ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.2023S114

# Early breast cancer: concept and therapeutic review

Maria Carolina Soliani Bastos[1*], Aline Prado de Almeida[1], Fábio Bagnoli[1], Vilmar Marques de Oliveira[1]

Brazilian Society of Mastology

## SUMMARY

**OBJECTIVE:** Breast cancer treatment has evolved significantly over the years, both in terms of local and systemic approaches. Halsted's radical mastectomy gave way to modified mastectomies and to conservative surgeries, along with breast reconstruction and repair. Although the use of new drugs has directly increased the survival of patients submitted to adjuvant or neoadjuvant systemic therapies, the de-escalation of drugs may also be beneficial in numerous cases. Therefore, breast cancer treatment must be increasingly customized and assessed using a multidisciplinary approach. This study aimed to review the concept and therapy of early breast cancer.

**METHODS:** A narrative review of the literature was carried out in the PubMed database in December 2022, where the keywords for the searches were as follows: early breast cancer, surgical treatment of breast cancer, systemic treatment of breast cancer, neoadjuvant chemotherapy in breast cancer, adjuvant treatment of luminal breast cancer, early triple negative tumor, and early positive Her-2 tumor. Articles that were historically important in the treatment of breast cancer and articles that impacted management with scientific relevance were selected for this review.

**DISCUSSION:** As new evidence continues to update existing knowledge, breast cancer treatment is becoming increasingly personalized and must now take into account the different tumor variants and their clinical stages, the age of patients and relevant comorbidities, as well as personal expectations and desires.

**CONCLUSION:** This literature review of current studies shows that the primary therapy for patients with early breast cancer continues to be surgery, although a customized and multidisciplinary approach is now required.

**KEYWORDS:** Breast neoplasms. Cancer treatment protocols. Breast conserving surgery.

## INTRODUCTION

Breast cancer treatment has evolved significantly over the years, both in terms of local and systemic approaches. Halsted's radical mastectomy gave way to modified mastectomies and to conservative surgeries, along with breast reconstruction and repair.

Although the use of new drugs has directly increased the survival of patients submitted to adjuvant or neoadjuvant systemic therapies, the de-escalation of drugs may also be beneficial in numerous cases. Therefore, breast cancer treatment must be increasingly customized and assessed using a multidisciplinary approach.

Although surgery is recommended as the primary therapy for patients with early breast cancer, neoadjuvant systemic therapy is recommended as the primary treatment for patients with[1] triple-negative and HER-2-positive tumors equal to or greater than 2 cm in size or with clinically active axillary lymph nodes, and for some selected cases of triple-negative tumors with a size between 1 and 2 cm or[2] luminal tumors in cases in which downstaging is favorable for an axillary approach or reduction of the tumor volume is favorable for breast surgery.

This study aimed to review the concept and therapy of early breast cancer.

### Surgical treatment

Historically, breast surgery has been the most widely applied treatment for breast cancers, regardless of their clinical stage. More specifically, the radical mastectomy as described by Halsted in 1894 reflected the prevalent belief in the local spread of tumors and thus that the more radical the procedure, the better the patients' recovery[1]. In fact, this approach was an outstanding development, since it helped reduce the overall mortality of breast cancer patients by nearly 20% and close to 50% when performed in patients with early tumors[2].

With the evolution of knowledge on breast cancer, radical mastectomies gave way to modified radical mastectomies. Patey and Dyson[3] described a modified radical mastectomy that preserved the pectoralis major, whereas Auchincloss[4] and Madden[5] described a mastectomy that also preserved the pectoralis minor[3-5]. The next developments were the skin-sparing mastectomy and the skin- and nipple-areola

[1]Santa Casa de Misericórdia de São Paulo – São Paulo (SP), Brazil.
*Corresponding author: carol.soliani@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on March 23, 2023. Accepted on March 23, 2023.

complex-sparing mastectomy, which are currently performed in patients who meet certain clinical-oncological criteria[6,7].

In the 1980s, other major breakthroughs came with the publication of the Milan studies, conducted by Umberto Veronesi, and of the NSABP (National Surgical Adjuvant Breast and Bowel Project B-06) study, conducted in the US by Bernard Fisher. The updated 20-year follow-up on these studies demonstrated not only the oncological safety of conservative surgery followed by radiotherapy, but also the psychosocial benefits they offered to patients[8,9].

Immediate breast reconstruction, either by myocutaneous flaps or implants, has become a standard practice in the surgical treatment of breast cancer. In fact, when there are no contraindications to this procedure, it should be offered to patients due to the numerous benefits it provides, such as its contribution to the patients' body image and the consequent improvement in their quality of life[10].

Oncoplasty, an association of oncological surgery and plastic surgery techniques, can now be used when unsatisfactory cosmetic results may arise from purely oncological surgery. Since this combination of techniques can also be used in conservative surgery for larger tumors, it has also helped increase breast preservation. The benefits of breast preservation cannot be overstated, and include improved recovery and adherence to treatment, higher self-esteem, better quality of life, higher survival rates, benefits on affective life and marital relationships, as well as an earlier return to work[11,12].

The belief that distant metastasis occurs via the lymphatic and hematogenous routes is one of the chief drivers of conservative surgery, decreasing the radicality of surgical treatment[13].

Systemic treatment, on the contrary, has also seen significant evolution.

## Systemic treatment

In 1975, the NSABP demonstrated that treatment using oral adjuvant 1-phenylalanine mustard improved patients' prognoses. This study thus confirmed the hypothesis that the worse prognosis in some patients was caused by the presence of distant micrometastases. This is how Fisher arrived at the concept that invasive diseases are systemic in character and, thus, the early treatment of micrometastases benefits patients[14].

As this concept became established, adjuvant systemic therapy – whether through chemotherapy or hormone therapy – grew increasingly important in post-surgical treatment[15].

The effectiveness of drugs in adjuvant treatment soon prompted studies in neoadjuvant settings, which aimed to render inoperable tumors operable. A particularly significant study on this procedure was conducted in Milan by Bonadona.

Subsequently, NSABP studies B-18 and B-27 not only demonstrated that the prognosis was identical for patients submitted to neoadjuvant or adjuvant chemotherapy, but also yielded higher breast preservation rates compared to mastectomies when systemic treatment was performed before surgery. Study B-18 treated patients with Adriamycin and Cyclophosphamide, and the cohort that began treatment with chemotherapy achieved higher rates of conservative surgery (19.8 vs. 59.8%) with comparable rates of local recurrence. Although the study indicated no difference in overall survival (OS), a 9-year follow-up study demonstrated that patients with pathological complete response (pCR) to neoadjuvant chemotherapy had 50% lower risk of death[17]. Study B-27, on the contrary, associated taxanes with the treatment and reached similar results to study B-18 in terms of OS and disease-free survival (DFS) when neoadjuvant or adjuvant treatment was performed, albeit with increased DFS and OS in patients who achieved pCR. Moreover, it is worth noting that the association of taxanes in B-27 led to higher pCR rates[18]. Based on this evidence and other studies, neoadjuvant chemotherapy has become an established practice to[1] render inoperable tumors operable[2], transform radical surgeries into conservative ones, and[3] provide initial treatment to locally advanced tumors (T3, T4, and N2-3)[19].

Three milestones that contributed to customized treatments were as follows[1]: the identification of estrogen and progesterone receptors by immunohistochemistry[2]; the advent of in situ hybridization techniques to detect HER-2 amplification; and[3] the study by Perou and Sorlie[21] that classified breast cancer into five molecular subtypes (luminal A, luminal B, HER-2-positive, triple-negative/basal-like, and triple-negative/normal-like)[20,21].

The increased use of chemotherapy, anti-hormone treatments, and targeted therapies has not only increased the recommendation of neoadjuvant chemotherapy for the previously mentioned indications, but also allowed the in vivo assessment of the tumor response to the agent used in the neoadjuvant therapy.

Among the targeted therapies, the use of the monoclonal antibody trastuzumab deserves special mention. Studies such as the NSABP B-31 and BCIRG 006, comparing commonly used chemotherapy schemes with and without the association of trastuzumab, found that the combined treatments provided higher DFS and OS rates[22,23]. In the neoadjuvant setting, the highest pCR rates are usually associated with triple-negative and HER-2-positive tumors (and for the latter, especially when associated with the target therapies). Thus, the current practice is to conduct neoadjuvant chemotherapy in tumors with smaller dimensions and with these biomolecular characteristics[24,25].

In the NOAH and GEPARQUINTO studies, the combination of trastuzumab and chemotherapy in tumors with positive

HER-2 expression yielded pCR rates of approximately 50%, or almost twice the result of treatments without this association[24-26]. Dual blockade with trastuzumab and pertuzumab achieved the highest pCR rate, with a nearly 20% rise compared to schemes that only used trastuzumab. In the NeoSphere study, the pCR rate amounted to 45.8% in the dual blockade group and 29% in the trastuzumab group. The data published in the AFFINITY study on adjuvant therapy (2017) ensured the definitive approval of the dual blockade[27]. The dual blockade in neoadjuvant therapy for HER-2-positive tumors, on the contrary, grew following the publication of the KATHERINE study, which randomized patients with[1] HER-2-positive tumors and residual invasive diseases in the breast or axilla after initial chemotherapy and[2] anti-HER-2 therapy (trastuzumab with or without pertuzumab). In the study's 14 postoperative cycles, these patients received either transtuzumab-entasine (TDM-1) or trastuzumab. Although these randomized patients had tumors of varying sizes and with or without axillary, skin, or chest wall involvement, none of them had metastases. The study also excluded patients with tumors smaller than 1 cm and axilla with no lymph node involvement. Although the group receiving TDM-1 had a 50% lower risk of recurrent invasive diseases, the benefit in OS was statistically insignificant[28].

With the aim of reducing cardiotoxicity, studies were carried out to assess the non-use of anthracyclines in neoadjuvant therapy associated with dual blockade schemes. The TRAIN-2 study analyzed 418 patients with stages II and III HER-2-positive tumors with no previous treatment. These patients were then randomized into (i) 206 patients treated with six cycles of paclitaxel+carboplatin+trastuzumab+pertuzumab followed by paclitaxel+carboplatin+trastuzumab+pertuzumb and (ii) 212 patients treated with six cycles of 5-fluoracil+epirubicin+cyclophosphamide+trastuzumab+pertuzumab followed by paclitaxel+carboplatin+transtuzumab+pertuzumab. A complete pathological response was seen in 141 patients in the anthracycline group and 140 patients in the non-anthracycline group. The updated analysis of the 48.8-month follow-up study indicated no difference in DFS and OS between these groups, although the anthracycline-free group had lower rates of cardiac toxicity[29].

If, on the one hand, new therapies have emerged, on the other, an attempt is being made to de-escalate adjuvant treatment in patients with positive HER-2 expression. Due to new evidence, this can be applied in some situations. In the APT trial, 410 patients with HER-2-positive breast cancer, tumors up to 3 cm, and negative lymph nodes were treated with paclitaxel associated with trastuzumab for 12 weeks. The trastuzumab was later maintained for another 9 months. After a median follow-up of 6.5 years, DFS stood at 93% and OS at 95%. It is worth mentioning that 91% of study participants had tumors of up to 2 cm, whereas 64% had tumors with positive estrogen expression[30].

Regarding the triple-negative tumors, the appropriate response to neoadjuvant therapies was widely known and consisted mainly of an association of anthracyclines and taxanes. Current studies have shown higher rates of pCR following the use of carboplatin, as seen in the ALLIANCE study, which reached pCR in the breast at 44 versus 60% and response in the breast and axilla at 54 versus 41%, both statistically significant, although reflecting no OS gains to date[31,32]. The indication of chemotherapy as primary therapy in triple-negative tumors increased with the results of the CREATE-X study, in which 910 HER-2-negative patients with residual invasive tumors and following neoadjuvant therapy with anthracyclines, taxanes, or both were randomized to 6–8 cycles of capecitabine or placebo. In 5 years, the cohort receiving the treatment reached higher DFS and OS. The subgroup of patients with triple-negative tumors achieved better results both in terms of DFS and OS. In this study, 15.4% of patients had tumors of up to 2 cm, and the remaining participants had larger tumors[33].

Similar in design, the study GEICAM/2003-11_CIBOMA/2004-01 did not deliver the same promising results. The study analyzed 876 patients with triple-negative tumors equal to or larger than 1 cm in size, with positive or negative lymph nodes, who were undergoing neoadjuvant chemotherapy using anthracyclines with or without taxanes. The study then randomized the patients who received no treatment or capecitabine for 14 consecutive days during 8 cycles of 21 days. After a 5-year follow-up study, the group treated with capecitabine reached higher DFS and OS, albeit with statistically insignificant results. Although the subgroup analysis suggested that capecitabine had benefited the non-baseline triple-negative patients, the results were statistically insignificant[34]. Published recently, a systematic review carried out a meta-analysis of nine randomized clinical trials comprising 3,842 patients with triple-negative tumors that were treated with neoadjuvant or adjuvant capecitabine. Bearing in mind the low heterogeneity of the samples, the meta-analysis showed that the association of capecitabine yielded statistically significant increases in DFS and OS. On the downside, capecitabine treatments have been associated with increased risks of diarrhea, stomatitis, and hand-foot syndrome[35].

Among the new drugs that have been researched in neoadjuvant treatment for patients with triple-negative tumors, immunotherapy stands out. The KEYNOTE-522 study analyzed stages II and III patients with previously untreated

triple-negative tumors. All patients underwent four cycles of 3-week treatments, receiving paclitaxel and carboplatin associated with either pembrolizumab (784 patients) or placebo (390 patients). Both of these groups then received four additional cycles of pembrolizumab or placebo, respectively, associated with doxorubicin-cyclophosphamide or epirubicin-cyclophosphamide. After surgery, these patients then received up to nine cycles of 3-week treatments with adjuvant pembrolizumab or placebo. Immunotherapy yielded higher pCR rates with a statistically significant difference between the groups, and patients with stage III or lymph node tumors benefited the most from this treatment. A median 39.1-month follow-up study indicated a higher DFS with statistical significance[36].

For patients with luminal tumors in early clinical stage, surgery is still the recommended primary therapy. The SENTINA and ACOSOG-Z71 studies discussed neoadjuvant therapy used for axillary downstaging, that is, with the aim of searching the sentinel lymph node in the primarily compromised axilla[37,38]. These studies assessed neoadjuvant hormone therapy, considering that the response rate of luminal tumors to chemotherapy is much lower when compared to triple-negative and HER-2-positive tumors. However, a systematic meta-analysis review showed that neoadjuvant therapy with aromatase inhibitors (AI) yielded a clinical response similar to chemotherapy, a similar radiology response, and similar rates of conservative surgery, but with the added benefit of lower toxicity.

Compared to tamoxifen, AI also achieved superior clinical and radiological responses with statistical significance[39].

A study with 97 patients with luminal tumors randomized the chemotherapy treatment (epirubicin+cyclophosphamide followed by docetaxel every 21 days, during four cycles) with hormone therapy (exemestane 25 mg for 24 weeks). From the patients undergoing chemotherapy, 51% were premenopausal; from those undergoing hormone therapy, 56% received goserelin with exemestane. A subgroup analysis showed significantly improved clinical response rates for premenopausal patients undergoing chemotherapy (75 vs. 44%, p=0.027) compared to postmenopausal patients (57 vs. 52%, p=0.78)[40].

## METHODS

A narrative review of the literature was carried out in the PubMed database, where the keywords for the searches were early breast cancer, surgical treatment of breast cancer, systemic treatment of breast cancer, neoadjuvant chemotherapy in breast cancer, adjuvant treatment of luminal breast cancer, early triple negative tumor, and early positive Her-2 tumor. Articles that were historically important in the treatment of breast cancer and articles that impacted changes in conduct with scientific relevance were selected for this review.

## DISCUSSION

As new evidence continues to update existing knowledge, breast cancer treatment is becoming increasingly personalized and must now take into account the different tumor variants and their clinical stages, the age of patients, any relevant comorbidities, as well as personal expectations and desires. With the exception of patients with stage IV tumors, inoperable tumors, or without the necessary clinical conditions for surgical treatment, the mandatory treatment for breast cancer continues to be surgery – which may also be associated with systemic approaches such as neoadjuvant, adjuvant, or both. Specifically for HER-2-positive tumors, the target therapies yielded high pCR rates, and the dual blockade treatment stands out in this particular. In the KATHERINE study, adjuvant treatment with TDM-1 increased the DFS in patients with no pCR for invasive diseases. The APT study, in turn, ensures the non-inferiority of trastuzumab associated with adjuvant paclitaxel with no anthracyclines for initial tumors with no lymph node tumors. The CREATE-X study is a milestone in the treatment of triple-negative tumors, since adjuvant capecitabine after neoadjuvant chemotherapy in patients with no pCR for invasive diseases yielded a higher DFS and OS, and the KEYNOTE-522 study with immunotherapy yielded higher pCR rates and higher DFS. The recommendation of neoadjuvant therapy based on the size of the tumor remains controversial, since the conclusions provided by different studies are inconsistent in this particular. Surgery continues to be the primary therapy for early luminal tumors, and a few special cases in this particular involve strategies for reducing tumor or axillary disease volumes.

## CONCLUSION

This literature review of current studies shows that the primary therapy for patients with early breast cancer continues to be surgery, although a customized and multidisciplinary approach is now required. Neoadjuvant therapy, on the contrary, is the primary treatment for triple-negative tumors equal to or greater than 2 cm and can be considered in selected cases of tumors between 1 and 2 cm and HER-2-positive tumors equal to or greater than 2 cm, or with axillary lymph node tumors and luminal tumors in which the axilla is involved, and the goal is to reduce the volume of the axillary disease.

## AUTHORS' CONTRIBUTIONS

**MCSB:** Conceptualization, Formal Analysis, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **APA:** Resources, Writing – original draft. **FB:** Conceptualization, Methodology, Resources, Supervision, Writing – original draft. **VMO:** Conceptualization, Methodology, Resources, Supervision, Writing – original draft.

## REFERENCES


1. Halsted WS. I. The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June, 1889, to January, 1894. Ann Surg. 1894;20(5):497-555. https://doi.org/10.1097/00000658-189407000-00075
2. Taylor GW, Wallace RH. Carcinoma of the breast; fifty years experience at the Massachusetts General Hospital. Ann Surg. 1950;132(4):833-43. https://doi.org/10.1097/00000658-195010000-00019
3. Patey DH, Dyson WH. The prognosis of carcinoma of the breast in relation to the type of operation performed. Br J Cancer. 1948;2(1):7-13. https://doi.org/10.1038/bjc.1948.2
4. Auchincloss H. Significance of location and number of axillary metastases in carcinoma of the breast. Ann Surg. 1963;158(1):37-46. https://doi.org/10.1097/00000658-196307000-00008
5. Madden JL. Modified radical mastectomy. Surg Gynecol Obstet. 1965;121(6):1221-30. PMID: 5851617
6. Cruz L, Moody AM, Tappy EE, Blankenship SA, Hecht EM. Overall survival, disease-free survival, local recurrence, and nipple-areolar recurrence in the setting of nipple-sparing mastectomy: a meta-analysis and systematic review. Ann Surg Oncol. 2015;22(10):3241-9. https://doi.org/10.1245/s10434-015-4739-1
7. Galimberti V, Morigi C, Bagnardi V, Corso G, Vicini E, Fontana SKR, et al. Oncological outcomes of nipple-sparing mastectomy: a single-center experience of 1989 patients. Ann Surg Oncol. 2018;25(13):3849-57. https://doi.org/10.1245/s10434-018-6759-0
8. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227-32. https://doi.org/10.1056/NEJMoa020989
9. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347(16):1233-41. https://doi.org/10.1056/NEJMoa022152
10. Fang SY, Shu BC, Chang YJ. The effect of breast reconstruction surgery on body image among women after mastectomy: a meta-analysis. Breast Cancer Res Treat. 2013;137(1):13-21. https://doi.org/10.1007/s10549-012-2349-1
11. Losken A, Dugal CS, Styblo TM, Carlson GW. A meta-analysis comparing breast conservation therapy alone to the oncoplastic technique. Ann Plast Surg. 2014;72(2):145-9. https://doi.org/10.1097/SAP.0b013e3182605598
12. Clough KB, Kroll SS, Audretsch W. An approach to the repair of partial mastectomy defects. Plast Reconstr Surg. 1999;104(2):409-20. https://doi.org/10.1097/00006534-199908000-00014
13. Wilder RJ. The historical development of the concept of metastasis. J Mt Sinai Hosp N Y. 1956;23(5):728-34. PMID: 13377138
14. Fisher B, Redmond C, Fisher ER. The contribution of recent NSABP clinical trials of primary breast cancer therapy to an understanding of tumor biology--an overview of findings. Cancer. 1980;46(4 Suppl):1009-25. https://doi.org/10.1002/1097-0142(19800815)46:4+<1009::aid-cncr2820461326>3.0.co;2-h
15. Bonadonna G, Valagussa P. Dose-response effect of adjuvant chemotherapy in breast cancer. N Engl J Med. 1981;304(1):10-5. https://doi.org/10.1056/NEJM198101013040103
16. Bonadonna G. Karnofsky memorial lecture. Conceptual and practical advances in the management of breast cancer. J Clin Oncol. 1989;7(10):1380-97. https://doi.org/10.1200/JCO.1989.7.10.1380
17. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr. 2001;(30):96-102. https://doi.org/10.1093/oxfordjournals.jncimonographs.a003469
18. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol. 2008;26(5):778-85. https://doi.org/10.1200/JCO.2007.15.0235
19. Chia S, Swain SM, Byrd DR, Mankoff DA. Locally advanced and inflammatory breast cancer. J Clin Oncol. 2008;26(5):786-90. https://doi.org/10.1200/JCO.2008.15.0243
20. Zaha DC. Significance of immunohistochemistry in breast cancer. World J Clin Oncol. 2014;5(3):382-92. https://doi.org/10.5306/wjco.v5.i3.382
21. Perou CM, Sørlie T, Eisen MB, Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747-52. https://doi.org/10.1038/35021093
22. Perez EA, Romond EH, Suman VJ, Jeong JH, Sledge G, Geyer CE, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014;32(33):3744-52. https://doi.org/10.1200/JCO.2014.55.5730
23. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273-83. https://doi.org/10.1056/NEJMoa0910383
24. Semiglazov V, Eiermann W, Zambetti M, Manikhas A, Bozhok A, Lluch A, et al. Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herceptin (NOAH) study. Eur J Surg Oncol. 2011;37(10):856-63. https://doi.org/10.1016/j.ejso.2011.07.003
25. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384(9938):164-72. https://doi.org/10.1016/S0140-6736(13)62422-8

26. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet. 2010;375(9712):377-84. https://doi.org/10.1016/S0140-6736(09)61964-4

27. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(1):25-32. https://doi.org/10.1016/S1470-2045(11)70336-9

28. Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med. 2019;380(7):617-28. https://doi.org/10.1056/NEJMoa1814017

29. Ramshorst MS, Voort A, Werkhoven ED, Mandjes IA, Kemper I, Dezentjé VO, 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):1630-40. https://doi.org/10.1016/S1470-2045(18)30570-9

30. Tolaney SM, Guo H, Pernas S, Barry WT, Dillon DA, Ritterhouse L, 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):1868-75. https://doi.org/10.1200/JCO.19.00066

31. Sikov WM, Berry DA, Perou CM, Singh B, Cirrincione CT, Tolaney SM, 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. https://doi.org/10.1200/JCO.2014.57.0572

32. Poggio F, Bruzzone M, Ceppi M, Pondé NF, Valle G, Del Mastro L, et al. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis. Ann Oncol. 2018;29(7):1497-508. https://doi.org/10.1093/annonc/mdy127

33. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017;376(22):2147-59. https://doi.org/10.1056/NEJMoa1612645

34. Lluch A, Barrios CH, Torrecillas L, Ruiz-Borrego M, Bines J, Segalla J, et al. Phase III trial of adjuvant capecitabine after standard neo-/adjuvant chemotherapy in patients with early triple-negative breast cancer (GEICAM/2003-11_CIBOMA/2004-01). J Clin Oncol. 2020;38(3):203-13. https://doi.org/10.1200/JCO.19.00904

35. Huo X, Li J, Zhao F, Ren D, Ahmad R, Yuan X, et al. The role of capecitabine-based neoadjuvant and adjuvant chemotherapy in early-stage triple-negative breast cancer: a systematic review and meta-analysis. BMC Cancer. 2021;21(1):78. https://doi.org/10.1186/s12885-021-07791-y

36. Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kümmel S, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. N Engl J Med. 2022;386(6):556-67. https://doi.org/10.1056/NEJMoa2112651

37. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol. 2013;14(7):609-18. https://doi.org/10.1016/S1470-2045(13)70166-9

38. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA. 2013;310(14):1455-61. https://doi.org/10.1001/jama.2013.278932

39. Spring LM, Gupta A, Reynolds KL, Gadd MA, Ellisen LW, Isakoff SJ, et al. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. JAMA Oncol. 2016;2(11):1477-86. https://doi.org/10.1001/jamaoncol.2016.1897

40. Alba E, Calvo L, Albanell J, Haba JR, Arcusa Lanza A, Chacon JI, 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):3069-74. https://doi.org/10.1093/annonc/mds132