuvant endocrine therapy. When NET is planned for postmenopausal patients with HR-positive/HER2-negative BC, 82% of the panel voted for AI[25] as the preferred option, given the higher response and breast-conservation rates with AI versus tamoxifen. The phase 2 trial American College of Surgeons Oncology Group ACOSOG Z1031 trial[64] demonstrated no differences in clinical or pathologic responses between steroidal and nonsteroidal AIs. For special situations in which NET is planned for premenopausal patients who have HR-positive/HER2-negative BC, (e.g., unfit for chemotherapy or low risk by genomic assays), 70%, 20%, and 10% of the panel voted for OFS/AI,[65] OFS/tamoxifen, and tamoxifen as the preferred regimens, respectively. It should be emphasized that all randomized trials have clearly demonstrated that neoadjuvant AIs are significantly more effective than tamoxifen in the rates of objective response and BCS in either premenopausal or postmenopausal women and hence they should be used as the preferred NET option whenever possible. To date, cyclin-dependent kinase 4/6 inhibitors are still not approved as neoadjuvant therapy for HR-positive/HER2-negative BC because they do not appear to improve the overall response or pCR rates compared with NET alone or NCT.[66]

The optimal duration of NET is not well defined. Most early NET studies applied from 3 to 6 months of therapy. More than one half of the panel (61%) believed that the optimum duration of NET before surgery (in the absence of progression) is 6–8 months, whereas 39% believed that it can be applied if there is a continuous response (maximum, 12 months). Of note, higher tumor response rates have been reported with longer treatment durations.[67]

Short preoperative ET in luminal early breast cancer: Ki67 response as a surrogate marker to predict outcome of NET. Most of the panel (80%) agreed on the clinical utility of short-term preoperative ET, to test for endocrine sensitivity. Several studies (POETIC, WSG ADAPT)[43,68] have demonstrated that a decrease in Ki67 after short-term preoperative ET is correlated with better outcomes and may

define a subgroup of postmenopausal patients with endocrine-sensitive disease for whom chemotherapy may be not warranted (consider omitting chemotherapy in patients who have a post-NET Ki67 ≤10%). Of note, in these trials, Ki67 was evaluated in a central laboratory, leaving uncertainties about how the trial results would apply in a real-world setting. Most of the panel (75%) did not endorse the implementation of a follow-up biopsy (at 2–4 weeks)[69] in patients receiving NET to evaluate a reduction in Ki67 outside the context of clinical trial, pointing to a preference for short-term NET followed by surgery rather than biopsy.

Triple-negative breast cancer

Indications and rationale: Preoperative rather than postoperative systemic therapy

With regard to the preferred treatment modality for nonmetastatic, cT1cN0 (1.1–2.0 cm) TNBC regardless of the planned surgery type, 76% versus 24% of the panel favored neoadjuvant therapy versus upfront surgery, respectively. Although this subgroup of patients (cT1cN0) was not typically included in the neoadjuvant trials, most of the panelists advocated extrapolating the benefits of neoadjuvant therapy originally used in later stage disease, including the ability to obtain better prognostic information and to individualize adjuvant therapy.[3] This is in line with the recent ASCO 2021 recommendations,[38] which preferred neoadjuvant therapy for cT1cN0 TNBC. Despite encouraging results of phase 2 studies supporting de-escalation of neoadjuvant regimens (if used) by using an anthracycline-free regimen (taxane-carboplatin) for cT1cN0 TNBC, this approach is still a clinical trial question being currently studied and is not yet a standard of care (discussed below). Moreover, the use of pembrolizumab in the neoadjuvant therapy for those patients lacks supporting evidence, because they were not included in the KEYNOTE-522 study.

On the other side, there was universal agreement between the panelists (100%) to recommend neoadjuvant therapy for ≥cT2 or N+ TNBC, regardless of the planned surgery type, based on the available phase 3 studies.[70]

Neoadjuvant therapy regimen

Many approaches have been tested to improve the pCR rate in TNBC given its correlation with improved survival compared with non-pCR cohorts.[3] This includes the use of sequential taxanes and anthracycline/cyclophosphamide therapy, adding carboplatin to weekly paclitaxel, and the use of dose-dense regimens (doxorubicin/cyclophosphamide every 2 weeks). The addition of the checkpoint inhibitor pembrolizumab to weekly paclitaxel and carboplatin followed by anthracycline/cyclophosphamide every 3 weeks in KEYNOTE-522[71] is now an approved therapy demonstrating improved outcomes. An important perspective is that immunotherapy has not been incorporated with dose-dense regimens according to the KEYNOTE-522 trial protocol. Moreover, an alternative nonanthracycline regimen with docetaxel and carboplatin has recently been evaluated with promising results in phase 2/3 trials and will be tested in a prospective randomized trial compared with the KEYNOTE-522 regimen.[72,73]

When the panel was asked about which neoadjuvant therapy regimen they preferred for ≥cT2 or N+ TNBC, 78% favored pembrolizumab (plus weekly paclitaxel/carboplatin, then doxorubicin/cyclophosphamide), irrespective of PD-L1 status. Also, most of the panel (75%) preferred conventional-dose anthracyclines-taxanes with carboplatin, although 35% of the panel favored dose-dense anthracycline regimens.[74]

Adding pembrolizumab to neoadjuvant therapy and continued as adjuvant therapy was preferred by 75% and 90% of the panel for stage 2 and stage 3 TNBC, respectively. The pCR rate in KEYNOTE-522[71] was more pronounced with adding pembrolizumab in patients who had node-positive disease (absolute benefit, 20.6% vs. 6.3% in the node-negative group); however, a similar, statistically significant, and clinically meaningful EFS benefit was observed regardless of node status (hazard ratio, 0.65 in node-positive patients vs. 0.58 in node-negative patients).[70] Therefore, the addition of pembrolizumab should be considered for patients with stage II and III disease in the neoadjuvant therapy setting.

With regard to adding carboplatin to the neoadjuvant regimen, 70% and 80% of panelists preferred adding it for stage II and III BC, respectively. Furthermore, 76% of panelists preferred adding it independent of g*BRCA* status because *BRCA* mutation status appears to confer some degree of chemotherapy sensitivity regardless of the use of platinum based on data demonstrating higher pCR rates in this population (patients with a *BRCA* mutation).[75,76] It is worth mentioning that pCR rates had a more pronounced increase with the addition of carboplatin in wild-type *BRCA* subgroups compared with *BRCA*-mutant subgroups in the GeparSixto and BrighTNess trials. However, 65% of panelists acknowledged that not all patients with TNBC require the addition of carboplatin as neoadjuvant therapy. These statements were in line with most of the international guidelines,[38,77,78] which highlighted the inclusion of a platinum in neoadjuvant therapy for TNBC; however, a clear consensus was reached among the conference panel regarding its use for high-risk (stage III) disease (80%) and in patients who have an inadequate response to anthracyclines (90%). Of note, pCR rates were significantly increased (in >50% of patients) by the addition of a platinum in the GeparSixto[79], Cancer and Leukemia Group B (CALGB) 40603,[80] and BrighTNess trials[76] (irrespective of *BRCA* status). DFS and EFS were consistently improved in the two studies with a hazard ratio of 0.5 (GeparSixto: hazard ratio, 0.56 [95% CI, 0.33–0.96][81]; BrighTNess: hazard ratio, 0.57 [95% CI 0.36–0.91][81]). Two recent meta-analyses[82,83] reported an OS benefit; however, carboplatin dose interruptions in the CALGB 40603 trial[84] were correlated with significantly worse EFS. Recent data reported by Gupta et al.[85] add to the existing body of evidence mentioned above, and definitively demonstrate both EFS and OS benefit from the addition of carboplatin to taxane and anthracycline–based neoadjuvant therapy for TNBC. Most important, these benefits were limited to younger patients (aged 50 years and younger) in that study. Hematologic toxicity

increased with the addition of carboplatin, and it is important to mention that these studies had started with the taxane/carboplatin combination followed by anthracycline/cyclophosphamide.

Of note, Sharma and colleagues[72] have piloted an anthracycline-free neoadjuvant regimen for TNBC in which docetaxel and carboplatin are given every 3 weeks for six cycles, and the results are intriguing. In their study, the pCR rate is 55%; however, the 3-year RFS rate was 90% and 66% in patients with and without a pCR, respectively (hazard ratio, 0.30; 95% CI, 0.14–0.62; $p = .0001$), and the 3-year OS rate was 94% and 79%, respectively (hazard ratio, 0.25; 95% CI, 0.10–0.63; $p = .001$). These results were also confirmed in another randomized phase 2 study.[73] Recent data[86] were also encouraging when this regimen was combined with pembrolizumab, demonstrating a pCR rate of 60% and a 2-year EFS rate of 98% and 82% for patients with and without a pCR, respectively, in the absence of adjuvant pembrolizumab.

Concerning the use of dose-dense anthracyclines in neoadjuvant therapy (if immunotherapy is not used), 80% and 95% of the panel favored its use in stage II and III TNBC, respectively; whereas, 85% favored it for young patients. This was based on the EBCTCG meta-analysis,[87] which showed significant reductions in recurrences and mortality with dose-dense regimens. Similar beneficial outcomes were observed in lymph node-negative and lymph node-positive subgroups.

HER2-positive breast cancer

Indications and rationale: Preoperative rather than postoperative systemic therapy

With regard to the preferred treatment modality for nonmetastatic cT1cN0 (1.1–2.0 cm) HER2-positive BC, regardless of the planned surgery type, 71% versus 29% of the panel favored neoadjuvant therapy versus upfront surgery, respectively. In fact, some experts may elect upfront surgery specifically for those patients to allow surgical staging to guide the de-escalation of adjuvant systemic therapy accordingly (the omission of dual HER2 blockade and/or the use of less intensive chemotherapy, i.e., the omission of anthracyclines) for pathologic T1 [pT1]N0 disease while maintaining favorable long-term outcomes, as demonstrated for patients who received 12 weeks of adjuvant paclitaxel plus 1 year of trastuzumab in recently published results from the APT trial.[88] The debate about how to manage cT1cN0, HER2-positive BC is driven by the fact that these patients were included in both the APT[89] adjuvant de-escalation trial (41%) and the Katherine[90] post-neoadjuvant escalation trial (≤10%).

For nonmetastatic, HER2-positive BC classified as ≥cT2 or N+, the panel unanimously (100%) voted for neoadjuvant therapy, regardless of the planned surgery type, given the supporting high-level evidence.[91,92]

Neoadjuvant therapy regimen

Sixty-nine percent of the panel preferred combined docetaxel, carboplatin, trastuzumab, and pertuzumab for six cycles over anthracycline-containing regimens as neoadjuvant therapy for HER2-positive BC. This recommendation is based on results from the phase 2 TRYPHAENA trial[93] and the phase 3 TRAIN-2 trial[94] demonstrating equivalent pCR rates, survival rates, and reduced overall toxicity compared with anthracycline-containing regimens. The recent ASCO[38] and St Gallen[78] guidelines (2021) continue to support the use of an anthracycline-containing neoadjuvant therapy regimen as the preferred therapeutic option. This was based on the reported reduction of BC recurrences or deaths with the use of anthracycline-containing regimens, which was confirmed in a recent (2023) EBCTCG meta-analysis.[95] The National Comprehensive Cancer Network guidelines are more specific because they acknowledged that nonanthracycline-containing regimens are preferred, whereas the anthracycline-containing regimens are useful in certain situations.[96] However, the recent German recommendations[97] advise using anthracyclines for stage III or cN+ disease and omitting them for stage II disease without nodal involvement (cN0). As expected, in the presence of cardiac comorbidities, 90% of the panel recommended combined docetaxel, carboplatin, trastuzumab, and pertuzumab as the preferred regimen.

If neoadjuvant therapy is planned for patients with cT1N0, HER2-positive BC, 78% of the panel agreed with a less intensive approach using the anthracycline-free and carboplatin-free APT regimen (12 weekly paclitaxel plus trastuzumab). This recommendation was based on updated results from the APT trial[89] with a median follow-up of 10.8 years, confirming that adjuvant paclitaxel plus trastuzumab was associated with excellent long-term outcomes for patients who had HER2-positive BC with negative lymph nodes and small tumors (≤3 cm), with just six distant relapses in 406 patients and an iDFS rate of 91.3%. Moreover, the ADAPT-HER2 study[68] demonstrated excellent results with neoadjuvant dual blockade (trastuzumab and pertuzumab) and 12 weeks of paclitaxel for HR-negative/HER2-positive BC. After a median follow-up of 5 years, the iDFS and OS rates were both 98%, which deem this regimen of major value to patients who have significant comorbidities.

De novo breast cancer with oligometastatic disease

Although there is no uniform definition for oligometastatic disease (OMD), the panel advocated for the European Society for Radiotherapy and Oncology and the European Society for Medical Oncology broad definition: low-volume, metastatic disease limited in the number and size of metastatic lesions (up to five lesions, not necessarily in the same organ), possibly amenable to local treatment with the objective of achieving complete remission.[98,99] For patients who have de novo BC with OMD, the majority of the panel preferred initiating primary systemic therapy and then considering local treatment for locoregional disease for patients who had a complete response in metastatic lesions (55% of voters) or any response in metastatic lesions (15% of voters), whereas only 30% preferred management with systemic therapy only. In patients with inflammatory BC, 76% of panelists preferred opting for locoregional

management in case of a complete response in metastatic lesions. When the panel was asked whether their decision would be affected by tumor biology, one half of the voters (50%) stated that they would consider locoregional management for any biologic subtype, whereas 25% and 20% encouraged this approach only for HR-positive/HER2-negative BC and HER2-positive BC, respectively. Interestingly, 32% of the panel had abstained from voting on these statements, reflecting the scarcity of high-level evidence to support uniform clinical practice and highlighting the need for well designed clinical trials in this context. It is important to point out that available phase 3 trials[100–103] did not report an OS benefit with locoregional management in OMD (except for one study,[104] with some caveats in design and patient population), and the remaining trials[100,101] demonstrated only slightly significantly better locoregional control with locoregional management.

Adjuvant therapy postneoadjuvant treatment

HR-positive/HER2-negative breast cancer

Tailoring adjuvant systemic therapy after NET may depend on several validated approaches, including the burden of residual disease as dictated by the preoperative endocrine prognostic index (PEPI) score[105] or the modified PEPI score[45] and the dynamics of Ki67 (POETIC,[43] IMPACT,[106] ADAPT[68]), as well as genomic assays (Oncotype DX, MammaPrint, EndoPredict [Myriad Genetics], Prosigna breast cancer assay [Verasite Inc.]) that may be used to tailor adjuvant therapy as used in many randomized controlled trial in the adjuvant setting. The PEPI score[105] incorporates residual tumor and node staging, Ki67, and the ER Allred score after NET to categorize three risk groups, in which patients with a PEPI score of 0 (pT1–pT2N0; Ki67, ≤2.7%; ER Allred score, 3–8) do not appear to benefit from chemotherapy. This prognostic score was further validated in several studies[106,107] as a tool to predict RFS. Indeed, most of the panelists (75%) preferred to use the PEPI score to determine the need for adjuvant chemotherapy after using NET, whereas 25% did not recommend its use.

Regarding the preferred adjuvant therapy after NET for HR-positive/HER2-negative BC, in patients who have a pCR or a PEPI score of 0, 89% of the panel recommended against use of adjuvant chemotherapy, and 95% preferred to continue the same endocrine agent. For patients with residual disease who have a PEPI score ≥1 after NET for HR-positive/HER2-negative BC, 75% of the panel considered adjuvant chemotherapy, taking into account the individual patient's clinicopathologic profile, and 60% considered changing the endocrine agent.

For patients who achieve a pCR after NCT for HR-positive/HER2-negative BC, 77% of the panel voted for adjuvant ET alone. However, 40% recommended adding abemaciclib for patients who initially have clinically involved lymph nodes (according to eligibility criteria for the per monarchE trial) who achieve a pCR after NCT, highlighting the rarity of such a condition (≤3% in the monarchE trial), and an efficacy analysis was not performed among those patients.

Conversely, for patients who have residual disease after NCT for HR-positive/HER2-negative BC, the panel universally recommended either 2 years of abemaciclib for those with initially clinically involved lymph nodes or postoperative pathologically involved lymph nodes according to monarchE trial eligibility criteria[108] or 1 year of olaparib for patients with g*BRCA* mutations and residual disease who have CPS + EG scores ≥3, according to the OlympiA trial,[32] as the preferred adjuvant therapy alongside ET. This recommendation was based on results from the monarchE trial, in which, among the subgroup of patients who received NCT (37%), abemaciclib demonstrated a clinically meaningful improvement in the risk of 3-year iDFS (absolute benefit, 6.4%) and 3-year distant RFS events (absolute benefit, 6.6%) versus ET alone.[109] In the OlympiA trial,[32] the addition of olaparib to adjuvant therapy for the subset of patients who had HR-positive/HER2-negative BC and residual disease (with a CPS + EG score ≥3) after NCT (10% of the cohort) resulted in improved 3-year iDFS compared with placebo (absolute benefit, 19%; hazard ratio, 0.52; 95% CI, 0.25–1.04) and an OS benefit irrespective of the receptor status. Interestingly, quantification of residual disease using the RCB score after NCT was found to be prognostic for EFS and distant metastasis-free survival in multivariate analysis, which may provide a more refined estimate of an individual's risk of recurrence based on the RCB score.[110] It is worth noting that the RCB score was not evaluated to investigate the prognosis post-NET.

In patients who have residual disease after neoadjuvant therapy for HR-positive/HER2-negative BC with g*BRCA* mutation and initially clinically involved lymph nodes (i.e., fulfilling eligibility criteria for both the OlympiA and monarchE trials), 60% of the panel opted for olaparib, and 25% opted for abemaciclib as the preferred adjuvant therapy. The panel acknowledged the greater absolute benefit with olaparib compared with abemaciclib in an indirect comparison of the two trials (OlympiA[32] and monarchE[111]). Fifteen percent of the panel considered the use of sequential olaparib and abemaciclib for patients with a high risk of recurrence. It is worth noting that the recommendations in this particular clinical situation should be implemented with caution because the monarchE trial did not report results according to g*BRCA* status. Moreover, patients with HR-positive/HER2-negative BC represented only <20% of the OlympiA population. However, some data suggest that g*BRCA* mutations are associated with less sensitivity to cyclin-dependent kinase 4/6 inhibitors.[112] Figure 1 illustrates the algorithm proposed for adjuvant treatment postneoadjuvant therapy for HR-positive/HER2-negative BC.

Triple-negative breast cancer

The panel unanimously agreed (92%) that no further adjuvant therapy should be planned for patients with TNBC if a pCR is achieved after neoadjuvant therapy that includes an anthracycline/taxane with or without carboplatin. However, if a pCR was attained after

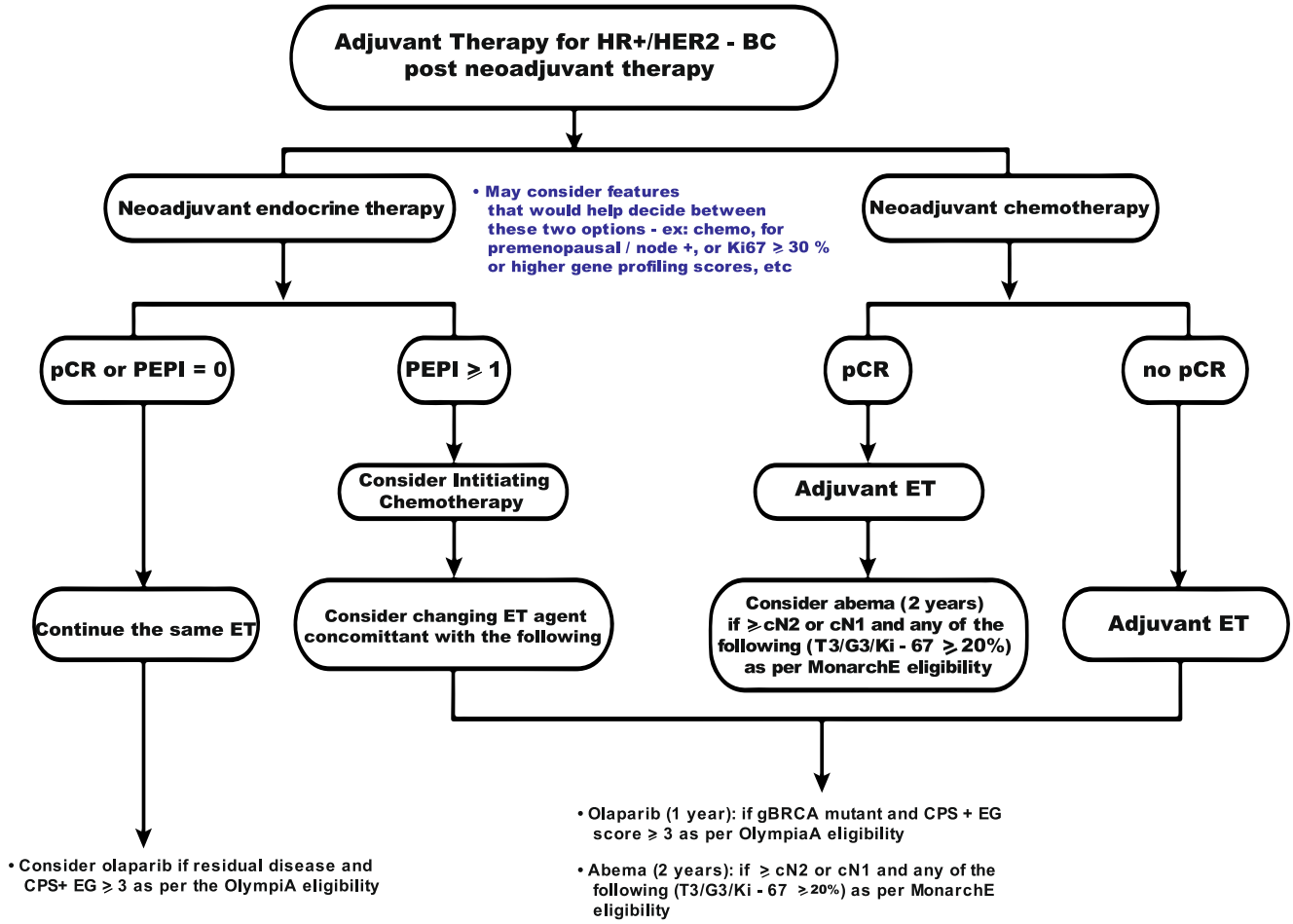

FIGURE 1 The algorithm proposed for adjuvant systemic therapy postneoadjuvant therapy for HR+/HER2− BC. Abema, abemaciclib; BC, breast cancer; cN, clinical lymph node status; CPS, clinical and pathologic stage; EG, estrogen receptor status and histologic grade; ET, endocrine therapy; G3, grade 3; gBRCA, germline BRCA; HR+/HER2− BC, hormone receptor-positive/human epidermal growth factor receptor-negative breast cancer; pCR, pathologic complete response; PEPI, preoperative endocrine prognostic index.

neoadjuvant therapy incorporating pembrolizumab, 68% of the panel favored continuing with nine more cycles of adjuvant pembrolizumab as the preferred therapy, whereas 32% preferred no further therapy. This was based on the preplanned exploratory analysis in KEYNOTE-522 study,[70] in which adding pembrolizumab in both the neoadjuvant and adjuvant settings was associated with a marginal and nonsignificant 3-year EFS benefit in the pCR group (94.4% vs. 92.5%); it is also important to note that this was associated with a significant 3-year EFS benefit in the non-pCR group (67.4% vs. 56.8%). It is impossible to separate out the benefit of continued pembrolizumab after surgery at this time, although planned studies[113] will evaluate this approach in patients who achieve a pCR after a neoadjuvant KEYNOTE-522 regimen.

If residual disease is detected after neoadjuvant therapy that includes an anthracycline/taxane with or without carboplatin in wild-type *BRCA* TNBC, the entire panel agreed that capecitabine (from six to eight cycles)[114] is the preferred adjuvant regimen. Noting that the survival benefit in the CREATE-X study was in the intention-to-treat TNBC population, the trial did not include an analysis according to *BRCA* status. If residual disease is detected after neoadjuvant therapy that incorporates pembrolizumab in patients who have wild-type *BRCA* TNBC, 73% of the panel favored continuing both pembrolizumab (nine cycles) and capecitabine (six to eight cycles) either concurrently or sequentially, 22% favored pembrolizumab alone, and 5% favored capecitabine alone as the preferred adjuvant therapy. Although no studies have addressed the clinical benefit of combining immunotherapy with capecitabine in such situations, safety data are available from a small phase 2 trial[115] and from a recent update of the IMpassion-031 trial[116] in which patients with residual disease received capecitabine and atezolizumab (6%) without any alarming safety signals.

If residual disease is detected after surgery after neoadjuvant therapy that includes an anthracycline/taxane with or without carboplatin in patients who have g*BRCA*-mutant TNBC, most of the panel (76%) opted to recommend olaparib for 1 year as the preferred adjuvant regimen, whereas 24% recommended the administration of olaparib and capecitabine sequentially for patients with a high risk of recurrence. It was highlighted that the preferential benefit of capecitabine may be evident in patients who have disease with a nonbasal phenotype (approximately 15% of TNBCs) rather than a basal

subtype.[117] While most g*BRCA*-mutant TNBCs (approximately 80%) are identified as a basal-like intrinsic subtype.[118]

Alternatively, if residual disease is detected after neoadjuvant therapy that includes pembrolizumab in *gBRCA*-mutant TNBC, 53% of the panel favored continuing both pembrolizumab (nine cycles) and olaparib (1 year) concurrently or sequentially, 33% favored olaparib alone, and 14% favored pembrolizumab alone as the preferred adjuvant therapy. This was based on the absolute benefit of adding olaparib (OS benefit) and pembrolizumab (EFS benefit) in the OlympiA[32] and KEYNOTE-522[70] trials, respectively. Treatment with 1 year of olaparib in patients who had high-risk, early stage BC associated with g*BRCA* mutations in the OlympiA trial was associated with significant improvements in 4-year iDFS (82.7% vs. 75.4%; Δ, 7.3%; 95% CI, 3.0%–11.5%), distant DFS (86.5% vs. 79.1%; Δ, 7.4%; 95% CI, 3.6%–11.3%), and OS (89.8% vs. 86.4%; hazard ratio, 0.68; 95% CI, 0.47–0.97) as well, irrespective of receptor status.[32] The addition of pembrolizumab was associated with significant EFS benefit, as mentioned above (3-year EFS benefit in the non-pCR group, 67.4% vs. 56.8%), with immature OS data. Moreover, the benefit in KEYNOTE-522 study was in the intention-to-treat TNBC population, which was not analyzed according to *BRCA* status. Safety data for combining immunotherapy with poly-adenosine diphosphate-ribose polymerase inhibitors can be extrapolated from phase 2 and 3 trials.[119,120] Figure 2 illustrates the algorithm proposed for adjuvant therapy after neoadjuvant therapy for TNBC.

HER2-positive breast cancer

For patients who achieve a pCR after neoadjuvant therapy (including trastuzumab plus pertuzumab) for HER2-positive BC with initial clinically negative nodes, 67% of the panel agreed that the preferred adjuvant therapy is de-escalation to trastuzumab alone to complete 1 year of therapy, whereas 34% preferred continuation with the same anti-HER2 regimen (trastuzumab plus pertuzumab). For patients with initial clinically positive nodes who attain a pCR after neoadjuvant therapy (including trastuzumab plus pertuzumab) for HER2-positive BC, most of the panel (79%) preferred continuation with the same anti-HER2 regimen (trastuzumab plus pertuzumab) to complete 1 year of therapy, and only 21% supported de-escalation to trastuzumab only. This recommendation was extrapolated from the updated results of the APHINITY trial,[121] which evaluated the benefit of adding pertuzumab to adjuvant therapy with trastuzumab after a median follow-up of 6 years in which all patients had undergone upfront surgery. There was no significant iDFS benefit from the addition of pertuzumab in the patients who had lymph node-negative disease, regardless of HR status, whereas patients who had lymph node-positive disease clearly benefitted from adjuvant, dual HER2 blockade (28% iDFS risk reduction; hazard ratio, 0.72; 95% CI, 0.59–0.87). It is important to recognize that a fair percentage of clinically node-negative tumors (approximately 30%) are actually pathologically lymph node-positive,[122] hence the emphasis on proper nodal assessment in the neoadjuvant setting.

For patients who have residual invasive disease after neoadjuvant therapy for HER2-positive BC (including trastuzumab with or without pertuzumab), the panel (95%) preferred adjuvant ado-trastuzumab emtansine (T-DM1; 14 cycles). The panel noted that adjuvant T-DM1 after neoadjuvant therapy including dual blockade (trastuzumab plus pertuzumab) has less supporting evidence because only approximately 18% of the KATHERINE[90] trial population received dual HER2 blockade in the neoadjuvant setting, and the evaluation of T-DM1 benefit in this small subgroup was underpowered (hazard ratio, 0.54; 95% CI, 0.27–1.06). The panel discussed the consideration of extended adjuvant therapy with the oral tyrosine kinase inhibitor neratinib for 1 year after neoadjuvant therapy (including trastuzumab with or without pertuzumab) for patients with HR-positive/HER2-positive BC. Sixty percent of the panel would recommend neratinib for patients with extensive residual disease, and 10% believed that neratinib could be considered for patients who have either a pCR or residual disease after NCT. These recommendations were based on results from the ExteNET trial,[123] in which approximately 25% of patients in each arm had received neoadjuvant therapy. In an unplanned subset analysis, OS appeared to be significantly improved with the addition of neratinib in patients who had residual disease but not for those who achieved a pCR. However, 24% of the panel recommended against the use of neratinib in the adjuvant setting, given the reported high rates of grade 3 diarrhea (40%), dose reductions (26%), and discontinuation (17%) using the dose schedule from the ExteNET trial. It should be noted that since publication of the ExteNET trial, new data show that dose escalation of neratinib over 3–4 weeks can significantly reduce the grade of diarrhea and improve adherence.[124] If extended adjuvant therapy with neratinib is considered for patients with HR-positive/HER2-positive BC and residual disease after neoadjuvant therapy, 55% of the panel recommended sequential use of neratinib for 1 year after 14 cycles of T-DM1. Thirty-five percent of the panel abstained from voting on this statement, highlighting the absence of data supporting the extended use of neratinib after adjuvant T-DM1 (in the case of residual disease) after neoadjuvant therapy with trastuzumab with or without pertuzumab. Figure 3 represents the algorithm proposed for adjuvant therapy post-neoadjuvant therapy for HER2-positive BC.

Locoregional management after neoadjuvant therapy

Breast surgery

Most panelists (75%) voted to wait for 4–6 weeks (to avoid the expected chemotherapy-induced nadir) as the preferred interval for surgery after completing most regimens of NCT; however, the interval could be shorter with a weekly paclitaxel regimen.[125,126]

For cT4b tumors with limited skin involvement (focal edema or direct invasion) in noninflammatory BC, the panel was split regarding whether or not breast conservation can be considered after neoadjuvant therapy. Fifty-five percent of the panelists would accept

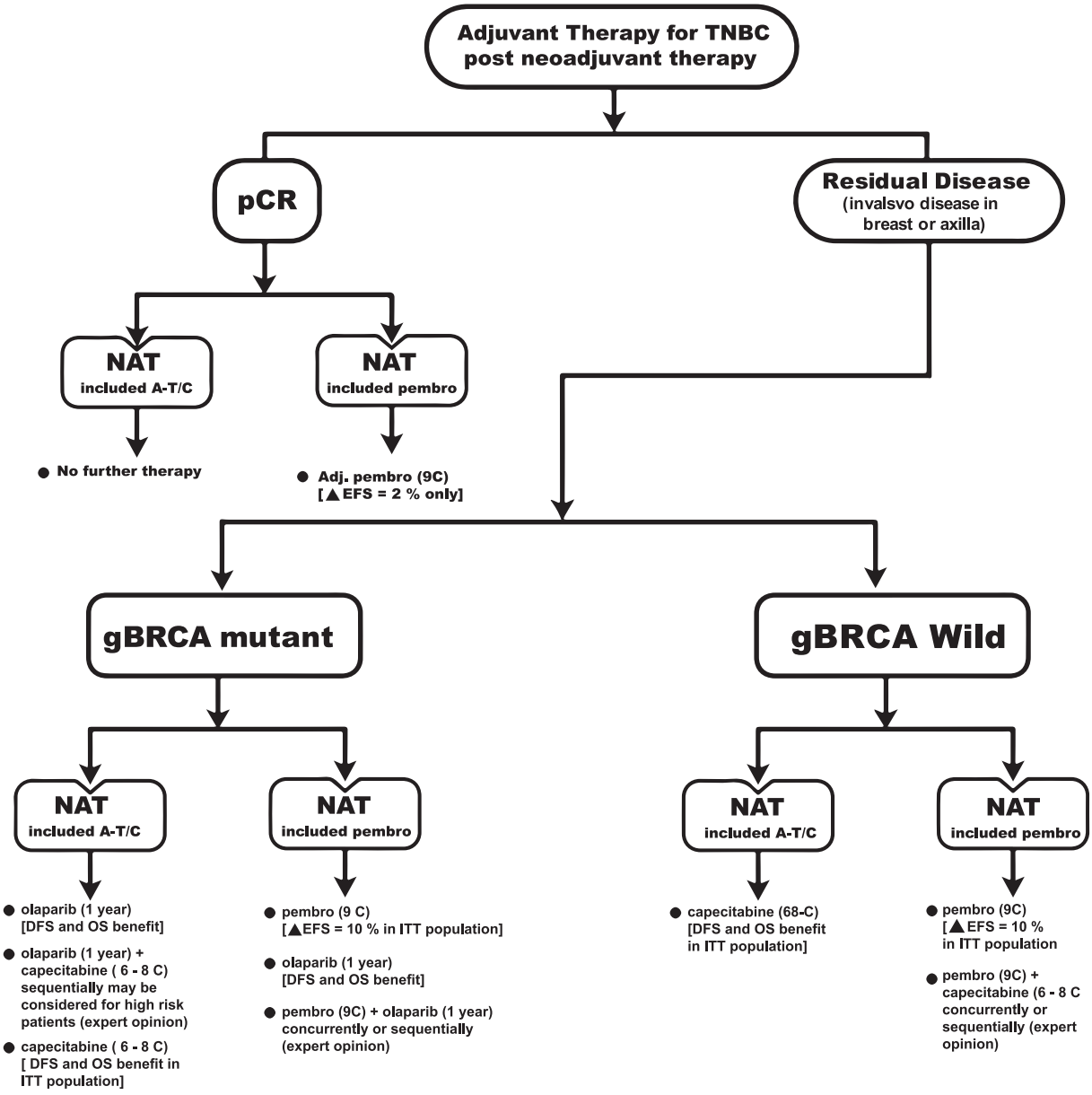

FIGURE 2 The algorithm proposed for adjuvant systemic therapy postneoadjuvant therapy for TNBC. ▲ indicates difference; A-T/C, anthracycline-taxane/carboplatin; Adj., adjuvant; C, cycles; DFS, disease-free survival; EFS, event-free survival; gBRCA, germline BRCA; ITT, intention to treat; OS, overall survival; NAT, neoadjuvant therapy; pCR, pathologic complete response; pembro, pembrolizumab; TNBC, triple-negative breast cancer.

BCS if the tumor can be excised with negative margins, even if the initial skin involvement did not completely resolve; whereas 30% mandates resolution of the initial skin involvement before adopting BCS. However, only 15% of the panelists rejected BCS for tumors with initially limited skin involvement.

Moreover, most panelists (76%) accepted that multicentricity (one or more quadrant[s]) would not be a contraindication for BCS after neoadjuvant therapy as long as excision with negative margins can be achieved while respecting the cosmesis, whereas 24% asserted multicentricity as an absolute contraindication for BCS. It is important to highlight that BCS should be offered when postoperative radiotherapy is accessible.

Management of regional lymph nodes

The preferred option for axillary lymph node management for initial cN1 and down-staged ycN0 disease after neoadjuvant therapy is SLNB performed with measures to decrease false-negative rates to <10% (marking the initially involved node and/or dual tracer and/or three or more SLNBs retrieved),[21,127–129] as supported by 77% of the panelists. The whole panel stated that it is of paramount importance to accurately re-stage the axilla (by ultrasound) after neoadjuvant therapy to determine the appropriate subsequent surgical approach.

The panel was split on the use of SLNB for more advanced stages. For initially cN1 disease before neoadjuvant therapy that is

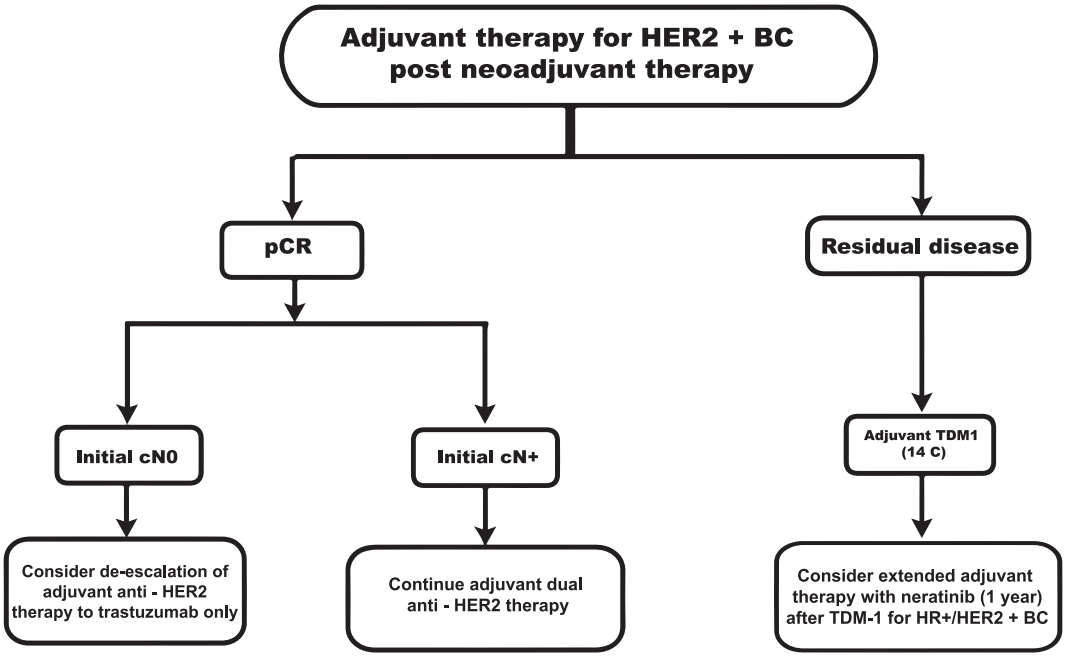

FIGURE 3 The algorithm proposed for adjuvant therapy postneoadjuvant therapy for HER2+ BC. BC indicates breast cancer; cN, clinical lymph node status; HER2+, human epidermal growth factor receptor 2-positive; pCR, pathologic complete response; T-DM1, ado-trastuzumab emtansine.

down-staged to ycN0, 55% of the panelists voted that SLNB may be considered for any cT stage, whereas 45% did not prefer it for cT4 tumors. This was based on the greater likelihood of axillary nodal involvement with increasing tumor stage, reaching >85% with T4 tumors.[130] Meanwhile, these patients (with T4 tumors) were either excluded[131] or minimally represented (<5%) in clinical trials evaluating the validity of SLNB after neoadjuvant therapy for initially node-positive cases.[21,22] Conversely, for those with cN2–cN3 who achieved ycN0, most of the panel (86%) opted for axillary lymph node dissection,[132] and 14% opted for SLNB (only if marking and/or dual tracer and/or three or more SLNBs are retrieved). It should be noted that patients may infrequently (≤5%) present with isolated internal mammary lymph nodes and negative axillary lymph nodes (cN2b), in which making a separate recommendation lacks any supporting evidence, and enrollment in clinical trials is encouraged.[133,134]

After surgery, for those who initially had cN1 disease and attained pathologically negative axilla after neoadjuvant therapy (ypN0), regional nodal irradiation is not indicated for all patients (SLNB or axillary lymph node dissection) by 55% of panelists. This was based on observational studies showing neither locoregional RFS benefit nor DFS/OS benefit with nodal irradiation.[135–137] However, 82% of the panel favored regional nodal irradiation for patients who had cN1 disease and achieved ypN0 status if an additional risk factor is present (e.g., cT3–cT4, grade 3, lymphovascular invasion). Results from ongoing trials[138] that address this question are awaited.

When regional nodal irradiation is prescribed for patients who have initially cN1 disease and convert to ypN0 status after neoadjuvant therapy, it is not routinely required to include all axillary levels (I–IV) (with internal mammary lymph nodes for central/medial tumors) according to 55% of the panel.[139] However, if only SLNB was done for those cases, it is preferred to include at least levels I and II of the axilla (60% of the panel).

CONCLUSION

In conclusion, this article provides comprehensive and focused guidance on neoadjuvant therapy for different subtypes of BC, including rationale and preferred regimens, for an area in which the complexity and diversity of trials are not conducive to formal, informative meta-analyses. Also, adjuvant therapy after neoadjuvant treatment was dissected for each BC subtype according to response. Moreover, important considerations for locoregional management after neoadjuvant therapy were discussed. The recommendations were based on validated approaches, clinical trial data, and expert consensus. These consensus recommendations serve as a valuable resource for clinicians to help their informed decisions. Further research and enrollment in clinical trials are always encouraged as part of an overall, comprehensive approach to patients with BC to refine and expand our understanding of optimal treatment strategies in this setting.

AUTHOR CONTRIBUTIONS

Hesham Elghazaly: Conceptualization, data curation, methodology, writing–review and editing, supervision, validation, writing–original draft. **Hamdy A. Azim**: Conceptualization, data curation, methodology, validation, writing–review and editing, supervision, writing–original

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REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol*. 2018;19(1):27-39. doi:10.1016/S1470-2045(17)30777-5
2. Conforti F, Pala L, Bagnardi V, et al. Surrogacy of pathologic complete response in trials of neoadjuvant therapy for early breast cancer: critical analysis of strengths, weaknesses, and misinterpretations. *JAMA Oncol*. 2022;8(11):1668-1675. doi:10.1001/jamaoncol.2022.3755
3. 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(9938):164-172. doi:10.1016/S0140-6736(13)62422-8
4. I-SPY2 Trial Consortium; Yee D, Demichele AM, et al. Association of event-free and distant recurrence-free survival with individual-level pathologic complete response in neoadjuvant treatment of stages 2 and 3 breast cancer: three-year follow-up analysis for the I-SPY2 adaptively randomized clinical trial. *JAMA Oncol*. 2020;6(9):1355-1362. doi:10.1001/jamaoncol.2020.2535

5. Nasa P, Jain R, Juneja D. Delphi methodology in healthcare research: how to decide its appropriateness. *World J Methodol*. 2021;11(4):116-129. doi:10.5662/wjm.v11.i4.116
6. Wöckel A, Festl J, Stüber T, et al. Interdisciplinary screening, diagnosis, therapy and follow-up of breast cancer. guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/045OL, December 2017)—Part 1 with recommendations for the screening, diagnosis and therapy of breast cancer, *Geburtshilfe Frauenheilkd*. 2018;78(10):927-948. doi:10.1055/a-0646-4522
7. Sickles EA, D'Orsi CJ, Bassett LW, Appleton CM, Berg WA, Burnside ES. ACR BI-RADS® mammography. In: D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA, eds. *ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System*. 5th ed. American College of Radiology; 2013:134-136.
8. Checka CM, Chun JE, Schnabel FR, Lee J, Toth H. The relationship of mammographic density and age: implications for breast cancer screening. *AJR Am J Roentgenol*. 2012;198(3):W292-W295. doi:10.2214/AJR.10.6049.
9. Kang YJ, Ahn SK, Kim SJ, Oh H, Han J, Ko E. Relationship between mammographic density and age in the United Arab Emirates population. *JAMA Oncol*. 2019;2019:7351350. doi:10.1155/2019/7351350
10. Solin LJ. Counterview: pre-operative breast MRI (magnetic resonance imaging) is not recommended for all patients with newly diagnosed breast cancer. *Breast*. 2010;19(1):7-9. doi:10.1016/j.breast.2009.11.004
11. Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. *Ann Surg*. 2013;257(2):249-255. doi:10.1097/SLA.0b013e31827a8d17
12. Thompson JL, Wright GP. The role of breast MRI in newly diagnosed breast cancer: an evidence-based review. *Am J Surg*. 2021;221(3):525-528. doi:10.1016/j.amjsurg.2020.12.018
13. Houssami N, Turner R, Macaskill P, et al. An individual person data meta-analysis of preoperative magnetic resonance imaging and breast cancer recurrence. *J Clin Oncol*. 2014;32(5):392-401. doi:10.1200/JCO.2013.52.7515
14. Gelardi F, Ragaini EM, Sollini M, Bernardi D, Chiti A. Contrast-enhanced mammography versus breast magnetic resonance imaging: a systematic review and meta-analysis. *Diagnostics (Basel)*. 2022;12(8):1890. doi:10.3390/diagnostics12081890
15. Cozzi A, Magni V, Zanardo M, Schiaffino S, Sardanelli F. Contrast-enhanced mammography: a systematic review and meta-analysis of diagnostic performance. *Radiology*. 2022;302(3):568-581. doi:10.1148/radiol.211412
16. Patel BK, Lobbes MBI, Lewin J. Contrast enhanced spectral mammography: a review. *Semin Ultrasound CT MR*. 2018;39(1):70-79. doi:10.1053/j.sult.2017.08.005
17. Fallenberg EM, Schmitzberger FF, Amer H, et al. Contrast-enhanced spectral mammography vs. mammography and MRI—clinical performance in a multi-reader evaluation. *Eur Radiol*. 2017;27(7):2752-2764. doi:10.1007/s00330-016-4650-6
18. Fortune-Greeley AK, Wheeler SB, Meyer AM, et al. Preoperative breast MRI and surgical outcomes in elderly women with invasive ductal and lobular carcinoma: a population-based study. *Breast Cancer Res Treat*. 2014;143(1):203-212. doi:10.1007/s10549-013-2787-4
19. Patel BK, Davis J, Ferraro C, et al. Value added of preoperative contrast-enhanced digital mammography in patients with invasive lobular carcinoma of the breast. *Clin Breast Cancer*. 2018;18(6):e1339-1345. doi:10.1016/j.clbc.2018.07.012
20. Chang JM, Leung JWT, Moy L, Ha SM, Moon WK. Axillary nodal evaluation in breast cancer: state of the art. *Radiology*. 2020;295(3):500-515. doi:10.1148/radiol.2020192534
21. Boughey JC, Ballman KV, Le-Petross HT, et al. Identification and resection of clipped node decreases the false-negative rate of sentinel lymph node surgery in patients presenting with node-positive breast cancer (T0–T4, N1–N2) who receive neoadjuvant chemotherapy: results from ACOSOG Z1071 (Alliance). *Ann Surg*. 2016;263(4):802-807. doi:10.1097/SLA.0000000000001375
22. Caudle AS, Yang WT, Krishnamurthy S, et al. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. *J Clin Oncol*. 2016;34(10):1072-1078. doi:10.1200/JCO.2015.64.0094
23. Provenzano E, Bossuyt V, Viale G, et al. Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. *Mod Pathol*. 2015;28(9):1185-1201. doi:10.1038/modpathol.2015.74
24. Majumder A, Singh M, Tyagi SC. Post-menopausal breast cancer: from estrogen to androgen receptor. *Oncotarget*. 2017;8(60):102739-102758. doi:10.18632/oncotarget.22156
25. Spring LM, Gupta A, Reynolds KL, et al. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. *JAMA Oncol*. 2016;2(11):1477-1486. doi:10.1001/jamaoncol.2016.1897
26. Alba E, Calvo L, Albanell J, et al. Chemotherapy (CT) and hormonotherapy (HT) as neoadjuvant treatment in luminal breast cancer patients: results from the GEICAM/2006-03, a multicenter, randomized, phase-II study. *Ann Oncol*. 2012;23(12):3069-3074. doi:10.1093/annonc/mds132
27. Kim HJ, Noh WC, Lee ES, et al. Efficacy of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy in premenopausal patients with oestrogen receptor-positive and HER2-negative, lymph node-positive breast cancer. *Breast Cancer Res*. 2020;22(1):54. doi:10.1186/s13058-020-01288-5
28. Von MG, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol*. 2012;30(15):1796-1804. doi:10.1200/JCO.2011.38.8595
29. Weber WP, Matrai Z, Hayoz S, et al. Tailored axillary surgery in patients with clinically node-positive breast cancer: pre-planned feasibility substudy of TAXIS (OPBC-03, SAKK 23/16, IBCSG 57-18, ABCSG-53, GBG 101). *Breast*. 2021;60:98-110. doi:10.1016/j.breast.2021.09.004
30. Yau C, Osdoit M, van der Noordaa M, et al. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. *Lancet Oncol*. 2022;23(1):149-160. doi:10.1016/S1470-2045(21)00589-1
31. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. *N Engl J Med*. 2021;384(25):2394-2405. doi:10.1056/NEJMoa2105215
32. Geyer CE, Garber JE, Gelber RD, et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. *Ann Oncol*. 2022;33(12):1250-1268. doi:10.1016/j.annonc.2022.09.159
33. Prat A, Galván P, Jimenez B, et al. Prediction of response to neoadjuvant chemotherapy using core needle biopsy samples with the Prosigna assay. *Clin Cancer Res*. 2016;22(3):560-566. doi:10.1158/1078-0432.CCR-15-0630
34. Qian Y, Daza J, Itzel T, et al. Prognostic cancer gene expression signatures: current status and challenges. *Cells*. 2021;10(3):648. doi:10.3390/cells10030648
35. Griguolo G, Bottosso M, Vernaci G, Miglietta F, Dieci MV, Guarneri V. Gene-expression signatures to inform neoadjuvant treatment decision in HR+/HER2− breast cancer: available evidence and

clinical implications. *Cancer Treat Rev*. 2022;102:1022323. doi:10.1016/j.ctrv.2021.102323

36. Boland MR, Al-Maksoud A, Ryan EJ, et al. Value of a 21-gene expression assay on core biopsy to predict neoadjuvant chemotherapy response in breast cancer: systematic review and meta-analysis. *Br J Surg*. 2021;108(1):24-31. doi:10.1093/bjs/znaa048
37. Davey MG, Ryan J, Boland MR, Barry MK, Lowery AJ, Kerin MJ. Clinical utility of the 21-gene assay in predicting response to neoadjuvant endocrine therapy in breast cancer: a systematic review and meta-analysis. *Breast*. 2021;58:113-120. doi:10.1016/j.breast.2021.04.010
38. 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(13):1485-1505. doi:10.1200/JCO.20.03399
39. Kuemmel S, Gluz O, Nitz U, et al. Abstract GS4-03: Neoadjuvant nab-paclitaxel weekly versus dose-dense paclitaxel followed by dose-dense EC in high risk HR+/HER2− early BC by: results from the neoadjuvant part of ADAPT HR+/HER2− trial. *Cancer Res*. 2021;81(4 suppl):GS4-G03. doi:10.1158/1538-7445.SABCS20-GS4-03
40. Iwata H, Masuda N, Yamamoto Y, et al. Validation of the 21-gene test as a predictor of clinical response to neoadjuvant hormonal therapy for ER+, HER2-negative breast cancer: the TransNEOS study. *Breast Cancer Res Treat*. 2019;173(1):123-133. doi:10.1007/s10549-018-4964-y
41. Curigliano G, Burstein HJ, Winer EP, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Ann Oncol*. 2019;30(7):1181. doi:10.1093/annonc/mdy537
42. Nielsen TO, Leung SCY, Rimm DL, et al. Assessment of Ki67 in breast cancer: updated recommendations from the International Ki67 in Breast Cancer Working Group. *J Natl Cancer Inst*. 2021;113(7):808-819. doi:10.1093/jnci/djaa201
43. Smith I, Robertson J, Kilburn L, et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. *Lancet Oncol*. 2020;21(11):1443-1454. doi:10.1016/S1470-2045(20)30458-7
44. Madigan LI, Dinh P, Graham JD. Neoadjuvant endocrine therapy in locally advanced estrogen or progesterone receptor-positive breast cancer: determining the optimal endocrine agent and treatment duration in postmenopausal women—a literature review and proposed guidelines. *Breast Cancer Res*. 2020;22(1):77. doi:10.1186/s13058-020-01314-6
45. Kurozumi S, Matsumoto H, Inoue K, et al. Impact of combining the progesterone receptor and preoperative endocrine prognostic index (PEPI) as a prognostic factor after neoadjuvant endocrine therapy using aromatase inhibitors in postmenopausal ER positive and HER2 negative breast cancer. *PLoS One*. 2018;13(8):e0201846. doi:10.1371/journal.pone.0201846
46. Ellis MJ, Suman VJ, Hoog J, et al. Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: results from the American College of Surgeons Oncology Group Z1031 Trial (Alliance). *J Clin Oncol*. 2017;35(10):1061-1069. doi:10.1200/JCO.2016.69.4406
47. Palmieri C, Cleator S, Kilburn LS, et al. NEOCENT: a randomised feasibility and translational study comparing neoadjuvant endocrine therapy with chemotherapy in ER-rich postmenopausal primary breast cancer. *Breast Cancer Res Treat*. 2014;148(3):581-590. doi:10.1007/s10549-014-3183-4
48. Torrisi R, Bagnardi V, Pruneri G, et al. Antitumour and biological effects of letrozole and GnRH analogue as primary therapy in premenopausal women with ER and PgR positive locally advanced operable breast cancer. *Br J Cancer*. 2007;97(6):802-808. doi:10.1038/sj.bjc.6603947
49. Zhang J, Lu CY, Chen HM, Wu SY. Neoadjuvant chemotherapy or endocrine therapy for invasive ductal carcinoma of the breast with high hormone receptor positivity and human epidermal growth factor receptor 2 negativity. *JAMA Netw Open*. 2021;4(3):e211785. doi:10.1001/jamanetworkopen.2021.1785
50. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018;379(2):111-121. doi:10.1056/NEJMoa1804710
51. Piccart M, van't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. *Lancet Oncol*. 2021;22(4):476-488. doi:10.1016/S1470-2045(21)00007-3
52. 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(2):377-387. doi:10.1007/s10549-015-3479-z
53. Kalinsky K, Barlow WE, Gralow JR, et al. 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. *N Engl J Med*. 2021;385(25):2336-2347. doi:10.1056/NEJMoa2108873
54. Kalinsky KM, Barlow WE, Gralow JR, et al. Abstract GS2-07: Updated results from a phase 3 randomized clinical trial in participants (pts) with 1–3 positive lymph nodes (LN), hormone receptor-positive (HR+) and HER2-negative (HER2−) breast cancer (BC) with recurrence score (RS) ≤ 25 randomized to endocrine therapy (ET) +/− chemotherapy (CT): SWOG S1007 (RxPONDER). *Cancer Res*. 2022;82(4 suppl):GS2-07. doi:10.1158/1538-7445.SABCS21-GS2-07
55. Piccart MJ, Kalinsky K, Gray R, et al. Gene expression signatures for tailoring adjuvant chemotherapy of luminal breast cancer: stronger evidence, greater trust. *Ann Oncol*. 2021;32(9):1077-1082. doi:10.1016/j.annonc.2021.05.804
56. Pagani O, Walley BA, Fleming GF, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer: long-term follow-up of the combined TEXT and SOFT trials. *J Clin Oncol*. 2023;41(7):1376-1382.doi:10.1200/JCO.22.01064
57. NRG Oncology. Evaluating the Addition of Adjuvant Chemotherapy to Ovarian Function Suppression Plus Endocrine Therapy in Premenopausal Patients With pN0–1, ER-Positive/HER2-Negative Breast Cancer and an Oncotype Recurrence Score Less Than or Equal to 25 (OFSET). ClinicalTrials.gov identifier NCT05879926. Accessed September 29, 2023. https://clinicaltrials.gov/study/NCT05879926?cond=BreastCancer&term=NCT05879926&rank=1
58. Azim HA, Malek RA, Azim HA Jr. Pathological features and prognosis of lobular carcinoma in Egyptian breast cancer patients. *Womens Health (Lond)*. 2014;10(5):511-518. doi:10.2217/whe.14.48
59. Oesterreich S, Nasrazadani A, Zou J, et al. Clinicopathological features and outcomes comparing patients with invasive ductal and lobular breast cancer. *J Natl Cancer Inst*. 2022;114(11):1511-1522. doi:10.1093/jnci/djac157
60. Weiser R, Polychronopoulou E, Hatch SS, et al. Adjuvant chemotherapy in patients with invasive lobular carcinoma and use of the 21-gene recurrence score: a National Cancer Database analysis. *Cancer*. 2022;128(9):1738-1747. doi:10.1002/cncr.34127
61. Loibl S, Volz C, Mau C, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. *Breast Cancer Res Treat*. 2014144(1):153-162. doi:10.1007/s10549-014-2861-6
62. Truin W, Voogd AC, Vreugdenhil G, van der Heiden-van der Loo M, Siesling S, Roumen RM. Effect of adjuvant chemotherapy in

postmenopausal patients with invasive ductal versus lobular breast cancer. *Ann Oncol*. 2012;23(11):2859-2865. doi:10.1093/annonc/mds180

63. Ruhstaller T, Giobbie-Hurder A, Colleoni M, et al. Adjuvant letrozole and tamoxifen alone or sequentially for postmenopausal women with hormone receptor-positive breast cancer: long-term follow-up of the BIG 1-98 trial. *J Clin Oncol*. 2019;37(2):105-114. doi:10.1200/JCO.18.00440
64. Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype—ACOSOG Z1031. *J Clin Oncol*. 2011;29(17):2342-2349. doi:10.1200/JCO.2010.31.6950
65. Bradley R, Braybrooke J, Gray R, et al. Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. *Lancet Oncol*. 2022;23(3):382-392. doi:10.1016/S1470-2045(21)00758-0
66. Johnston S, Puhalla S, Wheatley D, et al. Randomized phase II study evaluating palbociclib in addition to letrozole as neoadjuvant therapy in estrogen receptor-positive early breast cancer: PALLET trial. *J Clin Oncol*. 2019;37(3):178-189. doi:10.1200/JCO.18.01624
67. Lerebours F, Cabel L, Pierga JY. Neoadjuvant endocrine therapy in breast cancer management: state of the art. *Cancers (Basel)*. 2021;13(4):902. doi:10.3390/cancers13040902
68. Harbeck N, Gluz O, Kuemmel S, et al. Abstract GS4-04: Endocrine therapy alone in patients with intermediate or high-risk luminal early breast cancer (0–3 lymph nodes), recurrence score <26 and Ki67 response after preoperative endocrine therapy: Primary outcome results from the WSG-ADAPT HR+/HER2− trial. *Cancer Res*. 2021;81(4 suppl):GS4-04. doi:10.1158/1538-7445.SABCS20-GS4-04
69. Hunt KK, Suman VJ, Wingate HF, et al. Local-regional recurrence after neoadjuvant endocrine therapy: data from ACOSOG Z1031 (Alliance), a randomized phase 2 neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-positive clinical stage 2 or 3 breast cancer. *Ann Surg Oncol*. 2023;30(4):2111-2118. doi:10.1245/s10434-022-12972-5
70. Schmid P, Cortes J, Dent R, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. *N Engl J Med*. 2022;386(6):556-567. doi:10.1056/NEJMoa2112651
71. Schmid P, Cortes J, Dent R. Pembrolizumab in early triple-negative breast cancer. Reply. *N Engl J Med*. 2022;386(18):1771-1772. doi:10.1056/NEJMc2203316
72. Sharma P, Lopez-Tarruella S, García-Saenz JA, et al. Pathological response and survival in triple-negative breast cancer following neoadjuvant carboplatin plus docetaxel. *Clin Cancer Res*. 2018;24(23):5820-5829. doi:10.1158/1078-0432.CCR-18-0585
73. Sharma P, Kimler BF, O'Dea A, et al. Randomized phase II trial of anthracycline-free and anthracycline-containing neoadjuvant carboplatin chemotherapy regimens in stage I–III triple-negative breast cancer (NeoSTOP). *Clin Cancer Res* [Internet]. 2021;27(4):975-982. doi:10.1158/1078-0432.CCR-20-3646
74. Berruti A, Amoroso V, Gallo F, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. *J Clin Oncol*. 2014;32(34):3883-3891. doi:10.1200/JCO.2014.55.2836
75. Hahnen E, Lederer B, Hauke J, et al. Germline mutation status, pathological complete response, and disease-free survival in triple-negative breast cancer: secondary analysis of the GeparSixto randomized clinical trial. *JAMA Oncol*. 2017;3(10):1378-1385. doi:10.1001/jamaoncol.2017.1007
76. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. *Lancet Oncol*. 2018;19(4):497-509. doi:10.1016/S1470-2045(18)30111-6
77. Elghazaly H, Rugo HS, Azim HA, et al. Breast-Gynaecological & Immuno-Oncology International Cancer Conference (BGICC) consensus and recommendations for the management of triple-negative breast cancer. *Cancers (Basel)*. 2021;13(9):2262. doi:10.3390/cancers13092262
78. 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(10):1216-1235. doi:10.1016/j.annonc.2021.06.023
79. Loibl S, Weber KE, Timms KM, et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. *Ann Oncol*. 2018;29(12):2341-2347. doi:10.1093/annonc/mdy460
80. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J Clin Oncol*. 2015;33(1):13-21. doi:10.1200/JCO.2014.57.0572
81. Geyer CE, Sikov WM, Huober J, et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. *Ann Oncol*. 2022;33(4):384-394. doi:10.1016/j.annonc.2022.01.009
82. Bian L, Yu P, Wen J, et al. Survival benefit of platinum-based regimen in early stage triple negative breast cancer: a meta-analysis of randomized controlled trials. *NPJ Breast Cancer*. 2021;7(1):157. doi:10.1038/s41523-021-00367-w
83. Pathak N, Sharma A, Elavarasi A, et al. Moment of truth—adding carboplatin to neoadjuvant/adjuvant chemotherapy in triple negative breast cancer improves overall survival: an individual participant data and trial-level meta-analysis. *Breast*. 2022;64:7-18. doi:10.1016/j.breast.2022.04.006
84. Shepherd JH, Ballman K, Polley MYC, et al. CALGB 40603 (Alliance): long-term outcomes and genomic correlates of response and survival after neoadjuvant chemotherapy with or without carboplatin and bevacizumab in triple-negative breast cancer. *J Clin Oncol*. 2022;40(12):1323-1334. doi:10.1200/JCO.21.01506
85. Gupta S, Nair NS, Hawaldar R, et al. Abstract GS5-01: Addition of platinum to sequential taxane-anthracycline neoadjuvant chemotherapy in patients with triple-negative breast cancer: a phase III randomized controlled trial. *Cancer Res*. 2023;83(5 suppl):GS5-01. doi:10.1158/1538-7445.SABCS22-GS5-01
86. Sharma P, Stecklein SR, Yoder R, et al. Clinical and biomarker results of neoadjuvant phase II study of pembrolizumab and carboplatin plus docetaxel in triple-negative breast cancer (TNBC) (NeoPACT). 2022;40(16 suppl):513. doi:10.1200/JCO.2022.40.16_suppl.513
87. 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 randomised trials. *Lancet*. 2019;393(10179):1440-1452. doi:10.1016/S0140-6736(18)33137-4
88. 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(3):273-285. doi:10.1016/S1470-2045(23)00051-7

89. 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(22):1868-1875. doi:10.1200/JCO.19.00066
90. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. 2019;380(7):617-628. doi:10.1056/NEJMoa1814017
91. Untch M, Fasching PA, Konecny GE, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. *J Clin Oncol*. 2011;29(25):3351-3357. doi:10.1200/JCO.2010.31.4930
92. Jackisch C, Hegg R, Stroyakovskiy D, et al. HannaH phase III randomised study: association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. *Eur J Cancer*. 2016;62:62-75. doi:10.1016/j.ejca.2016.03.087
93. 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(9):2278-2284. doi:10.1093/annonc/mdt182
94. 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 multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19(12):1630-1640. doi:10.1016/S1470-2045(18)30570-9
95. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials. *Lancet*. 2023;401(10384):1277-1292. doi:10.1016/S0140-6736(23)00285-4
96. National Comprehensive Cancer Network (NCCN). Breast Cancer. NCCN Guidelines, Version 4. Accessed September 29, 2023. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419
97. Kolberg-Liedtke C, Lüftner D, Brucker SY, et al. Practice-changing perspectives regarding systemic therapy in early breast cancer: opinions of German experts regarding the 17th St. Gallen International Consensus Conference. *Breast Care (Basel)*. 2022;17(3):336-345. doi:10.1159/000517501
98. Lievens Y, Guckenberger M, Gomez D, et al. Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. *Radiother Oncol*. 2020;148:157-166. doi:10.1016/j.radonc.2020.04.003
99. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO International Consensus Guidelines for advanced breast cancer (ABC 5). *Ann Oncol*. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010
100. Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *Lancet Oncol*. 2015;16(13):1380-1388. doi:10.1016/S1470-2045(15)00135-6
101. Khan SA, Zhao F, Solin LJ, et al. A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: a trial of the ECOG-ACRIN Research Group (E2108) [abstract]. 2020;38(18 suppl):LBA2. doi:10.1200/JCO.2020.38.18_suppl.LBA2
102. Hong JC, Ayala-Peacock DN, Lee J, et al. Classification for long-term survival in oligometastatic patients treated with ablative radiotherapy: a multi-institutional pooled analysis. *PLoS One*. 2018;13(4):e0195149. doi:10.1371/journal.pone.0195149
103. King TA, Lyman JP, Gonen M, et al. Prognostic impact of 21-gene recurrence score in patients with stage IV breast cancer: TBCRC 013. *J Clin Oncol*. 2016;34(20):2359-2365. doi:10.1200/JCO.2015.63.1960
104. Soran A, Ozmen V, Ozbas S, et al. Randomized trial comparing resection of primary tumor with no surgery in stage IV breast cancer at presentation: protocol MF07-01. *Ann Surg Oncol*. 2018;25(11):3141-3149. doi:10.1245/s10434-018-6494-6
105. Ellis MJ, Tao Y, Luo J, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. *J Natl Cancer Inst*. 2008;100(19):1380-1388. doi:10.1093/jnci.djn309
106. Smith IE, Dowsett M, Ebbs SR, et al.; IMPACT Trialists Group. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. *J Clin Oncol*. 2005;23(22):5108-5116. doi:10.1200/JCO.2004.04.005
107. Ma CX, Suman V, Leitch AM, et al. Abstract GS4-05: Neoadjuvant chemotherapy (NCT) response in postmenopausal women with clinical stage II or III estrogen receptor positive (ER+) and HER2 negative (HER2−) breast cancer (BC) resistant to endocrine therapy (ET) in the ALTERNATE trial (Alliance A011106). *Cancer Res*. 2021;81(4 suppl):GS4-05. doi:10.1158/1538-7445.SABCS20-GS4-05
108. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2023;24(1):77-90. doi:10.1016/S1470-2-45(22)00694-5
109. Martin M, Hegg R, Kim SB, et al. Treatment with adjuvant abemaciclib plus endocrine therapy in patients with high-risk early breast cancer who received neoadjuvant chemotherapy: a prespecified analysis of the monarchE randomized clinical trial. *JAMA Oncol*. 2022;8(8):1190-1194. doi:10.1001/jamaoncol.2022.1488
110. Yau C, Osdoit M, van der Noordaa M, et al. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. *Lancet Oncol*. 2022;23(1):149-160. doi:10.1016/S1470-2045(21)00589-1
111. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2−, node-positive, high-risk, early breast cancer (monarchE). *J Clin Oncol*. 2020;38(34):3987-3998. doi:10.1200/JCO.20.02514
112. Bruno L, Ostinelli A, Waisberg F, et al. Cyclin-dependent kinase 4/6 inhibitor outcomes in patients with advanced breast cancer carrying germline pathogenic variants in DNA repair-related genes. *JCO Precis Oncol*. 2022;6:e210040. doi:10.1200/PO.21.00140
113. National Cancer Institute. Pembrolizumab vs. observation in people with triple-negative breast cancer who had a pathologic complete response after chemotherapy plus pembrolizumab (ClinicalTrials.gov identifier NCT05812807). Accessed September 4, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT05812807
114. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med*. 2017;376(22):2147-2159. doi:10.1056/NEJMoa1612645
115. Shah AN, Flaum L, Helenowski I, et al. Phase II study of pembrolizumab and capecitabine for triple negative and hormone receptor-positive, HER2-negative endocrine-refractory metastatic breast cancer. *J Immunother Cancer*. 2020;8(1):e000173. doi:10.1136/jitc-2019-000173

116. Barrios C, Harbeck N, Zhang HA, et al. LBA1 Final analysis of the placebo-controlled randomised phase III IMpassion031 trial evaluating neoadjuvant atezolizumab (atezo) plus chemotherapy (CT) followed by open-label adjuvant atezo in patients (pts) with early-stage triple-negative breast cancer (eTNBC) [abstract]. *ESMO Open*. 2023;8(1 suppl 4):101571. doi:10.1016/j.esmoop.2023.101571
117. Asleh K, Lluch A, Goytain A, et al. Triple-negative PAM50 non-basal breast cancer subtype predicts benefit from extended adjuvant capecitabine. *Clin Cancer Res*. 2023;29(2):389-400. doi:10.1158/1078-0432.CCR-22-2191
118. Prat A, Adamo B, Cheang MCU, Anders CK, Carey LA, Perou CM. Molecular characterization of basal-like and non-basal-like triple-negative breast cancer. *Oncologist*. 2013;18(2):123-133. doi:10.1634/theoncologisst.2012-0397
119. Pusztai L, Yau C, Wolf DM, et al. Durvalumab with olaparib and paclitaxel for high-risk HER2-negative stage II/III breast cancer: results from the adaptively randomized I-SPY2 trial. *Cancer Cell*. 2021;39(7):989-998.e5. doi:10.1016/j.ccell.2021.05.009
120. Antonarakis ES, Park SH, Goh JC, et al. Pembrolizumab plus olaparib for patients with previously treated and biomarker-unselected metastatic castration-resistant prostate cancer: the randomized, open-label, phase III KEYLYNK-010 Trial. *J Clin Oncol*. 2023;41(22):3839-3850. doi:10.1200/JCO.23.00233
121. 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(13):1448-1457. doi:10.1200/JCO.20.01204
122. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol*. 2010;11(10):927-933. doi:10.1016/S1470-2045(10)70207-2
123. 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(1):80-91.e7. doi:10.1016/j.clbc.2020.09.014
124. Barcenas CH, Hurvitz SA, Di Palma JA, et al. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: the CONTROL trial. *Ann Oncol*. 2020;31(9):1223-1230. doi:10.1016/j.annonc.2020.05.012
125. Cullinane C, Shrestha A, Al Maksoud A, et al. Optimal timing of surgery following breast cancer neoadjuvant chemotherapy: a systematic review and meta-analysis. *Eur J Surg Oncol*. 2021;47(7):1507-1513. doi:10.1016/j.ejso.2021.01.025
126. Suleman K, Almalik O, Haque E, et al. Does the timing of surgery after neoadjuvant therapy in breast cancer patients affect the outcome? *Oncology*. 2020;98(3):168-173. doi:10.1159/000504964
127. Tee SR, Devane LA, Evoy D, et al. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. *Br J Surg*. 2018;105(12):1541-1552. doi:10.1002/bjs/10986
128. Classe JM, Loaec C, Gimbergues P, et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. *Breast Cancer Res Treat*. 2019;173(2):343-352. doi:10.1007/s10549-018-5004-7
129. Boughey JC, Alvarado MD, Lancaster RB, et al. Surgical standards for management of the axilla in breast cancer clinical trials with pathological complete response endpoint. *NPJ Breast Cancer*. 2018;4(1):26. doi:10.1038/s41523-018-0074-6
130. Silverstein MJ, Skinner KA, Lomis TJ. Predicting axillary nodal positivity in 2282 patients with breast carcinoma. *World J Surg*. 2001;25(6):767-772. doi:10.1007/s00268-001-0003-x
131. Barrio AV, Montagna G, Mamtani A, et al. Nodal recurrence in patients with node-positive breast cancer treated with sentinel node biopsy alone after neoadjuvant chemotherapy—a rare event. *JAMA Oncol*. 2021;7(12):1851-1855. doi:10.1001/jamaoncol.2021.4394[
132. Dubsky P, Pinker K, Cardoso F, et al. Breast conservation and axillary management after primary systemic therapy in patients with early-stage breast cancer: the Lucerne toolbox. *Lancet Oncol*. 2021;22(1):e18-28. doi:10.1016/S1470-2045(20)30580-5
133. Morrow M, Foster RSJ. Staging of breast cancer: a new rationale for internal mammary node biopsy. *Arch Surg*. 1981;116(6):748-751.
134. Dogan BE, Dryden MJ, Wei W, et al. Sonography and sonographically guided needle biopsy of internal mammary nodes in staging of patients with breast cancer. *AJR Am J Roentgenol*. 2015;205(4):905-911. doi:10.2214/AJR.15.14307
135. Rusthoven CG, Rabinovitch RA, Jones BL, et al. The impact of postmastectomy and regional nodal radiation after neoadjuvant chemotherapy for clinically lymph node-positive breast cancer: a National Cancer Database (NCDB) analysis. *Ann Oncol*. 2016;27(5):818-827. doi:10.1093/annonc/mdw046
136. Daveau C, Stevens D, Brain E, et al. Is regional lymph node irradiation necessary in stage II to III breast cancer patients with negative pathologic node status after neoadjuvant chemotherapy? *Int J Radiat Oncol Biol Phys*. 2010;78(2):337-342. doi:10.1016/j.ijrobop.2009.08.053
137. Noh JM, Park W, Suh CO, et al. Is elective nodal irradiation beneficial in patients with pathologically negative lymph nodes after neoadjuvant chemotherapy and breast-conserving surgery for clinical stage I--III breast cancer? A multicentre retrospective study (KROG 12-05). *Br J Cancer*. 2014;110(6):1420-1426. doi:10.1038/bjc.2014.26
138. Mamounas EP, Bandos H, White JR, et al. Abstract OT2-03-02: NRG oncology/NSABP B-51/RTOG 1304: phase III trial to determine if chest wall and regional nodal radiotherapy (CWRNRT) post mastectomy (Mx) or the addition of RNRT to breast RT post breast-conserving surgery (BCS) reduces invasive breast cancer recurrence-free interval (IBCSR-FI) in patients (pts) with positive axillary (PAx) nodes who are ypN0 after neoadjuvant chemotherapy (NC). *Cancer Res*. 2018;78(4 suppl):OT2-03–02. doi:10.1158/1538-7445.SABCS17-OT2-03-02
139. Kim KH, Noh JM, Kim YB, et al. Does internal mammary node irradiation affect treatment outcome in clinical stage II–III breast cancer patients receiving neoadjuvant chemotherapy? *Breast Cancer Res Treat*. 2015;152(3):589-599. doi:10.1007/s10549-015-3505-1

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