Revista de Senología y Patología Mamaria 37 (2024) 100613

Sociedad Española de Senología y Patología Mamaria

Revista de Senología y patología mamaria
Journal of Senology and Breast Disease
www.elsevier.es/senologia

REVIEW

Is neoadjuvant treatment indicated in triple negative cT1N0 breast cancer?

Esmeralda García-Torralba[a,b,c,*], **Noel Blaya Boluda**[a,b,c], **María Esperanza Guirao García**[a,b,c], **Elisa García Garre**[a,b,c], **Francisco Ayala de la Peña**[a,b,c]

[a] *Department of Medical Oncology, University Hospital Morales Meseguer, Murcia, Spain*
[b] *Department of Medicine, Medical School, University of Murcia, Murcia, Spain*
[c] *Instituto Murciano de Investigación Biosanitaria (IMIB), Murcia, Spain*

Received 17 June 2024; accepted 20 June 2024

KEYWORDS
Triple negative breast cancer;
Neoadjuvant treatment;
Chemotherapy;
Immunotherapy;
Predictive biomarkers

Abstract Triple negative breast cancer (TNBC) is the most aggressive subtype, including early BC. Neoadjuvant chemotherapy (NAC) has shown benefit in achieving more conservative surgeries, but also it is useful to determine therapeutic sensitivity, prognostic estimation, and consequent choice of an individualized adjuvant treatment. Traditionally, NAC was indicated in patients with cT2 (2 cm or more) TNBC. However, recent guidelines consider neoadjuvant treatment for cT1 TNBC patients. In this paper, we review the current evidence on neoadjuvant treatment in cT1 TNBC patients, including available signals on efficacy, choice of optimal regimen and identification of patients with the greatest potential benefit.

PALABRAS CLAVE
Cáncer de mama triple negativo;
Tratamiento neoadyuvante;
Quimioterapia;
Inmunoterapia;
Biomarcadores predictivos

¿Está indicado el tratamiento neoadyuvante en el cáncer de mama triple negativo cT1N0?

Resumen El cáncer de mama triple negativo (CMTN) es el subtipo más agresivo de CM, incluida la enfermedad precoz. La quimioterapia neoadyuvante (QTN) ha demostrado ser beneficiosa para lograr cirugías más conservadoras, pero también es útil para determinar la sensibilidad terapéutica, la estimación pronóstica y la consiguiente elección de un tratamiento adyuvante individualizado. Tradicionalmente, la QTN estaba indicada en pacientes con CMTN cT2 (2 cm o más). Sin embargo, las directrices recientes consideran el tratamiento neoadyuvante para las pacientes con CMTN cT1. En este artículo, revisamos la evidencia actual sobre el tratamiento neoadyuvante en pacientes con CMTN cT1N0, incluyendo los datos disponibles sobre eficacia, elección del régimen óptimo e identificación de las pacientes con mayor beneficio potencial.

* Corresponding author.
E-mail address: esmeralda.garciat@um.es (E. García-Torralba).

https://doi.org/10.1016/j.senol.2024.100613

Introduction

Neoadjuvant chemotherapy (NAC) refers to the administration of cytotoxic treatment before tumor surgical removal. Initially aimed to convert inoperable BC into a surgically removable disease, the interest in NAC has significantly increased over the last decade.[1,2] NAC increases the rate of conservative surgery, enables treatment response monitoring and provides unique opportunities for developing novel and individualized therapeutic strategies.[3] Additionally, 2 more relevant observations contributed to the increase of NAC indications. First, pathological complete response (pCR) after NAC has been considered a robust predictor of disease-free survival (DFS), and overall survival (OS), especially for the most aggressive BC subtypes, such as triple negative BC (TNBC), a subtype in which both probability of reaching pCR after NAC and survival benefits from adjuvant chemotherapy are the highest.[4] Second, recent randomized trials demonstrated that in those patients with TNBC and residual invasive disease after pre-operative systemic treatment, adjuvant capecitabine[5] or olaparib (in carriers of BRCA1/2 mutations)[6] significantly improves survival.

In TNBC, the most aggressive subtype of BC, systemic treatment is associated with improved survival and NAC is a standard of care in most of the patients with clinical stage II–III TN disease, even when initial breast conservation may be achieved by frontline surgery.[7] With the aim of evaluating treatment efficacy by pathological response assessment, guiding risk stratification, reducing the extent of surgical need, and determining the adjuvant treatment plan, some authors have proposed to extend the traditional indication of NAC to cT1c stages. This is a frequent clinical scenario, which corresponds to around one third of stage I–III TNBC.[8] The last version of ESMO Early Breast Cancer Clinical Practice Guidelines has also included cT1N0 TNBC as an indication for NAC [category IA].[7]

The aim of this narrative review is to determine whether neoadjuvant treatment is the preferred treatment in cT1N0 TNBC, and if that is the case, which treatment regimen should be used.

Basis of "traditional" treatment of triple negative cT1N0 breast cancer and potential limitations for neoadjuvant systemic treatment

Previous guidelines from ESMO recommended primary surgery for cT1N0 TNBC, with NAC, which was reserved for tumors larger than 2 cm. This has been the classical strategy for tumors under 2 cm, based on the usually good results obtained with primary surgery followed by adjuvant chemotherapy. The rationale for surgery followed by adjuvant systemic treatment in patients with TNBC less than 2 cm (cT1N0) is varied.

Size-dependent benefit of adjuvant chemotherapy in small TNBC

First, the benefit of adjuvant chemotherapy in TN tumors without axillary involvement is clearly dependent on tumor size, with virtually negligible gains in T1a tumors, limited in T1b tumors and clearly established and substantial in tumors larger than 1 cm.[9–11] Most evidence on the benefit in these groups come from retrospective observational studies (Table 1).[10–19] Clinical practice guidelines recommend adjuvant treatment with chemotherapy in pT1cN0M0[20,21] and even pT1bN0M0 stages directly [IA][7] or after individual discussion with the patient [IIIB],[22] except in histological subtypes with a good prognosis (cystic adenoid, secretory). In tumor sizes close to 1 cm, therefore, inadequate estimation of tumor size could lead to overtreatment with chemotherapy.

Prognosis of small TNBC

Secondly, the results of the available series with initial surgery followed by adjuvant chemotherapy show, even in the cT1N0 tumor group, breast cancer-specific survival figures of around 94%,[9] so that escalating treatment in this group does not seem fully justified by the results. Some biomarkers of good prognosis have been proposed from retrospective data, such as high tumor lymphocyte infiltration (TIL),[23] which could probably justify omitting chemotherapy in some cT1N0 tumors. However, it is not clear if treatment escalation could improve results in groups with worse prognosis.

Under-representation of small TNBC in recent neoadjuvant trials

Thirdly, recent modifications of neoadjuvant systemic treatment, particularly the introduction of immunotherapy, are based on studies that excluded the population of patients with cT1N0 tumors as most trials required the presence of at least one tumor larger than 2 cm for inclusion. This exclusion is especially notable for the KEYNOTE-522 study with pembrolizumab,[24] which has established the indication for chemoimmunotherapy in the neoadjuvant and adjuvant setting, regardless of the levels of PD-L1 expression. Also, stage I patients were not included in the other neoadjuvant immunotherapy studies, such as IMpassion031[25] or NeoTRIP trials.[26] While it is biologically and clinically reasonable to consider that the results would be extrapolated to groups with a better prognosis, the absolute benefit of the new treatments will be lower in this lower risk group. Since the same toxicity is expected, the balance between benefit and toxicity is probably reduced in a group with a generally good

Table 1 Major studies evaluating chemotherapy results in T1N0 TNBC.

Reference [a]	N	Type of series	pT1a benefit	pT1b benefit	pT1c benefit
Oladeru, *JAMA Network Open* 2020[12]	16,180	National registry (NCDB)	Deleterious effect OS (HR 1.46, 95%CI 1.17–1.82)	OS benefit (HR 0.74, 95%CI 0.63–0.87), higher in >50 yr	–
Carbajal-Ochoa, *Breast Cancer Res Treat* 2024[13]	11,510	SEER database (US)	–	No improvement in BCSS, but in OS (HR 0.52; 95%CI 0.41–0.68).	Yes (OS HR 0.54; 95%CI 0.47–0.62)
Tarantino, *NPJ Breast Cancer* 2024)[14]	8601	Population-based (US)	No benefit in BCSS	No benefit in BCSS	Yes (BCSS, HR 0.64, 95% CI 0.48–0.85)
Stenbruggen, *Eur J Cancer* 2020[10]	4366	Population-based (Netherland)	No benefit (worse BCS for chemotherapy)	No benefit	Benefit (BCSS HR 0.60; 95%CI 0.43–0.82)
Shum, *Med Oncol* 2022[15]	610	Population-based (Canada)	No OS benefit pT1a-b (HR 0.40, 95%CI 0.02–2.5)		Yes (OS HR 0.40 95%CI 0.16–0.86)
Nonneville, *Eur J Cancer* 2017[16]	284	Multicentric (France)	No benefit (DFS, HR 0.77, 95%CI 0.40–1.46; DRFS, HR 1, 95%CI 0.46–2.19)		–
Wu, *Gland Surg* 2023[17]	441	Unicentric (China)	No benefit (5-yr BCFI, 93.6% vs 94.6%, p=.55)		Benefit (5-yr BCFI, 92.1% vs 79.5%, p=.03). No OS benefit
Fasano, *Breast Cancer Res Treat* 2022[18]	258	Multicentric (US)	No (100% 5-yr OS both groups)	No (100% vs 95.8% 5-yr OS, p=.24)	Yes (5-yr OS, 93.2% vs 75.2%, p=.008)
Vaz-Luis, *J Clin Oncol* 2014[19]	168	Multicentric (US)	Higher numerical 5-yr DRFS (100% vs 93%, no formal comparison)	Higher numerical 5-yr DRFS 96% vs 90%, no formal comparisons	–
An, *Cancer* 2020[11]	351	Unicentric (China)	No benefit in RFS	No benefit in RFS (HR 0.64, 95%CI 0.05–7.74)	Yes (RFS, HR 0.107, 95% CI 0.047–0.244)
An, *Cancer* 2020[11]	1525	Meta-analysis (7 studies)	No benefit in risk of recurrence (RR 0.64, 95%CI 0.31–1.33)	Benefit (RR 0.62, 95%CI 0.42–0.92)	Benefit for whole T1N0 group (RR 0.58, 95%CI 0.43–0.78)

BCS: breast cancer-specific survival; BCFI: breast cancer-free interval; DFS: disease-free survival; DRFS: distant relapse-free survival; OS: overall survival; RFS: relapse-free survival; RR: risk ratio.

[a] Unicentric studies included in the available meta-analysis (An, *Cancer* 2020) are not shown.

prognosis. A similar issue occurs with the administration of dose-dense schedules, generally recommended in this population, but of uncertain efficacy in the N0 tumor group, which was underrepresented in the Oxford meta-analysis.[27]

Opportunities for chemotherapy downscaling in small TNBC

In contrast, there are data on the use of neoadjuvant carboplatin in cT1cN0 patients, which were included in the randomized phase II studies WSG-ADAPT,[28] with 37% of cT1cN0 patients, and in the NeoSTOP trial,[29] with 17% of cT1cN0 patients. In the former, a short regimen (4 cycles) with carboplatin and nabpaclitaxel achieved 44% pCR and showed the possibility of tailoring the sequential administration of anthracyclines to whether or not pCR was achieved. In the neoSTOP study, the results were virtually equal in terms of pCR rate (54%) and overall survival for sequential paclitaxel–carboplatin and anthracycline schedules and for the 6-cycle carboplatin and docetaxel schedule.[29] Therefore, the administration of neoadjuvant carboplatin seems beneficial in these patients, improving pCR and survival rates,[30] irrespective of the presence or absence of BRCA1/2 mutations.[31]

Finally, it is in the adjuvant setting of cT1N0 TNBC that shorter, anthracycline-free systemic treatment regimens (6 cycles of docetaxel and cyclophosphamide or carboplatin and taxane) have been most frequently proposed. The equivalence of docetaxel and cyclophosphamide regimens is more questionable, with mainly retrospective data,[32] and these regimens should be restricted to patients with contraindications to anthracyclines, as the anthracycline–taxane sequence has generally shown better results in the pooled analysis of ABC trials, even in the N0 population.[33] However, in the PATTERN trial, the weekly adjuvant paclitaxel–carboplatin regimen showed comparable results to 6 cycles of a sequential anthracycline–taxane regimen and was even better in the N0 tumor subgroup.[34] Therefore, in cT1N0 tumors, such adjuvant schemes could be considered as an alternative to the use of anthracyclines, which is standard for NAC.

Potential overtreatment of small TNBC

The introduction of NAC in patients with cT1N0 tumors, therefore, poses the main problem of the risk of overtreatment due to imaging-based staging and the type of systemic treatment used.

The best approach to mitigate the risk of upstaging is to correctly assess tumor size through pre-treatment magnetic resonance imaging (MRI). Although MRI tend to overestimate tumor size, this seems to occur mostly in tumors larger than 2 cm.[35] Regarding nodal staging, in most cases (around 85%–89%), cT1 tumors will be N0, so the risk of overstaging is low and the possibility of understaging is more relevant because of its therapeutic consequences.[36] This risk can probably be reduced by half if correct axillary staging with ultrasound is performed.[36] More recently, precisely to avoid this risk, presurgical sentinel lymph node biopsy has been proposed again for cT1N0 tumors in which primary surgery is being considered. However, the selection criteria for this approach remain unclear and might be especially applicable in cases with a high risk of axillary involvement (lymphovascular invasion or low lymphocyte infiltration).

Secondly, the introduction of NAC, if the same treatment regimens are used as in larger tumors, could overtreat a substantial group of patients without clear data of additional benefit. In stage T1N0, results are available from the randomized phase II study BT1902/ICBSG 61–20 Neo-N, which has shown a pCR rate of 54% after 12 weeks of carboplatin, paclitaxel, and nivolumab, but without comparison with a non-immunotherapy arm.[37] Other non-comparative neoadjuvant immunotherapy studies that have included stage I patients have shown similar results, such as the NeoPACT trial, a phase II trial that included 18% of stage I patients larger than 1 cm and combined pembrolizumab with an anthracycline-free regimen (docetaxel and carboplatin), with a pCR rate of 58%.[38] Therefore, in the absence of sufficient comparative data against chemotherapy, immunotherapy with pembrolizumab[24] should not be used in these patients, as stated in the latest ESMO guidelines.[7] As for the introduction of carboplatin, although the level of evidence is limited (2 randomized phase II in the neoadjuvant setting and only 1 phase III in the adjuvant setting),[28,29,34] its use is probably reasonable and, especially in lower risk cases, carboplatin and taxane regimens could be considered as an alternative to the sequence of taxanes–carboplatin and anthracyclines.

Rationale for extending neoadjuvant treatment indication to cT1N0 triple negative breast cancer

Why, then, should we introduce NAC in tumors below 2 cm? First, in contrast to ESMO 2020 guidelines, ASCO guidelines excluded cT1a and cT1b of NAC indication, but they did not establish a clear recommendation for cT1c tumors.[39] In fact, some authors had proposed a cut-point of 1.5 cm to decide whether NAC should be the preferred treatment.[40] Thus, the use of NAC for smaller tumors is not new, and its clinical application has been evolving in the last years. The major rationale to extend NAC indication to cT1c TNBC is clearly based on the recent developments of NAC and in the value of pCR for prognostic stratification, which facilitates individualized tailoring of adjuvant treatment.

A second reason is the potential missed opportunities for offering better therapeutic strategies in those patients in which clinical staging underestimates the real extent of disease. In particular, some patients with cN0 tumors will be found to be pN1 after sentinel lymph node biopsy. This finding usually will not lead to a different surgical treatment, because high nodal burden leading to lymphadenectomy is infrequent in cN0 cases. On the contrary, if lymph node involvement is not clinically detected, neoadjuvant treatment would not include immunotherapy either, thereby limiting opportunities for the patient, as adjuvant immunotherapy alone[41] has not demonstrated prognostic improvement, unlike neoadjuvant immunotherapy.

However, these patients will have lost the chance to upscale adjuvant treatment in the event of chemotherapy resistance. Specifically, patients with pathogenic BRCA1/2 variants would not have a clear indication for adjuvant olaparib unless the absence of pCR is demonstrated. The same would be applicable for adjuvant capecitabine, according to the CreateX trial results, which included a small group (around 5%) of stage I patients and might benefit those TNBC patients without pCR[5] with better results and less toxicity than carboplatin.[42] Thus, there are potentially missed opportunities for systemic therapy when surgical treatment is the first therapy. In addition, those patients with cN0/pN1 stage undergoing primary surgery will receive nodal adjuvant radiation therapy, while those cN0 patients with occult nodal disease treated with NAC and getting an axillary pCR will avoid radiation therapy according to the recently reported results of NR Oncology/NSABP B-51/RTOG 1304 trial.[43]

Finally, practical reasons may further justify the neoadjuvant approach to minimize delays between diagnosis and first treatment[44] and to give some time for BRCA1/2 diagnosis, potentially leading to changes in BC surgery and adjuvant therapy.[45]

Discussion

Thus, based on this rationale, the recent recommendation of NAC for cT1cN0 TNBC seems appropriate in the context of low risk of overestimation of tumor size, potential loss of additional therapeutic opportunities, and response-guided decisions for adjuvant systemic therapy in patients not achieving pCR after NAC. However, decisions in this group of patients should not be uncritically applied, and the cT1cN0 tumors should be considered as a heterogeneous and continuous spectrum in which some factors might refine the indication of NAC versus primary surgical treatment. We further discuss some of these factors.

The need for more precise radiological staging

A precise clinical and radiological initial staging is mandatory. MRI determination of tumor size and ultrasound assessment of nodal status may avoid overtreatment of patients with small size tumors. Since benefits of treatment are limited as we approach the 1 cm tumor size, in those cT1cN0 tumors with total diameters around 10 mm, special

care should be taken to determine the final size of the invasive tumor and to avoid including DCIS or enhancement areas into the measurement. This issue will not be a concern in tumors around or larger than 1.5 cm, in which NAC poses less risk of overtreatment.

The need for a better prognostic stratification

Some patient characteristics, such as the presence of lymphatic and vascular invasion (associated with a higher frequency of axillary involvement)[46] could increase the likelihood of occult nodal disease and therefore direct the decision towards NAC. Conversely, older age or greater comorbidity could tip the balance towards primary surgery given the greater difficulty and risk of NAC administration. The question of whether a pre-treatment sentinel lymph node biopsy should be performed in those cT1cN0 stages with risk factors for lymph node involvement has been discussed recently. This approach would prevent missed opportunities for immunotherapy in the cN0/pN+ group of patients and definitively establish the indication for neoadjuvant therapy. However, it would also raise additional questions about post-chemotherapy axillary evaluation and the surgical and radiotherapeutic management of the axilla.

Similarly, although not considered fully validated as biomarkers, the presence of high sTIL levels in a cT1N0 tumor could justify a primary surgical approach as the risk of distant relapse appears to be around 2% without chemotherapy.[23] The use of high lymphocyte infiltration (equal to or greater than 50% in those over 40, greater than 75% in those under 40) to avoid adjuvant chemotherapy in triple-negative pT1abcN0 tumors will be evaluated in the OPTImaL study (EORTC 2257: Optimization of treatment for patients with low-stage TNBC with high sTIL). Other trials, such as NeoTRACT (NCT05645380), are also evaluating the use of sTIL to tailor neoadjuvant treatment intensity in early stages, a strategy supported by recent data showing that sTIL (with a 30% cut-off point) could improve prognostic stratification beyond pCR and stage, probably allowing de-escalation to anthracycline-free regimens.[47] Other immune biomarkers could also be useful.

The choice of appropriate neoadjuvant regimens for small TNBC

Regarding the NAC regimen and duration, the ESMO guidelines clearly states that immunotherapy should not be administered in the setting of cT1cN0 TNBC. However, the neoadjuvant strategy for cT1cN0 based on chemotherapy only addresses the problem of the lack of information provided by the pCR status but does not solve the problem of nodal understaging and missed opportunities for immunotherapy in this group of women. As previously discussed, further nodal staging, especially in high-risk patients, might be valuable in this setting. The chemotherapy schedule should include at least carboplatin and taxanes, and the regimens without anthracyclines might be used unless high-risk factors are present.

The duration of chemotherapy is usually between 6 and 8 cycles (depending on whether the NAC regime includes or not anthracyclines). Several de-escalation strategies aimed to reduce the duration of NAC are currently being pursued based on previous data showing similar results with 4 and 6 cycles of adjuvant chemotherapy in ER-negative disease[48] and on the results of WSG-ADAPT trial,[28] in which anthracyclines were administered in patients not achieving pCR after a 4-cycles course of nabpaclitaxel–carboplatin chemotherapy. Alternative strategies including early MRI[49] or PET-TC[50] evaluation of response have not been proved to be sufficiently reliable to predict pCR and reduce NAC duration.

Research challenges in small TNBC

Finally, the neoadjuvant approach in stage I is also a suitable platform for the investigation of new de-escalation strategies, as demonstrated by its inclusion in recent studies aimed at the neoadjuvant use of iPARP in patients carrying BRCA1/2 mutations[51,52] or ADC substitution for chemotherapy (NeoSTAR study with sacituzumab–govitecan),[53] which achieve pCR rates of 40%–50% as single agents. Some ongoing or forthcoming studies, such as Olympia-N (NCT05498155), with olaparib, or ADAPT-TN-III (NCT06081244), which will compare an adaptive neoadjuvant design with sacituzumab–govitecan with or without pembrolizumab, are specifically targeting stage I TNBC patients.

Conclusion

Neoadjuvant approach is the preferred option for cT1N0 TNBC, especially for patients with higher risk (tumors larger than 1.5 cm or with evidence of lymphovascular invasion). The chemotherapy schedule should include at least carboplatin and taxanes, and anthracyclines if high-risk factors are present. Further evidence about the role of immunotherapy in this subset of patients is necessary. A precise clinical and radiological initial staging (including MRI) may avoid either overtreatment or loss of therapeutic opportunities. The development of predictive biomarkers could decrease therapeutic uncertainty. An individualized approach is mandatory.

Funding

This research received no external funding.

Ethical disclosures

Not applicable.

Declaration of competing interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

1. Kaufmann M, von Minckwitz G, Bear HD, Buzdar A, McGale P, Bonnefoi H, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol Off J Eur Soc Med Oncol. 2007 Dec;18(12):1927–34.
2. 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 Jan;19(1):27–39.
3. Untch M, Konecny GE, Paepke S, von Minckwitz G. Current and future role of neoadjuvant therapy for breast cancer. Breast Edinb Scotl. 2014 Oct;23(5):526–37.
4. 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 Lond Engl. 2014 Jul 12;384(9938):164–72.
5. 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 Jun 1;376(22):2147–59.
6. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. N Engl J Med. 2021 Jun 24;384(25):2394–405.
7. Loibl S, André F, Bachelot T, Barrios CH, Bergh J, Burstein HJ, et al. Early breast cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 2024 Feb;35(2):159–82.
8. Howlader N, Cronin KA, Kurian AW, Andridge R. Differences in breast cancer survival by molecular subtypes in the United States. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2018 Jun;27(6):619–26.
9. Tarantino P, Leone J, Vallejo CT, Freedman RA, Waks AG, Martínez-Sáez O, et al. Prognosis and trends in chemotherapy use for patients with stage IA triple-negative breast cancer (TNBC): a population-based study. J Clin Oncol. 2023 Jun 1;41(16_suppl):510.
10. Steenbruggen TG, van Werkhoven E, van Ramshorst MS, Dezentjé VO, Kok M, Linn SC, et al. Adjuvant chemotherapy in small node-negative triple-negative breast cancer. Eur J Cancer Oxf Engl. 2020 Aug;1990(135):66–74.
11. An X, Lei X, Huang R, Luo R, Li H, Xu F, et al. Adjuvant chemotherapy for small, lymph node-negative, triple-negative breast cancer: a single-center study and a meta-analysis of the published literature. Cancer. 2020 Aug;15(126 Suppl 16):3837–46.
12. Oladeru OT, Singh AK, Ma SJ. Association of adjuvant chemotherapy with overall survival among women with small, node-negative, triple-negative breast cancer. JAMA Netw Open. 2020 Sep 1;3(9), e2016247.
13. Carbajal-Ochoa W, Bravo-Solarte DC, Bernal AM, Anampa JD. Benefit of adjuvant chemotherapy in lymph node-negative, T1b and T1c triple-negative breast cancer. Breast Cancer Res Treat. 2024 Jan;203(2):257–69.
14. Tarantino P, Leone J, Vallejo CT, Freedman RA, Waks AG, Martínez-Sáez O, et al. Prognosis and treatment outcomes for patients with stage IA triple-negative breast cancer. NPJ Breast Cancer. 2024 Apr 4;10(1):26.
15. Shum K, Hussein A, Hamm C. Are we overtreating stage I triple-negative breast cancer in Ontario? A population-based retrospective epidemiological analysis using the ICES database. Med Oncol Northwood Lond Engl. 2022 Sep 29;39(12):228.
16. de Nonneville A, Gonçalves A, Zemmour C, Classe JM, Cohen M, Lambaudie E, et al. Benefit of adjuvant chemotherapy with or without trastuzumab in pT1ab node-negative human epidermal growth factor receptor 2-positive breast carcinomas: results of a national multi-institutional study. Breast Cancer Res Treat. 2017 Apr;162(2):307–16.
17. Wu C, Huang O, Wu J, Shen K, Chen X, Zhu S. Tumor size is associated with adjuvant chemotherapy benefit in T1N0M0 triple-negative breast cancer: a multicenter and propensity score matched analysis. Gland Surg. 2023 Oct 30;12(10):1375–86.
18. Fasano GA, Bayard S, Chen Y, Varella L, Cigler T, Bensenhaver J, et al. Benefit of adjuvant chemotherapy in node-negative T1a versus T1b and T1c triple-negative breast cancer. Breast Cancer Res Treat. 2022 Feb;192(1):163–73.
19. Vaz-Luis I, Ottesen RA, Hughes ME, Mamet R, Burstein HJ, Edge SB, et al. Outcomes by tumor subtype and treatment pattern in women with small, node-negative breast cancer: a multi-institutional study. J Clin Oncol Off J Am Soc Clin Oncol. 2014 Jul 10;32(20):2142–50.
20. Gradishar WJ, Moran MS, Abraham J, Abramson V, Aft R, Agnese D, et al. NCCN guidelines® insights: breast cancer, version 4.2023. J Natl Compr Cancer Netw JNCCN. 2023 Jun;21(6):594–608.
21. Burstein HJ, Curigliano G, Thürlimann B, Weber WP, Poortmans P, Regan MM, 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 Off J Eur Soc Med Oncol. 2021 Oct;32(10):1216–35.
22. Ayala de la Peña F, Antolín Novoa S, Gavilá Gregori J, González Cortijo L, Henao Carrasco F, Martínez Martínez MT, et al. SEOM-GEICAM-SOLTI clinical guidelines for early-stage breast cancer (2022). Clin Transl Oncol Off Publ Fed Span Oncol Soc Natl Cancer Inst Mex. 2023 Sep;25(9):2647–64.
23. de Jong VMT, Wang Y, Ter Hoeve ND, Opdam M, Stathonikos N, Jóźwiak K, et al. Prognostic value of stromal tumor-infiltrating lymphocytes in young, node-negative, triple-negative breast cancer patients who did not receive (neo)adjuvant systemic therapy. J Clin Oncol Off J Am Soc Clin Oncol. 2022 Jul 20;40(21):2361–74.
24. 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 Feb 10;386(6):556–67.
25. Mittendorf EA, Zhang H, Barrios CH, Saji S, Jung KH, Hegg R, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet Lond Engl. 2020 Oct 10;396(10257):1090–100.
26. Gianni L, Huang CS, Egle D, Bermejo B, Zamagni C, Thill M, et al. Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple-negative, early high-risk and locally advanced breast cancer: NeoTRIP Michelangelo randomized study. Ann Oncol Off J Eur Soc Med Oncol. 2022 May;33(5):534–43.
27. 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 Lond Engl. 2019 Apr 6;393(10179):1440–52.
28. Gluz O, Nitz U, Kolberg-Liedtke C, Prat A, Christgen M, Kuemmel S, et al. De-escalated neoadjuvant chemotherapy in early triple-negative breast cancer (TNBC): impact of molecular markers and final survival analysis of the WSG-ADAPT-TN trial. Clin Cancer Res Off J Am Assoc Cancer Res. 2022 Nov 14;28(22):4995–5003.
29. Sharma P, Kimler BF, O'Dea A, Nye L, Wang YY, Yoder R, 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 Off J Am Assoc Cancer Res. 2021 Feb 15;27(4):975–82.
30. Mason SR, Willson ML, Egger SJ, Beith J, Dear RF, Goodwin A. Platinum-based chemotherapy for early triple-negative breast cancer. Cochrane Database Syst Rev. 2023 Sep 8;9(9), CD014805.
31. Metzger-Filho O, Collier K, Asad S, Ansell PJ, Watson M, Bae J, et al. Matched cohort study of germline BRCA mutation carriers with triple negative breast cancer in brightness. NPJ Breast Cancer. 2021 Nov 11;7(1):142.
32. Guo S, Shi Y, Lu S, He Y, Jin G, Zhang S, et al. The taxane-based chemotherapy triplet is superior to the doublet in one to nine node-positive but not node-negative triple-negative breast cancer: results from a retrospective analysis. J Cancer. 2020;11(22):6653–62.
33. Blum JL, Flynn PJ, Yothers G, Asmar L, Geyer CEJ, Jacobs SA, et al. Anthracyclines in early breast cancer: the ABC trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG oncology). J Clin Oncol Off J Am Soc Clin Oncol. 2017 Aug 10;35(23):2647–55.
34. Yu KD, Ye FG, He M, Fan L, Ma D, Mo M, et al. Effect of adjuvant paclitaxel and carboplatin on survival in women with triple-negative breast cancer: a phase 3 randomized clinical trial. JAMA Oncol. 2020 Sep 1;6(9):1390–6.
35. Onesti JK, Mangus BE, Helmer SD, Osland JS. Breast cancer tumor size: correlation between magnetic resonance imaging and pathology measurements. Am J Surg. 2008 Dec;196(6):844–8 discussion 849–850.
36. Mittendorf EA, Kantor O, Weiss A, Richardson E, Garrido-Castro A, Portnow LH, et al. Nodal positivity in early-stage triple-negative breast cancer: implications for preoperative immunotherapy. Ann Surg Oncol. 2023 Jan;30(1):100–6.
37. Zdenkowski N. Randomized phase II study of neoadjuvant nivolumab (n) monotherapy 2-week lead-in followed by 12 weeks of concurrent n+carboplatin plus paclitaxel (cbp) vs concurrent n+cbp in triple negative breast cancer (TNBC): (BCT1902/IBCSG 61–20 Neo-N).2023 San Antonio Breast Cancer Symposium; 2023 Dec 5. San Antonio, TX.
38. Sharma P, Stecklein SR, Yoder R, Staley JM, Schwensen K, O'Dea A, et al. Clinical and biomarker findings of neoadjuvant pembrolizumab and carboplatin plus docetaxel in triple-negative breast cancer: NeoPACT phase 2 clinical trial. JAMA Oncol. 2024 Feb 1;10(2):227–35.
39. Korde LA, Somerfield MR, Carey LA, Crews JR, Denduluri N, Hwang ES, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. J Clin Oncol Off J Am Soc Clin Oncol. 2021 May 1;39 (13):1485–505.
40. Han HS, Vikas P, Costa RLB, Jahan N, Taye A, Stringer-Reasor EM. Early-stage triple-negative breast cancer journey: beginning, end, and everything in between. Am Soc Clin Oncol Educ Book. 2023 Jun 1;43, e390464.
41. Ignatiadis M. Adding atezolizumab to adjuvant chemotherapy for stage II and III triple-negative breast cancer is unlikely to improve efficacy: interim analysis of the ALEXANDRA/IMpassion030 phase 3 trial.2023 San Antonio Breast Cancer Symposium; 2023 Dec 5. San Antonio, TX.
42. Mayer IA, Zhao F, Arteaga CL, Symmans WF, Park BH, Burnette BL, et al. Randomized phase III postoperative trial of platinum-based chemotherapy versus capecitabine in patients with residual triple-negative breast cancer following neoadjuvant chemotherapy: ECOG-ACRIN EA1131. J Clin Oncol Off J Am Soc Clin Oncol. 2021 Aug 10;39(23):2539–51.
43. Mamounas E. Loco-regional irradiation in patients with biopsy-proven axillary node involvement at presentation who become pathologically node-negative after neoadjuvant chemotherapy: primary outcomes of NRG oncology/NSABP B-51/RTOG 1304.2023 San Antonio Breast Cancer Symposium; 2023 Dec 5. San Antonio, TX.
44. Hatzipanagiotou ME, Pigerl M, Gerken M, Räpple S, Zeltner V, Hetterich M, et al. Clinical impact of delaying initiation of adjuvant chemotherapy in patients with early triple negative breast cancer. Breast Cancer Res Treat. 2024 Apr;204(3): 607–15.
45. Tung NM, Boughey JC, Pierce LJ, Robson ME, Bedrosian I, Dietz JR, et al. Management of hereditary breast cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. J Clin Oncol Off J Am Soc Clin Oncol. 2020 Jun 20;38(18):2080–106.
46. Chintapally N, Englander K, Gallagher J, Elleson K, Sun W, Whiting J, et al. Tumor characteristics associated with axillary nodal positivity in triple negative breast cancer. Dis Basel Switz. 2023 Sep 8;11(3).
47. Martín M, Yoder R, Salgado R, Del Monte-Millán M, Álvarez EL, Echavarría I, et al. Tumor-infiltrating lymphocytes refine outcomes in triple-negative breast cancer treated with anthracycline-free neoadjuvant chemotherapy. Clin Cancer Res Off J Am Assoc Cancer Res. 2024 May 15;30(10):2160–9.
48. Shulman LN, Cirrincione CT, Berry DA, Becker HP, Perez EA, O'Regan R, et al. Six cycles of doxorubicin and cyclophosphamide or paclitaxel are not superior to four cycles as adjuvant chemotherapy for breast cancer in women with zero to three positive axillary nodes: Cancer and Leukemia Group B 40101. J Clin Oncol Off J Am Soc Clin Oncol. 2012 Nov 20;30(33):4071–6.
49. Golshan M, Wong SM, Loibl S, Huober JB, O'Shaughnessy J, Rugo HS, et al. Early assessment with magnetic resonance imaging for prediction of pathologic response to neoadjuvant chemotherapy in triple-negative breast cancer: results from the phase III BrighTNess trial. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2020 Feb;46(2):223–8.
50. Humbert O, Riedinger JM, Charon-Barra C, Berriolo-Riedinger A, Desmoulins I, Lorgis V, et al. Identification of biomarkers including 18FDG-PET/CT for early prediction of response to neoadjuvant chemotherapy in triple-negative breast cancer. Clin Cancer Res Off J Am Assoc Cancer Res. 2015 Dec 15;21(24): 5460–8.
51. Litton JK, Beck JT, Jones JM, Andersen J, Blum JL, Mina LA, et al. Neoadjuvant talazoparib in patients with germline BRCA1/2 mutation-positive, early-stage triple-negative breast cancer: results of a phase ii study. Oncologist. 2023 Oct 3;28 (10):845–55.
52. Spring LM, Han H, Liu MC, Hamilton E, Irie H, Santa-Maria CA, et al. Neoadjuvant study of niraparib in patients with HER2-negative, BRCA-mutated, resectable breast cancer. Nat Cancer. 2022 Aug;3(8):927–31.
53. Spring LM, Tolaney SM, Fell G, Bossuyt V, Abelman RO, Wu B, et al. Response-guided neoadjuvant sacituzumab govitecan for localized triple-negative breast cancer: results from the NeoSTAR trial. Ann Oncol Off J Eur Soc Med Oncol. 2024 Mar;35(3):293–301.