

Neoadjuvant Management of Early Breast Cancer: A Clinical and Investigational Position Statement

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ABSTRACT

Background. Neoadjuvant treatment is increasingly one of the preferred therapeutic options for early breast cancer and may have some unique outcomes, such as identifying predictive and prognostic factors of response or increasing the knowledge of individual tumor biology.

Design. A panel of experts from different specialties reviewed published clinical studies on the neoadjuvant management of breast cancer. Recommendations were made that emphasized the clinical multidisciplinary management and the investigational leverage in early breast cancer.

Results. Neoadjuvant therapy has equivalent efficacy to adjuvant therapy, and it has some additional benefits that include increasing breast conservation, assessing tumor response, establishing prognosis based on the pathological response, and providing a “second opportunity” for nonresponding patients. Achieving pathological complete remission because

of neoadjuvant therapy has been correlated with long-term clinical benefit, particularly in HER2-positive and triple-negative breast cancer. In addition, the neoadjuvant setting is a powerful model for the development of new drugs and the identification of prognostic markers. Finally, neoadjuvant therapy has proven to be cost-effective by reducing nondrug costs, avoiding radical surgery, and reducing hospital stays when compared with other treatment approaches.

Conclusion. Neoadjuvant therapy has clinical benefits in early breast cancer and provides in vivo information of individual breast cancer biology while allowing the investigation of new treatment approaches. Access to neoadjuvant therapy should be an option available to all patients with breast cancer through multidisciplinary tumor management. *The Oncologist* 2019;24:1–9

Implications for Practice: Neoadjuvant treatment should be strongly considered as a therapeutic option for localized breast cancer and is a powerful tool for understanding breast cancer biology and investigating new treatment approaches.

INTRODUCTION

In early breast cancer, neoadjuvant therapy has become one of the preferred treatment options [1–5]. Its efficacy has been proven to be equivalent to adjuvant therapy, in terms of both overall survival (OS) and progression-free survival (PFS), and it has also shown value from research and cost perspectives [6, 7]. In most specialist hospitals, it is standard practice to assess patients with early breast cancer in multidisciplinary

committees before local treatment delivery, and this has been shown to extend the efficacy of neoadjuvant care [8].

Systemic medical therapy reduces the risk of distant metastasis and increases OS, when initiated either after surgery (adjuvant therapy) or before surgery (neoadjuvant therapy), because often the same drugs and regimens are employed [9]. In general, any patient who is a candidate

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for adjuvant systemic therapy can be considered for neoadjuvant therapy [1]. Neoadjuvant therapy has some particular advantages that distinguish it from adjuvant treatment. First, it reduces tumor size, which facilitates surgical resectability and increases breast-conserving surgery (BCS) rates [10], and it also can eliminate axillary node metastasis that may be detected in sentinel node biopsy after neoadjuvant treatment [11]. Second, it enables an objective evaluation of treatment efficacy, allowing an *in vivo* test of cancer cells' sensitivity to treatment. If no response occurs, the therapy can be modified, thus avoiding side effects from ineffective treatment [12]. Pathological complete response (pCR) is associated with longer PFS and OS, especially in the case of triple-negative and HER2-positive tumors [13–17]. Third, it allows the design of clinical trials with novel research approaches for adjuvant treatment, because there is no standard treatment after failure to respond to neoadjuvant therapy. Patients with residual disease after neoadjuvant therapy could benefit from clinical trials involving new treatments in the adjuvant setting. Fourth, it provides information about tumor biology, enabling prognostic and predictive biomarkers to be sought. Obtaining tumor specimens and blood samples from the patient before, during, and after neoadjuvant treatment can reveal biomarkers that might prove crucial to research. Lastly, clinical trials involving neoadjuvant treatment offer advantages compared with the adjuvant setting. For example, they require smaller patient populations, results are obtained early, pathological response is a reliable endpoint that can be related to long-term prognosis, and such trials lend themselves to innovative designs for the development of new drugs.

In this study, a panel of experts was convened by the Spanish Society of Medical Oncology (SEOM) in order to review published clinical and investigational studies related to the neoadjuvant management of breast cancer and define a comprehensive clinical and research position involving all forms of neoadjuvant therapies. Recommendations are made emphasizing the clinical multidisciplinary management and the investigational leverage of the neoadjuvant approach in early breast cancer.

OVERALL MANAGEMENT OF NEOADJUVANT THERAPY

Selecting Cases for Neoadjuvant Therapy

Relevant clinical practice guidelines for localized breast cancer (National Comprehensive Cancer Network [NCCN] [18], European Society for Medical Oncology [ESMO] [19], or SEOM [2]) recommend using neoadjuvant therapy depending on such aspects as tumor size and molecular features, nodal involvement, patient performance status, and comorbidities. Full clinical information must be provided to patients, explaining the advantages and disadvantages of BCS and neoadjuvant treatments in a comprehensible manner.

There are several clinical goals for neoadjuvant therapy: first, achieving a pCR (which has prognostic utility in HER-2 and triple-negative subtypes); second, increasing breast preservation rate (applicable to all tumors); third, providing a “second opportunity” for those patients not achieving a pCR

Table 1. Patient selection criteria for neoadjuvant therapy in early breast cancer

Selection criteria	Level of evidence [reference]
Clinical lymph node involvement	A [1, 2]
Size >2 cm	B [1, 2]
Triple-negative	B [22, 23]
HER2-positive	B [24, 25]
High proliferative index	B [26]
Unresectable tumors	A [1, 2]
Inflammatory carcinoma	B [1–3]

(particularly patients with estrogen-receptor [ER]-negative tumors) by introducing a non-cross-resistant adjuvant therapy [20].

Extent

For patients with operable breast cancer, including those who are candidates for surgery at diagnosis, neoadjuvant therapy followed by surgery has become an alternative option to initial surgery. There is no one single definition of a tumor size or clinical characteristic that can establish whether the patient will benefit from neoadjuvant therapy, although some centers favor those cases in which a breast carcinoma is either larger than 2 cm or has clinically involved axillary nodes (Table 1). However, when assessing clinical advantages and treatment, if the surgical options and/or the long-term outcomes are improved, then the indication for neoadjuvant therapy is clear. Tumor characteristics and axillary status at diagnosis and before neoadjuvant therapy and response after neoadjuvant therapy are important in surgical decision making [21].

Histological and Molecular Features

The breast cancer subtypes that benefit most from neoadjuvant therapy are those that will show the greatest treatment response, which are triple-negative and HER2-positive tumors (Table 1). Up to 45% of triple-negative tumors show a pCR after neoadjuvant chemotherapy. This is important because triple-negative tumors with a pCR have a similar prognosis to other subtypes that also display a pCR. In contrast, triple-negative tumors with residual disease have a high probability of recurrence [22, 23].

For HER2-positive tumors, several studies have demonstrated a high pCR rate after neoadjuvant therapy that includes anti-HER2 treatment, which can be up to 60% pCR with the newest drug regimens and is higher in ER-negative than in ER-positive cases. An association is seen between pCR and increased PFS and OS in HER2-positive tumors [24].

Regarding luminal-like tumors, neoadjuvant chemotherapy achieves a lower rate of pCR in comparison with other subtypes, with a pCR rate of around 10%–24% [25]. It has been shown that in this ER-positive population, high Ki67 expression increases the probability of a pCR [26, 27].

Genomic platforms may be useful in defining which cases of hormone-sensitive early breast cancer may benefit of the addition of chemotherapy to hormonal therapy. A very recent publication shows that adjuvant chemotherapy is not indicated in patients with hormone receptor-positive, lymph node-negative cancer who are at intermediate Oncotype

Dx risk [28]. In these cases, the use of neoadjuvant chemotherapy would likewise not be of benefit.

Clinical Status

The patient's general state of health and comorbidities will drive the indications for treatment. Age by itself is not a contraindication for surgery.

Accurate clinical staging at baseline is critical because in certain clinical situations, some or all forms of neoadjuvant systemic therapy might not be the best clinical choice [18]. Tumors with extensive involvement of carcinoma in situ, for example, in which the extent of the invasive component is not well defined, would better be staged surgically.

Patient Information

Neoadjuvant therapy as a treatment option must always be thoroughly discussed with patients, in order to consider benefits and risks and the impact of neoadjuvant therapy on surgical options. Patients' opinions and preferences about preserving the breast and the management of the axilla after neoadjuvant therapy must be carefully considered and recorded.

Importance of Multidisciplinary Breast Cancer Committees in Neoadjuvant Therapy

The best management of breast cancer requires a multidisciplinary approach to the disease. Accordingly, many hospitals have set up multidisciplinary breast cancer committees, which discuss the different features of each case in order to decide the best treatment option. In Spanish hospitals, 74% of breast cancer cases are discussed in multidisciplinary committees at the time of diagnosis [29].

Because the development and operation of committees differ between hospitals, and to ensure fairness of patient access to neoadjuvant treatment, it is essential to understand the advantages and implement all recommendations about multidisciplinary management of neoadjuvant therapy.

Selecting Drugs for Neoadjuvant Therapy

Neoadjuvant medical treatment in breast cancer can include chemotherapy, targeted treatments such as anti-HER2 therapy, and hormone therapy.

Chemotherapy

The choice of chemotherapy regimen will depend on the patient's clinical status and tumor subtype. Therapies with proven efficacy include doxorubicin and cyclophosphamide (AC); epirubicin and cyclophosphamide (EC); fluorouracil, epirubicin, and cyclophosphamide (FEC) or fluorouracil, doxorubicin, and cyclophosphamide (FAC); AC followed by weekly paclitaxel (AC → P); AC followed by docetaxel (AC → D); taxane, doxorubicin, and cyclophosphamide (TAC); or carboplatin and taxane (CbT) in triple-negative tumors. The preplanned number of treatment cycles must be completed whenever possible if tolerated, even if the tumor is significantly reduced or disappears.

Using weekly paclitaxel has shown efficacy and a good toxicity profile [30]. Adding carboplatin can be considered in patients with a mutation in the *BRCA* gene, although clinical studies are inconclusive on this point [31, 32]. Regimens

containing EC or AC may be dose-dense in the case of high-grade and hormone receptor-negative tumors [33, 34]. There seems to be insufficient evidence for routinely substituting paclitaxel for nab-paclitaxel as a component of neoadjuvant chemotherapy, given the differing results of the ETNA and the GBG69 trials [35–37].

A recent review shows that information provided by genomic platforms may be useful in predicting the response to chemotherapy, although platforms might not be useful in indicating anti-HER2 therapy [38].

Anti-HER2 Therapy

In HER2-positive breast tumors, neoadjuvant trastuzumab used in combination with standard chemotherapy is capable of inducing a 30% pCR rate [25, 39, 40].

More recently, a dual HER2 antibody blockade using trastuzumab plus pertuzumab combined with chemotherapy achieved pCR rates in the range of 50% to 60% (NeoSphere and TRYPHAENA studies) [41–43]. This pCR rate was confirmed in the GeparSepto [44], KRISTINE [45], Symphony [46], and BERENICE [47] studies.

Before surgery, the most common chemotherapy combinations used are AC or FEC for 3–4 months followed by weekly paclitaxel for 12 weeks, AC or FEC for 3–4 months followed by docetaxel for 3–4 months, and docetaxel and carboplatin for 6 months. After surgery, anti-HER2 therapy is continued for 12 months.

The overall results of various studies involving lapatinib, a HER2 tyrosine kinase inhibitor, in neoadjuvant therapy do not support its use in this indication [47–52].

Using anthracyclines in combination with trastuzumab may increase the risk of cardiac toxicity. However, no increase was seen in the BERENICE study, in which pertuzumab was added to the standard treatment, even when administered simultaneously with anthracyclines [53].

Hormone Therapy

Neoadjuvant hormone therapy is indicated to reduce the extent of the tumor and allow appropriate surgery in patients who are eligible for neoadjuvant treatment but not with chemotherapy, such as elderly patients. In postmenopausal women, an aromatase inhibitor (such as anastrozole, letrozole, or exemestane) is preferred over tamoxifen [54–56]. Currently, there is no evidence that one aromatase inhibitor is more effective than any other [57]. In premenopausal patients, there is also little evidence on this point. Some authors have suggested using surgery as the first option, even if BCS is not feasible [58, 59].

The minimum duration of treatment is 3 to 4 months, and this period can be extended until maximal response is achieved prior to surgery [60, 61]. Some clinical trials have compared the use of neoadjuvant hormone treatment with the use of neoadjuvant chemotherapy in postmenopausal women with ER-positive breast cancer and have reported similar results between the two neoadjuvant approaches. A phase II study carried out in 239 patients with ER-positive and/or PR-positive tumors found no differences between aromatase inhibitors (anastrozole or exemestane) and four cycles of doxorubicin-paclitaxel chemotherapy either in response rate (64.5% vs. 63.6%, respectively; $p > .5$) or in BCS (33% vs. 24%,

respectively; $p = .058$) [62]. In a phase II study by the Spanish Breast Cancer Research Group (GEICAM) in luminal tumors, exemestane was compared with chemotherapy (four cycles of epirubicin-cyclophosphamide followed by four cycles of docetaxel). The authors reported that response rates showed nonsignificant differences (48% vs. 66%, respectively; $p = .075$) and that there were no differences in BCS rates between the two treatment arms (56% vs. 47%, respectively; $p = .23$) [63].

A limitation of neoadjuvant endocrine therapy is that pCR is uncommon and, thus, not an effective surrogate of clinical outcome [64]. Several phase II studies have evaluated the effects of neoadjuvant cyclin-dependent kinase inhibitors in combination with endocrine therapy or endocrine therapy plus anti-HER2 therapies in ER-positive/HER2-positive breast carcinoma [65–67]. Early evaluation of proliferation markers shows an effect of adding palbociclib, although pCRs are still limited.

Surgical Issues Regarding Neoadjuvant Treatment

Mammography and breast and axillary ultrasound are the most common imaging studies performed to assess tumor size and axillary status. In addition, magnetic resonance imaging has been shown to improve accuracy in estimating post-chemotherapy residual disease [68]. Baseline characteristics are important, and assessing what type of surgery is planned is crucial for the decision-making process after neoadjuvant therapy [69]. Initial tumor size should not influence the type of surgery that the patient is eligible to undergo until the response is assessed. Breast cancer surgery rates have not increased in correlation with the higher pCR rates, and, as seen when analyzed in the NeoALTO trial, improvements in this approach are needed [70]. By reducing the size of the primary tumor with neoadjuvant chemotherapy, there is potential for improving the cosmetic result of surgery, even for patients who were candidates for BCS at presentation. Neoadjuvant therapy also downstages axillary lymph node involvement in a significant proportion of patients—close to 40% when treatment includes an anthracycline plus a taxane, and in more than half of patients with HER2-positive breast cancer who receive chemotherapy plus anti-HER2 therapy. This is clinically important because the use of sentinel lymph node biopsy after neoadjuvant therapy has been increasing. In those patients with clinically negative nodes at diagnosis, sentinel lymph node biopsy has proven to be accurate and to have high identification rates; patients with negative results can be spared a full axillary lymph node dissection. In patients with clinically positive nodes before neoadjuvant therapy that convert to negative, several randomized trials have reported a false negative rate of <10% when a dual tracer is used and more than two sentinel lymph nodes are excised. False negative rates can be lowered with the use of targeted axillary dissection [71]. Whether patients who are downstaged to a negative axilla can be safely spared an axillary lymph node dissection is still controversial, and further research is needed.

A recent meta-analysis of neoadjuvant chemotherapy from 10 EBCTG trials performed before 2005 confirmed an improvement in BCS rate over adjuvant chemotherapy, without

compromising on distant recurrence, breast cancer survival, or OS [72]. The authors observed a higher local recurrence rate with breast-conserving therapy over mastectomy, which is one part of breast-conserving procedures [73].

Standardization of Pathological Studies

Neoadjuvant treatment has an important impact for pathologists, as the handling and reporting of breast cancer specimens in this setting require specific considerations. Multicenter breast cancer clinical trial studies have indicated that there is a huge variation in the handling and reporting of specimens [74]. The pathologist's task in assessing post-neoadjuvant therapy specimens may be further complicated by the fact that the definition of pCR is not uniformly standardized, which can create further challenging issues with the interpretation and reporting of the data. The Residual Disease Characterization Working Group on behalf of the Breast International Group-North American Breast Cancer Group Collaboration has published recommendations for the standardization of the pathological evaluation and reporting of post-neoadjuvant specimens in clinical trials of breast cancer [75]. These recommendations include information about pCR as defined by the U.S. Food and Drug Administration (FDA). A group of Spanish pathologists with expertise in neoadjuvant therapy for breast cancer has recently reported a consensus on these important issues with the aim of standardizing the handling, analysis, and reporting of breast cancer specimens, both in the context of clinical trials and in daily practice [76].

NEOADJUVANT THERAPY AS A MODEL FOR ADVANCING NEW DRUG RESEARCH

The Value of pCR as an Endpoint for New Drug Development

After Cortazar et al. published a pooled analysis of neoadjuvant clinical trial results in 2014 that included data from almost 12,000 patients, the predictive value of achieving pCR at the time of surgery after standard neoadjuvant therapy was firmly established for the various breast cancer subtypes [14]. This analysis found that achieving a pCR was associated with longer recurrence-free survival (RFS) and OS, especially in triple-negative tumors treated with chemotherapy (RFS: hazard ratio [HR] 0.24, 95% confidence interval [CI] 0.18–0.33; OS: HR 0.16, 95% CI 0.11–0.25) and in HER2-positive, hormone receptor-negative tumors treated with trastuzumab plus chemotherapy (RFS: HR 0.15, 95% CI 0.09–0.27; OS: HR 0.08, 95% CI 0.03–0.22). For other tumor types, the same trend was seen, although it did not attain statistical significance.

Based on the association between pCR and long-term outcomes for patients with breast cancer, the FDA published guidelines in 2014 proposing the use of pCR as a valid outcome measure for obtaining accelerated approval of new drugs in development [77, 78]. In that document, the FDA clearly stated its intention to facilitate the development of new drugs to treat breast cancer using the neoadjuvant model as a platform for testing new medicines that might improve patient survival, especially in the case

of more aggressive tumors. The FDA's proposed model for achieving drug approval requires a randomized study, with the primary objective of demonstrating superiority of the study drug in terms of pCR, and a subsequent confirmatory trial demonstrating a clinically and statistically significant benefit in RFS, PFS, or OS for the test drug.

This proposal became a reality after the pCR results obtained in the NeoSphere and TRYPHAENA studies [41–43], with the FDA granting approval for pertuzumab plus trastuzumab in the neoadjuvant treatment of patients with HER2-positive breast cancer.

The Neoadjuvant Setting in Research

Using the neoadjuvant model in research has brought about a paradigm shift in the approval of new drugs for treating breast cancer. Traditionally, drugs were developed to treat metastatic disease, and it took years for them to be used in early treatment of the disease. The current aim is to enable patients to benefit as soon as possible from more effective treatments without losing sight of the necessary balance between safety and efficacy, when the disease is curable [78]. Clinical practice provides examples of drugs being developed in parallel in the neoadjuvant and metastatic settings. These include cyclin inhibitors, phosphoinositide 3-kinase (PI3K) inhibitors, and the tyrosine kinase inhibitor neratinib.

Investigational Advantages of the Neoadjuvant Model

Using the neoadjuvant model in research has three advantages: first, clinically objective results are obtained in a few months; second, the potential for obtaining evidence of efficacy by treating fewer patients than required in studies in the adjuvant setting; and third, the possibility of conducting in vivo studies of biomarkers that can be used as prognostic factors or predictors of response to a standard neoadjuvant therapy or in studies of short duration (window studies).

New predictive biomarkers can be identified from a baseline biopsy. One such example might be the identification of mutations in *GATA3* and suppression of cell proliferation with aromatase inhibitors. This has been done in two phase II studies by massive sequencing of samples obtained from patients treated with aromatase inhibitors [79].

Early biomarkers of response can also be identified from the biopsy of a cancer specimen once treatment has started. Ki67 and the preoperative endocrine prognostic index (PEPI) are examples. After 2 weeks of exposure to endocrine therapy for hormone receptor-positive tumors, Ki67 expression showed a statistically significant association with lower RFS ($p = .004$). This was not the case with the baseline biopsy [80]. Another study tested the effect of everolimus on Ki67 levels when added to letrozole in the neoadjuvant setting. Everolimus was found to increase the efficacy of letrozole by reducing Ki67 levels compared with placebo [81]. The results of this small study heralded the benefit of combined exemestane and everolimus in metastatic disease, as demonstrated years later in the BOLERO-2 phase III registry study [82].

Residual tissue obtained during surgery on patients who fail to achieve pCR can be used to identify biomarkers of resistance. This is a valuable information source for discovering mechanisms of resistance to the treatment used,

by identifying compensatory alternative pathways in residual cells. For example, the use of NanoString technology in triple-negative tumors identified the *DUSP4* gene, a negative regulator of ERK, low expression of which was associated with greater proliferation, worse survival, and greater sensitivity to MEK inhibition [83]. More recently, Karagianis et al. observed an increase of the mammalian-enabled protein (MENA), which regulates actin structure and cell motility, in 20 cases of residual tumor after therapy [84]. These findings help identify mechanisms of resistance to neoadjuvant chemotherapy, for which experimental drugs may prove effective in breaking [85]. Because only cases without a pCR having residual malignant tissue can be evaluated after neoadjuvant therapy, markers of response to therapy cannot be evaluated at the molecular level.

Investigational Limitations of the Neoadjuvant Model

Despite the great advantages of using the neoadjuvant model for research, limitations also exist. Although an increase in pCR obtained by a cancer drug generally translates into a benefit in the adjuvant or metastatic setting, there are some exceptions, bevacizumab being one such case. The GeparQuinto study demonstrated an increase in pCR in triple-negative tumors treated with neoadjuvant bevacizumab [86]. However, this benefit has not been achieved in the adjuvant setting, as confirmed by the BEATRICE phase III trial [53, 87]. Therefore, study results obtained in a certain indication cannot always be extended to other indications within the same disease.

The risk-benefit balance of neoadjuvant treatment must be carefully evaluated. Neoadjuvant therapy should be used in high-risk populations such as patients with triple-negative or HER2-positive disease or with luminal tumors in the presence of an additional risk factor such as high-grade or high Ki67 [3].

Developing early pharmacodynamic or metabolic markers of response, as was suggested several years ago, may help in addressing some of these limitations. In recent research, Ki67 showed a significant drop in the NeoPredict trial [88] that can be used to adapt the therapies, and FDG PET/CT identified patients with an increased likelihood of pCR in the neoadjuvant NeoALTTO trial [89].

FUTURE DIRECTIONS OF NEOADJUVANT THERAPY EVALUATION

Currently, economic considerations are generally not part of the management of early breast cancer, particularly because there are many situations in which the cost cannot be estimated. In some homogeneous subsets of cases, however, economic analysis may be reasonable. From 2000 to 2015, several studies were published evaluating the cost-effectiveness of drugs, of which only three were in the neoadjuvant setting (37 drugs were in the metastatic setting, and 101 were in the adjuvant setting) [90]. A substantial number of these studies have focused on HER2-positive breast cancer. Table 2 highlights the most relevant of these studies.

The three published studies of neoadjuvant therapy analyzed the addition of pertuzumab in HER2-positive tumors from the results of the TRYPHAENA and the NeoSphere trials. The Canadian article of Attard et al. described a favorable

Table 2. Summary of the most important cost-effectiveness analyses on targeted HER2 therapies

Comparators	Country	ICER/QALY	Conclusion
Neoadjuvant therapy			
Pertuzumab + trastuzumab + taxane vs. trastuzumab + taxane	Canada (pCODR)	Can\$17,103–Can\$27,550 per QALY	Yes
	Spain	€637,000 avoided	Yes
	U.K. (NICE)	Not determined because of uncertainty in neoadjuvant therapy variation across NHS sites, clinical benefit, cost, and utility assumptions	No (appraisal not final)
Adjuvant therapy			
1-year trastuzumab → standard chemotherapy vs. standard chemotherapy alone	Canada	Can\$13,095–Can\$127,862 per QALY	Yes
	U.S.	U.S. \$18,970–\$39,982 per QALY	Yes
	U.K.	£25,803 per QALY	Yes
	U.K. (NICE)	£18,000 per QALY	Yes
	Europe	€5,828–€41,500 per QALY	Yes
	Spain	€10,771 per QALY gained	Yes
	Australia	A\$22,793 per QALY	Yes
	Australia (PBAC)	A\$45,000–A\$75,000 per QALY	Yes
	Certain developing countries	U.S. \$51,302–\$71,491 per QALY	No
MBC therapy			
Trastuzumab first-line MBC	U.S.	U.S. \$125,000–145,000 per QALY	Yes
	U.K. (NICE)	£37,500 per QALY	Yes
	France	€15,370 and €27,492 per LY gained	Yes
	Australia (PBAC)	A\$45,000–A\$75,000 per QALY	Yes
Pertuzumab + trastuzumab + taxane vs. trastuzumab + taxane	U.S.	U.S. \$713,219 per QALY	No
	Japan	¥90,000 per QALY	No
	Canada (pCODR)	Can\$262,263–Can\$303,726 per QALY	No
	U.K. (NICE)	£125,000 per QALY	No
	Australia (PBAC)	A\$45,000–A\$75,000 per ALY	Yes
Lapatinib + capecitabine vs. capecitabine alone	U.K.	£77,993 per QALY	No
	Brazil	R\$284,864 per QALY	No
Trastuzumab emtansine vs. lapatinib + capecitabine	U.K. (NICE)	£166,400 per QALY	No
	Canada (pCODR)	Can\$145,403 per QALY	No
	Australia (PBAC)	A\$45,000–A\$75,000 per QALY	No conclusion because of uncertainty
Trastuzumab emtansine vs. trastuzumab + capecitabine	Canada (pCODR)	Can\$90,540 per QALY	No

Abbreviations: ALY, adjusted life-year; ICER, incremental cost-effectiveness ratio; LY, life-year; MBC, metastatic breast cancer; NHS, U.K. National Health Service; NICE, U.K. National Institute for Health and Care Excellence; PBAC, Australian Pharmaceutical Benefits Advisory Committee; pCODR, Pan-Canadian Oncology Drug Review; QALY, quality-adjusted life-year.
Source: Nixon et al., 2016 [94].

cost per quality-adjusted life-years (QALYs) [91]. The Spanish cost-offset study of Albanell et al. quantified the benefit in avoiding costs related to disease relapse [92]. An appraisal by NICE in the U.K. recommends the use of neoadjuvant pertuzumab as an option for the neoadjuvant treatment of HER2-positive breast cancer [93].

RECOMMENDATIONS

After reviewing the existing scientific evidence, this group of breast cancer experts, on behalf of SEOM, reached the

following conclusions regarding the use of neoadjuvant therapy in the treatment of breast cancer:

- Neoadjuvant systemic therapy involving chemotherapy, targeted therapy, and sometimes hormonal therapy is a preferred therapeutic option in early breast cancer before definitive breast surgery and has the same indications as adjuvant treatment.
- Multidisciplinary committees play an essential role in the appropriate selection of patients eligible for neoadjuvant therapy.

- Concerning chemotherapy, the recommended treatment regimen consists of anthracyclines followed by taxanes. A dose-dense anthracycline regimen may be used in patients with high-grade or hormone receptor-negative tumors.
- In patients with triple-negative tumors and mutated *BRCA*, it is reasonable to supplement the taxane with carboplatin.
- In patients with HER2-positive tumors, neoadjuvant administration of dual anti-HER2 therapy (trastuzumab and pertuzumab) is indicated together with chemotherapy.
- In hormone receptor-positive postmenopausal patients not eligible for chemotherapy, neoadjuvant endocrine therapy is an appropriate option.
- Neoadjuvant treatment can significantly impact surgical treatment by downstaging the tumor without compromising locoregional control. It facilitates BCS and limited axillary surgery in selected patients.
- The neoadjuvant model offers great advantages for new drug development in breast cancer and for individual investigations into the mechanisms of action of drugs.
- pCR can be used as an endpoint for early drug approval.
- Neoadjuvant therapies allow the early identification of efficacy markers.
- Given the clinical benefit demonstrated by neoadjuvant therapy, future clinical trials should include specific evaluations of economic cost and cost-offset analysis.

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DISCLOSURES

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