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Update on systemic treatment in early triple negative breast cancer

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***Abstract*:** Triple negative breast cancer (TNBC) is a heterogeneous disease representing about 15% of all breast cancers. TNBC are usually high-grade histological tumors, and are generally more aggressive and difficult to treat due to the lack of targeted therapies available, and chemotherapy remains the standard treatment. There is a close relationship between pathological complete response after chemotherapy treatment and higher rates of disease-free survival and overall survival. In this review of systemic treatment in early triple negative breast cancer, our purpose is to analyze and compare different therapies, as well as to highlight the novelties of treatment in this breast cancer subtype.

Keywords: chemotherapy, immunotherapy, neoadjuvant therapy, precision medicine, systemic treatment, triple negative breast cancer

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Introduction

Rationale

Triple negative breast cancer (TNBC) represents 15% to 20% of all breast cancers. According to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, TNBC is defined in a standard way by ⩽1% immunohistochemistry (IHC) expression of estrogen and progesterone receptor and absence of erbb2 (HER2) overexpression and/or amplification.[1,2] In addition, TNBC usually have high histological grade and proliferation, and abundant necrotic tissue. This type of cancer is more common in women under 40 years of age, in African, American or Latino women, or in those who carry a BRCA mutation, mainly in the *BRCA1* gene.[3] The biological behavior of TNBC is usually more aggressive, with early recurrences, and has a greater tendency to present distant metastases compared with other breast cancer subtypes.[4–7]

TNBC has a poor prognosis, due mainly to the lack of targeted treatments. The high response rates to chemotherapy (CT) are not prolonged in time due to the early development of resistance mechanisms.[8] The relative 5-year survival rate of localized TNBC is 91%, 65% in locally advanced and 11% in metastatic stages.[8]

Objectives

Here, we present a bibliographic review and a summary of the scientific literature on the systematic treatment of localized and locally advanced TNBC, comparing different therapies and their efficacy, as well as highlighting therapeutic novelties, especially the appearance of immunotherapy for these types of tumors.

Methods

We performed a review of the literature about systemic treatment in early TNBC.

Study selection criteria

Clinical trials, prospective or retrospective cohort studies, and meta-analyses published between January 1995 and October 2020 whose stated primary intent was to assess the systemic treatment of patients with local, or locally advanced, TNBC were included in the review. No limits were placed on the language of publication or on the treatment

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regimen received. Exclusion criteria were studies that did not include TNBC subtype, studies analyzing only metastatic breast cancer, and those with a sample size of fewer than 15 patients.

Search strategy and screening of articles

An electronic search was conducted in three databases: Cochrane Library, MEDLINE and EMBASE. As guidance, literature were reviewed using journals with a high impact factor and therapeutic guidelines from medical societies such as ASCO (American Society of Clinical Oncology), NCCN (National Comprehensive Cancer Network) and ESMO (European Society for Medical Oncology).

Discussion

The therapeutic strategy in the local or locally advanced TNBC includes CT, surgery, and radiotherapy. The choice of treatment must be individualized and carried out by a multidisciplinary tumor board made up of, at least, medical oncologists, radiation oncologists, surgeons, pathologists, and radiologists. The selected therapy is based on the size and location of the primary tumor, the number of lesions, adenopathic involvement, as well as age, menopausal status, and general health conditions, always considering the preferences of each patient.[9] In premenopausal and young patients, the genetic desires of the patients must be taken into account and fertility preservation techniques must be offered before the start of any systemic treatment; *BRCA1/2* status should also be tested.

From the beginning of the disease, TNBC should be considered as a systemic disease,[10] since the presence of micrometastases not visible by conventional imaging techniques has been observed in early stages of the tumor, so we must use CT to attempt a potential healing. Some of the chemotherapeutic agents that have been shown to be effective in TNBC are anthracyclines such as doxorubicin or epirubicin, cyclophosphamide, taxanes, platinum salts, fluoropyrimidines, eribuline, and gemcitabine, among others.[11] Two treatment strategies can be used, administering CT before (neoadjuvant) or after (adjuvant) surgery.

Is CT better before or after surgery?

Neoadjuvant CT (NACT) is the standard treatment in locally advanced breast cancer.[12] The concept of NACT is a newer addition to the anti-neoplastic drug strategies employed in routine cancer management. Several important and unique goals associated with this approach are as follows: to increase the resectability rate by decreasing tumor size (especially tumors >2 cm) thus allowing conservative surgeries to be performed, early control of micrometastatic disease, and testing of the chemosensitivity or chemo-resistance of the tumor *in vivo*. Response to NACT is a predictor of long-term response and gives prognostic information after a short follow-up time, unlike adjuvant studies, which provide results at 5–10 years of follow up. A drawback to NACT is the surgical challenge posed by patients who present a tumor progression to this therapy.[13]

Some studies have confirmed the importance of achieving a pathological complete response (pCR) after NACT since pCR confers a better prognosis and survival.[4,14]

The study conducted by Symmans *et al.* and published in 2017,[15] aimed to measure residual disease after NACT in order to improve the prognostic information that could be obtained from evaluating pathologic response. Pathologic slides and reports were reviewed from 382 patients in two different treatment cohorts: sequential paclitaxel followed by fluorouracil, doxorubicin, and cyclophosphamide (FAC) in 241 patients, and a single regimen of FAC in 141 patients. Residual cancer burden (RCB) was calculated as a continuous index combining pathologic measurements of primary tumor (size and cellularity) and nodal metastases (number and size) for prediction of distant relapse-free survival (DRFS). RCB was independently prognostic in a multivariate model that included age, pretreatment clinical stage, hormone receptor status, and hormone therapy. Minimal RD (RCB-I) obtained in 17% of the patients carried the same prognosis as pCR (RCB-0). Extensive residual disease (RCB-III) reached in 13% of the patients was associated with poor prognosis, regardless of hormone receptor status or adjuvant hormone therapy. The generalizability of RCB for prognosis of distant relapse was confirmed in the FAC-treated validation cohort.[15] RCB determined from routine pathologic materials was a significant predictor of DRFS, and can be used to define categories of near-complete response and CT resistance.[15]

A recent meta-analysis carried out by Spring *et al.*,[16] which included 27,895 individuals from

52 different studies from 1999 to 2016, aimed to assess the prognostic significance of pCR after NACT, using different CT schemes. pCR following NACT appeared to be associated with improved survival outcomes among patients with breast cancer. Patients who experienced pCR were 69% less likely to have disease recurrence compared with their counterparts with residual disease. Moreover, disease-free survival (DFS) and overall survival (OS) outcomes appeared comparable regardless of whether or not patients received adjuvant chemotherapy.[16] The association between pCR and DFS was strongest among patients with TNBC or HER2-positive breast cancer, who were 82% and 68%, respectively, less likely to have disease recurrence following pCR. In addition, patients with pCR showed a 78% lower risk of mortality compared with those who did not have pCR – a trend that was consistent among the TNBC subgroup. In the TNBC subtype, 5-year DFS (90% *versus* 57%), and OS (84% *versus* 47%) were also significantly higher in patients with pCR compared with those with residual disease. The results of this comprehensive meta-analysis overall suggest that pCR is a strong surrogate endpoint for TNBC.[16] Further research is needed to evaluate the clinical utility of escalation or de-escalation strategies in the adjuvant setting based on neoadjuvant response.

NACT was first used in the 1980s in patients with locally advanced breast cancer; its goal was to make inoperable tumors operable.[12,13]

Throughout these years, different randomized phase III trials have been designed with the aim of answering whether NACT is better than adjuvant CT, administering the same CT regimens before and after surgery. The main outcomes in most of these studies were OS and DFS. The first well-designed study with a good sample size was NSABP-B18,[17] in which 1523 patients with local or locally advanced breast cancer were randomized (1:1) to receive four cycles of anthracyclines before or after surgery. Breast tumor size was reduced in 80% of the patients after preoperative therapy and 36% had a pCR. An increase in the percentage of clinical response and pCR was observed in the group with NACT. Breast conserving surgery was greater in the group in which NACT was administered. In a subgroup analysis, this was the first trial to demonstrate that obtaining pCR was associated with higher DFS and OS compared with those with lower degrees of response.[13,18]

In the ECTO study published in 2005,[18] 1355 women were randomized to four cycles of doxorubicin and paclitaxel followed by four cycles of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) in a neoadjuvant way, compared with the same adjuvant scheme and another arm with four cycles of doxorubicin followed by four cycles of CMF. The pCR in the NACT arm was 20%. The percentage of breast conserving surgery was higher with NACT. At 5 years of follow up, DFS and OS were similar in the different schemes.[19]

The meta-analysis of Mauri *et al.* was also published in 2005.[20] The authors evaluated nine randomized studies, including a total of 3946 patients with breast cancer, that compared neoadjuvant therapy with adjuvant therapy regardless of what additional surgery and/or radiation treatment was used. The objective was to answer the question of whether NACT was better than adjuvant CT. This meta-analysis did not find statistically or clinically significant difference in DFS or OS between neoadjuvant therapy and adjuvant therapy, and the probability of progression during the NACT was extremely low (<5%). A higher rate of conservative surgery was observed in the NACT group. NACT was associated with an increased risk of locoregional recurrence, especially when radiotherapy was performed without surgery only in patients who achieved a complete clinical or radiological response. The latter emphasized the importance of incorporating surgery in the locoregional treatment after NACT.[13,20]

A meta-analysis carried out by Mieog,[21] including 14 studies with 5500 patients, was presented in 2007, in which no differences in OS between the use of NACT or adjuvant CT were observed. A lower percentage of mastectomies were detected in the neoadjuvant group. This review demonstrated that the increase in the percentage of local recurrence associated with NACT is reduced significantly after excluding studies in which patients receive RT exclusively after complete tumor regression on imaging tests.[21]

Which CT scheme is more effective?

The clinical response by physical examination as well as the tumor radiological response by imaging tests such as magnetic resonance is observed in 70–90% of patients with NACT, which varies depending on the CT scheme and the number of cycles administered,[22] so several studies have been designed to answer this question.

The NSABP-B27 study included more than 2400 patients to receive four cycles of neoadjuvant AC (doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2), four cycles of AC followed by four cycles of preoperative docetaxel 100 mg/m^2, or four cycles of AC followed by surgery and then four cycles of adjuvant docetaxel every 3 weeks.[23] It was observed that the addition of four cycles of preoperative docetaxel after four cycles of AC significantly increased the rates of pCR (40.1% *versus* 63.6%). In the ACCOG study,[24] 363 patients with inflammatory or locally advanced TNBC were randomized to six cycles of AC (doxorubicin plus cyclophosphamide) or AD (doxorubicin plus docetaxel). At 2 months follow up, there were no significant differences between the two arms in terms of percentage of tumor responses, breast conserving surgery, pCR, and DFS.

The optimal NACT scheme has not been established, although a combination of four anthracycline cycles followed by four of taxanes (weekly paclitaxel or 3-weekly docetaxel) is the combination that achieves the highest percentage of pCR (about 30%).[25]

Despite the fact that the standard treatment is based on CT with anthracyclines and taxanes, in those patients with a high risk of cardiovascular toxicity, this scheme could be substituted by the administration of four cycles of docetaxel and cyclophosphamide despite obtaining somewhat lower results.[26,27]

Sequential or concurrent NACT administration? Paclitaxel weekly or tri-weekly?

Other questions that needed to be answered were whether the administration of anthracyclines and taxanes had to be sequential or concurrent, and whether the latter were to be administered weekly or tri-weekly. To do this, several studies were designed, such as those of GeparDuo *et al.*,[28] AGO,[29] or Green,[30] where it was observed that the anthracycline and taxanes sequential scheme was associated with better results than the concurrent scheme, in addition to achieving a higher rate of pCR and conservative surgery. However, it is impossible to determine whether the observed benefit results from sequential use or from differences in CT doses administered (highest in the sequential arm) or duration of treatment (highest in the sequential arm).[31] It is also concluded that the weekly paclitaxel scheme is more active than the 3-weekly docetaxel.[13,31]

How can we improve efficacy? Adding platinums salts? Role of Nab-paclitaxel? Adding antiangiogenics?

To assess the use of other CT regimens, several clinical trials were carried out, such as the CALGB 40,603 study,[32,33] which assessed the impact of adding carboplatin and/or bevacizumab in early TNBC. A total of 443 patients with stage II to III TNBC received paclitaxel 80 mg/m^2 once per week for 12 weeks, followed by doxorubicin plus cyclophosphamide once every 2 weeks for four cycles, and were randomly assigned to concurrent carboplatin [area under curve (AUC) 6] once every 3 weeks for four cycles and/or bevacizumab 10 mg/kg once every 2 weeks for nine cycles. As expected, regardless of treatment, patients who achieved a pCR were associated with better DFS and OS than those who did not obtain this response. It was observed that the addition of either carboplatin (60% *versus* 44%) or bevacizumab (59% *versus* 48%) significantly increased pCR breast, whereas only carboplatin (54% *versus* 41%) significantly raised pCR breast/axilla. This trial evidenced that the addition of carboplatin or bevazizumab to the NACT improved up to 14% more the number of pCR without obtaining a significantly better DFS.[34]

In the GeparSixto study,[35] 595 patients with previously untreated, non-metastatic, stage II–III, TNBC and HER2-positive breast cancer were randomized 1:1. Patients were treated for 18 weeks with paclitaxel 80 mg/m^2 once a week and non-pegylated liposomal doxorubicin (npDOX) 20 mg/m^2 once a week. Patients with TNBC received simultaneous bevacizumab 15 mg/kg intravenously (iv) every 3 weeks. Patients with HER2-positive disease received simultaneous trastuzumab (8 mg/kg initial dose with subsequent doses of 6 mg/kg iv every 3 weeks) and lapatinib 750 mg daily. In the carboplatin arm, the pCR rate was 53.2% *versus* 36.9% in the other arm. Definitive data were published in 2018, and it was observed that the addition of carboplatin correlated with better DFS, especially in tumors with deficiencies in homologous recombination.[36]

GeparSixto and CALGB 40603 showed that adding carboplatin increases the rate of pCR by 15%. A retrospective analysis of CALGB40603 gene expression found an increase in pCR with the addition of carboplatin (from 47% to 61%) in patients with TNBC – an increase that did not differ significantly from the total study population.[37]

In other subsequent studies such as those published by Alba *et al.*,[38] Sharma *et al.*[39] and Ando *et al.*[40] that compared different combinations of NACT with or without the addition of carboplatin; these studies concluded that better pCR rates were obtained in patients under treatment with platinum-based NACT.

In 2018, the BrighTNess trial included 634 patients that were randomly assigned (2:1:1) to one of three segment 1 regimens[41]: paclitaxel (80 mg/m^2 intravenously weekly for 12 doses) plus carboplatin (AUC 6 every 3 weeks, for four cycles) plus veliparib 50 mg orally twice a day; paclitaxel plus carboplatin plus veliparib/placebo (twice a day); or paclitaxel plus carboplatin/placebo (every 3 weeks for four cycles) plus veliparib/placebo. Following segment 1, all patients were assigned to segment 2, in which they received standard doxorubicin and cyclophosphamide every 2–3 weeks for four cycles. This trial demonstrated that the addition of veliparib to carboplatin and paclitaxel followed by doxorubicin and cyclophosphamide did not improve the rate of pCR. However, the addition of carboplatin to the paclitaxel regimen followed by doxorubicin and cyclophosphamide obtained a pCR rate of 58% *versus* 31%, with an increase in toxicities in the carboplatin arm.[41]

Poggio's meta-analysis, including 2109 patients from nine trials who had received neoadjuvant treatment with platinum-based CT *versus* platinum-free CT, was also published in 2018.[42] The results showed that platinum-based NACT increased the pCR rate significantly from 37% to 52.1% at the expense of increased hematologic toxicities. No difference in DFS was found. Among the 96 BRCA mutation patients included in two trials, the addition of carboplatin was not associated with a significant increase in the rate of pCR.[42]

In the same year, another study published by Sharma *et al.* analyzed the pCR of NACT in TNBC with anthracycline-free platinum plus taxane.[43] A total of 190 patients with stage I–III TNBC were treated with neoadjuvant carboplatin (AUC6) plus docetaxel (75 mg/m^2) every 21 days × 6 cycles, obtaining a pCR rate of 55% and were not influenced by germline BRCA mutation status (pCR 59% in BRCA-associated TNBC *versus* 56% in BRCA wild-type TNBC). The 3-year DFS was 90% in patients with pCR and 66% in those without pCR; 3-year OS was 94% in patients with pCR and 79% in those without pCR.[43]

The results of the phase II trial [ClinicalTrials.gov identifier: NCT02413320] were published in 2019.[44] A total of 100 patients with stage I–III TNBC were randomized (1:1) to receive to either paclitaxel 80 mg/m^2 every week x 12 plus carboplatin (AUC 6) every 3 weeks × 4, followed by doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 2 weeks × 4, or to carboplatin (AUC 6) plus docetaxel (75 mg/m^2) every 21 days × 6 cycles. pCR was 55% in the anthracycline arm, and 52% in the non-anthracycline platinum arm; obtaining similar rates of pCR, but with a more favorable toxicity profile and higher treatment completion in the non-anthracycline regimen. The carboplatin + docetaxel regimen should be further explored as a way to de-escalate therapy in TNBC.[44]

The role of nab-paclitaxel was evaluated in the GeparSepto clinical trial published in 2019,[45] in which 1206 patients were randomized to receive nab-paclitaxel 150 mg/m^2 (after study amendment, 125 mg/m^2) on days 1, 8, and 15 for four 3-week cycles, or solvent-based intravenous paclitaxel 80 mg/m^2 on days 1, 8, and 15 for four 3-week cycles followed by four cycles of epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2, obtaining a higher pCR rate in nab-paclitaxel arm (38% *versus* 29%). At 4-year follow up, a higher DFS was observed in the nab-paclitaxel arm (84.0% *versus* 76.3%) without significant differences in OS.[46]

Various antiangiogenic strategies have been explored in breast cancer using anti-VEGF monoclonal antibodies. Specifically, bevacizumab is the only one that has shown statistically significant benefits in breast cancer but most of the trials were performed in metastatic patients.[47,48] In addition, this type of treatment has an incidence, greater than its comparative arms, of serious adverse events related to bevacizumab such as hypertension, proteinuria, bleeding, heart failure, and thromboembolic events, so currently there is no indication for neoadjuvant treatment with bevacizumab in early TNBC, limiting its use to advanced disease.[49]

What do we do with patients who do not achieve pCR? Can we improve their survival?

Regarding residual disease, patients who do not achieve a pCR after NACT can benefit from adjuvant treatment. In 2017 the CreateX and, more recently, the clinical trial GEICAM/2003-11_CIBOMA/2004-01 were published,[50,51] which

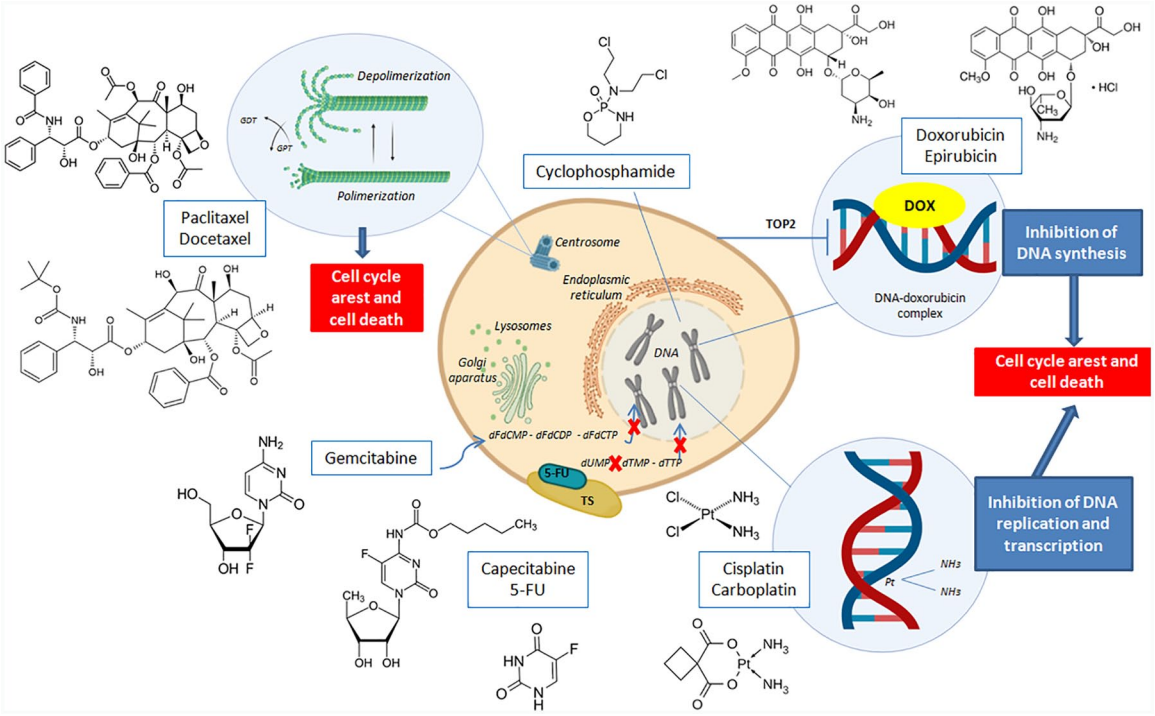

Figure 1. Mechanisms of action of the main chemotherapeutic agents in TNBC. There are several mechanisms by which chemotherapy act in the cancer cell: promote microtubule polymerization and stabilization (taxanes); act as pyrimidine nucleoside antimetabolite (gemcitabine); inhibit TS (5-fluorouracil); form DNA crosslinks (platinum salts); intercalate into DNA and disrupt topoisomerase-II-mediated DNA repair (anthracyclines); cytotoxic effects due to cross-linking of strands of DNA and RNA, and inhibition of protein synthesis (cyclophosphamide). Commonly, most of them cause inhibition of DNA replication and transcription and tumor cell death.
TNBC, triple negative breast cancer; TS, thymidylate synthase

aimed to objectify the benefit of adjuvant capecitabine (1250 mg/m^2 for 6–8 cycles in CreateX and 1000 mg/m^2 for eight cycles in the GEICAM trial) in patients who did not obtain pCR. Both studies showed improvement in DFS in patients who received capecitabine, with a benefit around 14% in CreateX and 3% in GEICAM trial. Recently, the results of the phase III trial conducted by Wang in patients with operable TNBC who were randomly assigned to receive capecitabine as maintenance therapy *versus* observation after standard local and systemic treatment for curative intent were presented at the ASCO Symposium 2020.[52] A total of 434 patients were randomly assigned to capecitabine (650 mg/m^2 twice daily continuously for 1 year) or observation. The 5-year DFS was significantly better with capecitabine *versus* observation (83% *versus* 73%). However, 5-year OS was not significantly different between the two groups (85% *versus* 81%, $p = 0.203$). In a subgroup analysis of the FinXX trial,[53] where capecitabine was added to the adjuvant CT with anthracyclines and taxanes, the 5- and 10-year survival data demonstrated a higher DFS and OS in the triple negative histological subtype with the addition of capecitabine.

Different phase II studies have demonstrated an improvement in DFS and OS with the use of olaparib in patients with metastatic breast cancer with BRCA mutations.[54] The Olympia phase III clinical trial is also evaluating the efficacy of olaparib 300 mg orally for 12 months compare with placebo as an adjuvant treatment in patients with TNBC and BRCA1/2 germline mutations that did not achieve a pCR after NACT.[54]

Immunotherapy

Immunotherapy offers a new opportunity in the treatment of TNBC. Studies with NACT plus immunotherapy with anti-programmed cell death-1 (PD-1) or anti-programmed death-ligand 1 (PD-L1) in early TNBC have been published recently. GeparNew is a phase II randomized trial with durvalumab 1500 mg iv or placebo administered every

4 weeks in addition to nab-paclitaxel 125 mg/m^2 weekly for 12 weeks, followed by standard treatment with epirubicin 75–90 mg/m^2 and cyclophosphamide 600 mg/m^2 every 21 days, for four cycles in TNBC patients.[55] In the window phase, durvalumab/placebo was administered 2 weeks before the start of nab-paclitaxel. The primary pCR rate was 53.4% in the durvalumab arm *versus* 44.2% in the placebo arm without being statistically significant. Subgroup analysis suggested that patients with the highest expression of tumor infiltrating lymphocytes (TILs) had the best results, with the greatest benefit from durvalumab. From this study, it appears that durvalumab could obtain a benefit in rate of pCR, especially in patients with high lymphocytic infiltrate in the tumor.[55]

In the phase III KEYNOTE-522 trial,[56] patients with stage II or III TNBC were randomized to receive therapy with four cycles of 200 mg pembrolizumab every 3 weeks plus paclitaxel 80 mg/m^2 on days 1, 8, and 15 and carboplatin (AUC 5 every 3 weeks on day 1 or AUC 1.5 weekly on days 1, 8, 15) or placebo every 3 weeks instead of pembrolizumab. The two groups subsequently received four additional cycles of pembrolizumab or placebo, and anthracyclines (doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2) plus cyclophosphamide 600 mg/m^2 on day 1 every 3 weeks were administered in both arms. After definitive surgery, patients received pembrolizumab or adjuvant placebo every 3 weeks for a total of nine cycles. The primary endpoint was the pCR rate at the time of surgery and DFS. In this study, a significantly higher pCR rate was observed when pembrolizumab was added to sequential CT with taxanes and platinums followed by anthracyclines and cyclophosphamide, reaching almost 64.8% *versus* 51.2% of pCR, this benefit being independent of PD-L1 expression. At 18 months, 91.3% of patients were disease-free in the pembrolizumab arm *versus* 85.3% in the placebo arm without a large increase in toxicity.[56] With these data, we consider that the addition of immunotherapy to the NACT will become the new standard of treatment in early TNBC.

However, the phase III NeoTRIP clinical trial concluded that the addition of atezolizumab 1200 mg iv infusion every 3 weeks to nab-paclitaxel 125 mg/m^2 and carboplatin AUC 2 given iv on day 1 and day 8 every 3 weeks for a total of eight cycles did not significantly increase the pCR (43.5% *versus* 40.8%) in a population of patients

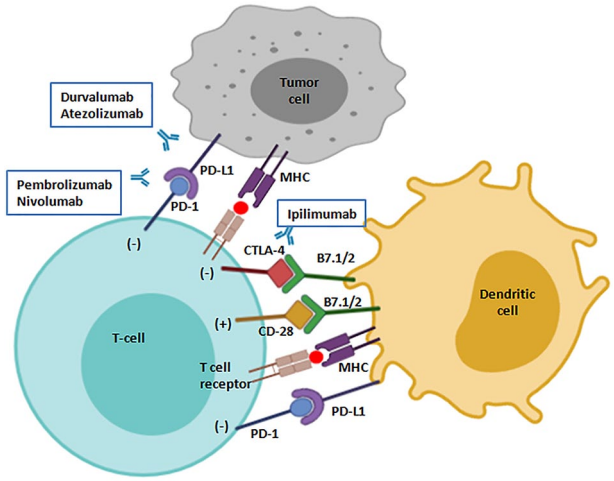

Figure 2. Immunotherapy mechanism of action. PD-1 is expressed on activated T cells and, when it binds to its ligand PD-L1 on tumor cells, leads to T cell exhaustion. CTLA-4 competes with CD28 (costimulatory T cell molecule) for B7 ligands and, upon activation, decreases T cell proliferation as well as activity. Blockade of CTLA-4 (ipilimumab) and PD-1 (pembrolizumab, nivolumab) or PD-L1 (durvalumab, atezolizumab) stimulates effector T cells to produce antitumor responses.
CTLA-4, cytotoxic T-Lymphocyte antigen 4; (PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1

similar to that of the KEYNOTE-522 trial.[56–58] Nevertheless, the main objective in the NeoTRIP study was DFS (not yet reached) instead of pCR as in GeparNew and KEYNOTE-522. Furthermore, the NACT scheme was different between clinical trials, excluding the neoadjuvant anthracyclines and cyclophosphamide in the NeoTRIP trial, both quite immunogenic chemotherapeutic agents.

Results from the Impassion 031 trial were presented at the ESMO Virtual Congress 2020.[59] Impassion031 is a phase III, double-blind, randomized, multicenter, placebo-controlled study for which patients with a TNBC and primary tumor size >2 cm were eligible. A total of 333 patients were randomized (1:1) to receive NACT plus intravenous atezolizumab at 840 mg or placebo every 2 weeks. Chemotherapy comprised of nab-paclitaxel 125 mg/m^2 every week for 12 weeks followed by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 weeks for 8 weeks, followed by surgery. After surgery, 11 doses of atezolizumab were administered every 3 weeks in the immunotherapy group. pCR was significantly documented in 57.6% of the patients in the atezolizumab plus CT group, and in around 41% of the patients in the placebo plus CT group. In the PD-L1-positive population, pCR was

observed in 68.8% of the patients in the atezolizumab *versus* 49.3% in the placebo group.[59]

New strategies

Clinical trials or researching with new drugs and targeted therapies based on molecular characterization to improve pCR and survival are currently underway in TNBC.

The I-SPY trial (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis) is a multi-institutional study of stage II and III breast cancer patients, including a TNBC subgroup, to identify diagnostic markers, validate hypotheses, and develop new treatment strategies against breast cancer.[60] The estimated enrollment is about 4000 participants, and the primary outcome is to determine whether adding experimental agents to standard neoadjuvant medications increases the probability of pCR over standard NACT for each biomarker signature established at trial entry. There are 21 different arms in this trial.[60]

The luminal androgen receptor (LAR) subtype, which is characterized by >10% IHC expression of the androgen receptor (AR) is currently the target of ongoing clinical trials.[61] Notwithstanding the role of the AR in several signaling pathways, its impact, from a biological and clinical standpoint, is still controversial. The LAR subtype has been associated with better prognosis, less CT responsiveness and lower pCR after NACT. Clinical evidence suggests a role for anti-androgen therapies such as bicalutamide, enzalutamide, and abiraterone, offering an interesting chemo-free alternative for chemo-unresponsive patients, and therefore potentially shifting current treatment strategies.[61]

ARTEMIS is a non-randomized phase II clinical trial, and one of the very few trials trying to identify CT-insensitive TNBC during AC neoadjuvant therapy.[62] Patients received four cycles of doxorubicin-based NACT (AC scheme). If the patient's tumor was CT-sensitive by imaging, AC CT was continued, but if not the patient was offered the chance to participate in one of the single-arm therapeutic clinical trials based on molecular profiling of pre-treatment biopsies, pCR being the primary outcome.[62] These trials could be a study with enzalutamide and paclitaxel before surgery in patients with stage I–III LAR subtype. Another sub-trial consisted of treatment with pegylated liposomal doxorubicin, bevacizumab, and everolimus. Another study was based on panitumumab, carboplatin, and paclitaxel. The last of the ARTEMIS trials consisted of the association of nab-paclitaxel with atezolizumab in patients who had evidence of lymphocytic infiltration into the tumor. In the LAR subtype, the threshold for selecting enzalutamide (ZT) was 160 or 120 mg orally daily plus paclitaxel 80 mg/m^2 weekly for 12 cycles; 17 patients with AC-insensitive TNBC received ZT. Out of 15 patients, 5 (33.3%) had responses (pCR or minimal residual cancer burden). Among patients with AC-insensitive TNBC, baseline upregulated androgen response pathway and LAR subtype may benefit from the ZT regimen, potentially by phosphatidylinositol 3-kinase (PI3K) targeting.[62]

A few studies, such as a phase II trial with 50 participants enrolled [ClinicalTrials.gov identifier: NCT02750358] are evaluating anti-androgen drugs in the adjuvant setting.[63] This study is designed to determine the feasibility of 1 year of adjuvant enzalutamide 160 mg orally daily, for the treatment of patients with early TNBC with LAR subtype.[63]

Regarding the PI3K/AKT/mammalian target of the rapamycin (mTOR) pathway, we find some ongoing clinical trials with targeted therapies such as [ClinicalTrials.govidentifier:NCT04216472],[64] a phase II trial comparing nab-paclitaxel and alpelisib for the neoadjuvant treatment of anthracycline refractory TNBC with PIK3CA or PTEN alterations.

A study published in 2014 using everolimus (mTOR inhibitor) in the neoadjuvant setting of TNBC obtained negative results.[65] In this clinical trial, 50 patients were randomized (1:1) to receive NACT with paclitaxel followed by FEC (5-fluorouracil, epirubicin, and cyclophosphamide) *versus* the combination of paclitaxel and everolimus followed by FEC in early TNBC. The addition of everolimus to neoadjuvant paclitaxel did not improve the pCR rate.[65]

AKT inhibition has also been studied in the neoadjuvant context through the randomized phase II FAIRLANE trial with 151 participants.[66,67] Subjects with early TNBC were assigned (1:1) to receive weekly paclitaxel 80 mg/m^2 with ipatasertib (small molecule inhibitor of AKT) 400 mg or placebo on days 1–21 every 28 days for 12 weeks

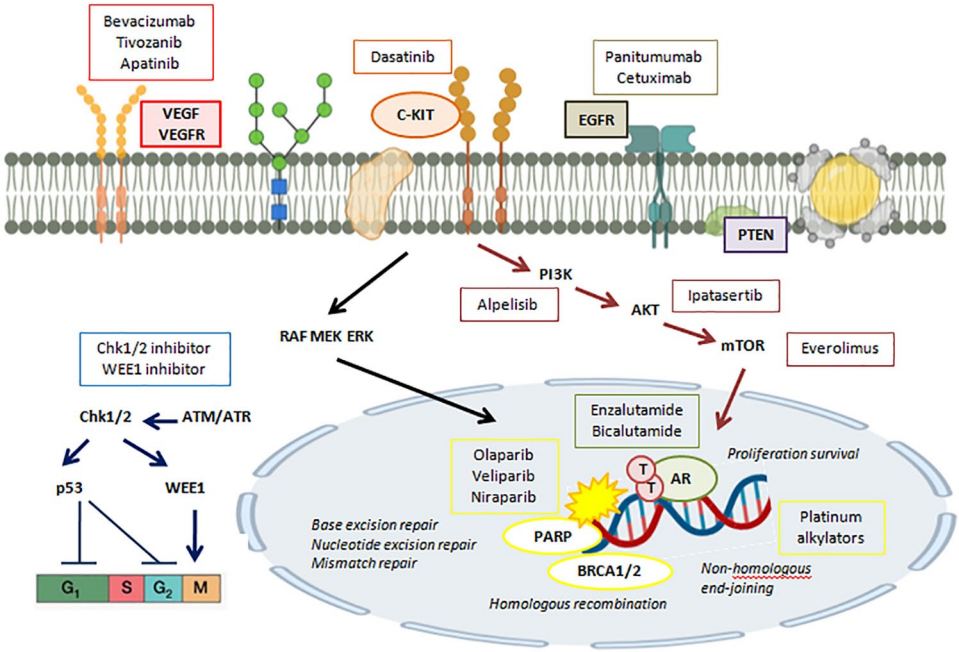

Figure 3. Schematic representation of potential therapeutic targets in TNBC. The potential therapeutic targets involved are presented with their specific inhibitors.
TNBC, triple negative breast cancer

before surgery. The addition of ipatasertib to neoadjuvant paclitaxel did not increase the pCR rate, although the overall response rate by magnetic resonance imaging was numerically higher with this agent. The antitumor effect of ipatasertib was most pronounced in biomarker-selected patients. All patients with a complete response had PIK3CA/AKT1/PTEN altered tumors.[66]

EGFR inhibitors such as panitumumab are being studied for their effectiveness in early TNBC. In a one-single-arm phase II trial published in 2018,[68] a pCR rate of 42% (8/19 patients) was observed with the addition of panitumumab (2.5 mg/kg) to NACT with nab-paclitaxel and carboplatin weekly during 12 weeks followed by four cycles of FEC every 3 weeks.[68] A randomized phase II study is ongoing to determine the role of panitumumab in patients with TNBC and to further validate predictive biomarkers.[68]

Some tyrosine kinase inhibitors agents as apatinib (anti-VEGFR) are under study. In a phase II trial published in September 2020,[69] 17 patients with TNBC stage IIB–IIIC were randomly assigned (2:1) to receive taxanes and platinums based chemotherapy with apatinib 500 mg daily *versus* placebo added to NACT for six cycles every 3 weeks. The addition of apatinib to NACT significantly increased the pCR rate (72.7% *versus* 50%).[69]

Nowadays, there are few studies with new therapies based on antibody drug conjugates. Antibody–drug conjugate is usually composed of a humanized antibody and small molecular drug *via* a chemical linker. Sacituzumab govitecan is a first-in-class antibody-drug conjugate composed of an anti–Trop-2 antibody coupled to the active metabolite of irinotecan, SN-38, *via* a unique hydrolyzable linker that allows for SN-38 release intracellularly and in the tumor microenvironment.[70] The results of the ASCENT study were presented at the ESMO Virtual Congress 2020.[71] A total of 529 patients with TNBC who had relapsed or had refractory disease after at least two prior CTs in the advanced/metastatic setting (prior taxane required) were randomized (1:1) to receive sacituzumab govitecan (10 mg/kg iv on days 1 and 8 every 3 weeks) or single-agent CT (capecitabine, eribulin, vinorelbine, or gemcitabine) until disease progression or unacceptable toxicity. Sacituzumab govitecan significantly improved PFS and median OS.[71] Actually, this drug is being tested in the neoadjuvant setting in the phase II NeoSTAR trial.[72] The primary outcome is the pCR and secondary outcomes are

DFS, OS, change in breast conserving surgery rate, number of participants with treatment-related adverse events and assessment of quality of life. The results are expected in 2022.[72]

Role of immune biomarkers, TILs, and BRCA

There is a close relationship between the immune system and the development of cancer. The immune response has the potential to specifically destroy tumor cells without damaging healthy body tissue, and to create long-term immune memory capable of preventing recurrences. The immune system has, on the one hand, the ability to detect and eliminate tumor cells and, on the other, it can provide a favorable microenvironment for tumor growth. Due to the dual function of some cytokines and molecules of the immune system, it has not yet been possible to clearly distinguish tumor-promoting inflammatory immunity from tumor suppressor immunity. Chronic inflammation in the tumor microenvironment and the tumor's ability to evade the immune response are conditioning factors for oncogenesis.[53] The tumor microenvironment consists of cancer cells, inflammatory cells, and stromal cells. The dynamic interactions of the cells that are part of this microenvironment dictate the environmental conditions in which tumor development occurs. There is sufficient evidence to support the fact that immune cells in the tumor microenvironment can effectively promote or inhibit tumor growth,[73] which could be a prognostic indicator also for breast cancer.

The presence of TILs has been shown in several studies to be the most constant prognostic factor in TNBC,[74] which implicates the immune system in the pathophysiology and, potentially, in the treatment of these tumors.[75] The stratification of the TNBC based on the quantitative evaluation of the TILs distinguishes a subset called "hot" (high percentage of TILs) and another of "cold" (low percentage of TILs) tumors, which seems to be correlated with the response to immunotherapy. It has been verified that a greater lymphocytic infiltration in the initial biopsy predicts a higher rate of pCR after neoadjuvant therapy, thus providing a better prognosis in early TNBC regardless of the systemic treatment used and conferring an improvement of around 10% in DFS and OS due to each 10% increase in TILs.[76–78] Furthermore, the expression of TILs may also be a predictor of response to CT with carboplatin in neodayuvance.[79]

It has been observed that patients with high expression of TILs have a similar DFS and OS regardless of whether or not they received NACT in very early stages of TNBC. The pooled analysis published by Park in late 2019 included data of 476 patients from four centers diagnosed between 1989 and 2015, using four cohorts of TNBC patients not treated with CT.[80] The median tumor size was 1.6 cm and 83% were node-negative. The average expression of TILs was 10%. In patients with pathological stage I tumors with TILs $\geqslant$30%, the 5-year DFS was 91%, metastasis-free survival was 97%, and OS was 98%,[80] these results being superimposable for patients treated with CT. Furthermore, De Jong and colleagues investigated in the PARADIGM study group the prognostic value of stromal TILs to resolve whether all women younger than 40 years with node negative TNBC benefit from CT.[81] For study inclusion, the investigators reviewed the Netherlands Cancer Registry from 1989 to 2000 to identify all women $<$40 years who were diagnosed with node-negative TNBC but did not receive systemic adjuvant treatment. This study was published recently at the ESMO Virtual Congress 2020. The analysis comprised 481 patients with TNBC with a median age of 35 years. A 15-year OS of 59% was found in patients with $<$30% stromal TILs; an OS of 76% in patients with TILS between 30% and 75%, and a 93% of OS in very low-risk patients with $\geqslant$75% stromal TILs.[81] Nevertheless, evidence for the role of TILs as a possible biomarker for de-escalation is mostly from retrospective studies and needs confirmation in prospective cohorts.

Despite the action of the immune system to attack cancer, evasion of immune destruction can occur through mechanisms such as the expression of the ligand of the transmembrane type 1 protein (PD-L1) in tumor cells, which has an immunosuppressive role by binding to their PD-1 or B7 receptors, transmitting an inhibitory signal to T lymphocytes that reduces their proliferation and decreases the immune response.[82] PD-L1 is not detected in normal breast tissue, although its expression has been described in about half of TNBC cases. Furthermore, the tumor expression of PD-L1 and the existence of TILs with PD-1 expression have been associated with a high histological degree, negativity for hormone receptors, and a greater lymphocytic infiltration of the tumor.[83] Unexpectedly, despite a higher relapse rate in patients with positive PD-L1; their OS was better than in patients with

negative PD-L1 − a fact that is attributed to a stronger underlying antitumor immune response due to treatment.[83] Furthermore, PD-L1 protein concentration has been correlated positively with the expression of other immune regulators, such as cytotoxic T-Lymphocyte antigen 4 (CTLA-4) and indoleamine 2,3-dioxygenase 1 (IDO1) as well as with the *BRCA1* gene mutation.[84]

Despite their mismatch in absolute reported PD-L1 concentrations in breast cancer, the data from the previously mentioned studies support the view that therapy with immune checkpoint inhibitors has the potential to improve the prognosis of TNBC by increasing the efficacy of the tumor-associated immune response in killing breast cancer cells. A number of studies are currently underway with PD-1 and PD-L1 inhibitors in combination with chemotherapy, radiation therapy, targeted therapy, and other checkpoint inhibitors. These combined approaches could offer hope to improve current results and to validate some of these drugs in daily clinical practice in breast cancer.[85]

CTLA-4 is a protein receptor located on the cell membrane of T lymphocytes. The function of the T lymphocyte is inhibited by stimulation of the CTLA-4 receptor. A significant CTLA-4 overexpression of more than 50% has been found in TNBC.[86] Furthermore, increased expression of CTLA-4 has also been linked to mutated BRCA1 TNBC due to its increased expression of immunomodulatory genes and an increased somatic mutational load.[87] Studies are currently being carried out with ipilimumab (CTLA-4 inhibitor). A phase II trial [ClinicalTrials.gov identifier: NCT03546686] aims to assess the treatment of Ipilimumab + Nivolumab and perioperative cryoablation *versus* standard CT in patients with early TNBC.[88] The phase II trial [ClinicalTrials.gov identifier: NCT03342417] seeks to evaluate the combination of nivolumab and neoadjuvant ipilimumab in patients with stage II and III TNBC.[89]

Another important enzyme in immune regulation in TNBC is IDO1. This immunomodulatory enzyme is produced primarily by alternately activated macrophages. High expression of IDO1 has been correlated with vascular density and poor prognosis in patients with breast cancer.[90] There are currently initial studies with IDO1 inhibitors alongside CT in the setting of advanced disease.

Mutation of BRCA1/2 tumor suppressor genes occurs in 10–35% of patients with TNBC, and mutation can occur in both the germline and somatic lines.[91] Of note, there is emerging evidence of different sensitivity of systemic agents in BRCA-associated breast cancer, and, more specifically, of increased sensitivity of platinums and poly ADP-ribose polymerase (PARP) inhibitors.[92]

Caramelo's 2019 meta-analysis includes seven studies with a total of 808 patients with early TNBC, of which 159 had BRCA mutation.[93] It was shown that the addition of platinum to NACT regimens tends to increase the rate of pCR in patients with mutated BRCA compared with non-mutated patients, although without being significant.[93]

As previously discussed, in the BrighTNess trial published in 2018,[41] adding veliparib (PARP inhibitor) to carboplatin and paclitaxel followed by doxorubicin and cyclophosphamide did not improve the rate of pCR, although the study did not stratify patients according to the BRCA mutation.

More promising data are shown in the small phase II trial [ClinicalTrials.gov identifier: NCT02282345] with 17 patients that evaluated neoadjuvant single-agent talazoparib for 6 months in patients with locally advanced mutated BRCA TNBC, reporting 59% of pCR.[94] To explore this further, recruitment for a larger phase II trial [ClinicalTrials.gov identifier: NCT03499353] is underway and results are expected from 2021.[95]

GeparOLA is a phase II study comparing olaparib + neoadjuvant paclitaxel *versus* carboplatin + paclitaxel, followed by a standard regimen of epirubicin + cyclophosphamide in patients with early HER2– breast cancer, including, among others, BRCA mutations.[96] The combination of olaparib + paclitaxel has shown a pCR rate of 55%, similar to that of carboplatin-paclitaxel (49%), pending the analysis of response rates in the different subgroups.[96]

In addition, to evaluate the use of PARP inhibitors in the adjuvant setting, the phase III Olympia study is being conducted,[54] comparing the adjuvant use of olaparib *versus* placebo in patients with high-risk TNBC with germline mutations in BRCA; first results are expected from the end of 2020.

Table 1. Trials including platinum-based NACT and complete response rates comparison.

Clinical trial	TNBC patients	NACT scheme	pCR
CALGB40603 SABCS 2013[37]	433	Paclitaxel + AC *versus* Paclitaxel + Carboplatin + AC (+/– Bevacizumab)	41% *versus* 54%
Geparsixto Lancet Onc 2014[35]	315	npDOX + Paclitaxel + Bevacizumab *versus* npDOX + Paclitaxel + Bevacizumab + Carboplatin	42% *versus* 57%
Ando *et al*. J Clin Oncol 2014[40]	75	Paclitaxel + FEC *versus* Paclitaxel + Carboplatin + FEC	26% *versus* 62%
Alba *et al*. BCR 2012[38]	94	EC + Docetaxel *versus* EC + Docetaxel + Carboplatin	30% *versus* 35%
BrighTNess Lancet 2018[41]	634	Paclitaxel *versus* Paclitaxel + Carboplatin + Veliparib *versus* Paclitaxel + Carboplatin	31% *versus* 53% *versus* 58%
Sharma *et al*. J ClinOnc 2019[39]	100	Paclitaxel + Carboplatin + AC *versus* Carboplatin + Docetaxel	55% *versus* 52%

NACT, neoadjuvant chemotherapy; pCR, pathological complete response; TNBC, triple negative breast cancer

Table 2. Comparison of characteristics between clinical trials with neoadjuvant immunotherapy in TNBC.

Clinical trial	Phase	Immunotherapy drug	NACT scheme	Primary endpoint	pCR
GeparNew	II	Durvalumab	Nab-paclitaxel followed by anthracyclines and cyclophosphamide	pCR	53.4%
KEYNOTE-522	III	Pembrolizumab	Paclitaxel and carboplatin followed by anthracyclines and cyclophosphamide	pCR and DFS	64.8%
NeoTRIP	III	Atezolizumab	Nab-paclitaxel and carboplatin	DFS	43.5%
IMPassion 031	III	Atezolizumab	Nab-paclitaxel followed by anthracyclines and cyclophosphamide	pCR	57.6%

DFS, disease-free survival; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; TNBC, triple negative breast cancer

Proposal treatment for early TNBC

To assign a level of evidence and a grade of recommendation to the different statements of treatments in this proposal, it was decided to use the Infectious Diseases Society of America–US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines.[97]

Systemic treatment proposal in early TNBC according to evidence-based grade of recommendations is as follows (see Tables 1, 2, and 3):

- Consider NACT in all patients with TNBC tumors ⩾2 cm (I, A).
- A sequential regimen of anthracyclines and taxanes is recommended for the vast majority of patients (I, A).
- Weekly nab-paclitaxel could replace neoadjuvant paclitaxel (I, B).
- The addition of a platinum (usually carboplatin) compound in the NACT scheme may be considered (I, A).
- For anthracycline non-fit patients, the NACT regimen could consist in carboplatin plus docetaxel (I, B).
- In high-risk, patients not achieving pCR after standard NACT, the addition of 6–8 cycles of capecitabine postoperatively may be considered (I, B).
- In the near future, immunotherapy drugs such as durvalumab, atezolizumab, or pembrolizumab should be considered during NACT (I, B).
- In some special cases, such as stage I tumors with TILS ⩾30%, we could consider saving

Table 3. Strength of recommendation and quality of evidence score.

Category, grade	Description
Strength of recommendation:	
A	Good evidence to support a recommendation for use, strongly recommended
B	Moderate evidence to support a recommendation for use, generally recommended
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use, generally not recommended
E	Good evidence to support a recommendation against use, never recommended
Quality of evidence:	
I	Evidence from ⩾1 properly randomized, controlled trial
II	Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

CT based on some data from retrospective studies (III, C).

- We should consider clinical trials with new strategies for all patients, especially with antiandrogen drugs for the luminal androgen receptor subtype or PARP inhibitors for *BRCA1/2* mutations.

Conclusion

Achieving pCR after NACT constitutes the main factor that correlates with better outcomes and improved survival in early TNBC. pCR occurs in about 35% of the patients treated with NACT using the standard four-cycle anthracycline regimen followed by weekly paclitaxel for 12 weeks. However, patients who do not reach pCR have a high recurrence rate, so under these circumstances they would benefit from adjuvant treatment with capecitabine. To improve the prognosis of these patients, new agents are currently being associated with NACT, such as combinations with carboplatin and the substitution of paclitaxel by nab-paclitaxel, which can lead to a 40–60% pCR that can be increased with the addition of immunotherapy. In patients with very early stages and high expression of TILs, we could save the use of CT, since optimal surgery would be potentially curative, but prospective studies are needed. In addition, several trials with new therapeutic agents such as PARP inhibitors, antiandrogen drugs, antibody-drug conjugates or immunotherapy doublets among others are underway to find out the impact of various therapies and improve cure rates in early TNBC. Prospective clinical trials based on specific biomarkers are required in order to personalize TNBC treatment in the near future.

Conflict of interest statement

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References

1. Dimitrova N, Saz-Parkinson Z, Bramesfeld A, *et al.* European guidelines for breast cancer screening and diagnosis: the European breast guidelines. https://ec.europa.eu/jrc/en/publication/

european-guidelines-breast-cancer-screening-and-diagnosis-european-breast-guidelines (2016).

2. Hammond ME, Hayes DF, Dowsett M, *et al*. American society of clinical oncology/ college of American pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *Arch Pathol Lab Med* 2010; 134: e48–e72.

3. Gonzalez-Angulo AM, Timms KM, Liu S, *et al*. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. *Clin Cancer Res* 2011; 17: 1082–1089.

4. Liedtke C, Mazouni C, Hess KR, *et al*. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *Int J Clin Oncol* 2008; 26: 1275–1281.

5. Yao Y, Chu Y, Xu B, *et al*. Risk factors for distant metastasis of patients with primary triple-negative breast cancer. *Biosci Rep* 2019; 39: BSR20190288.

6. Zaharia M and Gómez H. Cáncer de mama triple negativo: una enfermedad de difícil diagnóstico y tratamiento. *Revista Peruana de Medicina Experimental y Salud Pública* 2013; 30: 649–656.

7. Carey LA, Perou CM, Livasy CA, *et al*. Race, breast cancer subtypes, and survival in the Carolina breast cancer study. *JAMA Oncol* 2006; 295: 2492–2502.

8. Carey LA, Dees EC, Sawyer L, *et al*. The triple-negative paradox: primary tumor chemosensitivity of breast cancer subtypes. *Clin Cancer Res* 2007; 13: 2329–2334

9. Cardoso F, Kyriakides S, Ohno S, *et al*.; ESMO Guidelines Committee. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019; 30: 1194–1220.

10. Redig AJ and Allister S. Breast cancer as a systemic disease: a view of metastasis. *J Intern Med* 2013; 274: 113–126.

11. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 365: 1687–1717.

12. Kaufmann M, Von MincNwitz G, Smith R, *et al*. Internacional expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: review and recommendations. *Clin Oncol* 2003; 21: 2600–2608.

13. Velasco M, Martínez S, Cerdà P, *et al*. Quimioterapia neoadyuvante en el cáncer de mama localmente avanzado. *Revista de Senología y Patología Mamaria* 2012; 25: 14–21.

14. Haque W, Verma V, Hatch S, *et al*. Response rates and pathologic complete response by breast cancer molecular subtype following neoadjuvant chemotherapy. *Breast Cancer Res Treat* 2018; 170: 559–567.

15. Symmans WF, Peintinger F, Hatzis C, *et al*. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol* 2007; 25: 4414–4422.

16. Spring LM, Fell G, Arfe A, *et al*. Pathologic complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: a comprehensive meta-analysis. *Clin Cancer Res* 2020; 26: 2838–2848.

17. Fisher B, Bryant J, Wolmar N, *et al*. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *Clin Oncol* 1998; 16: 2672–2685.

18. Gianni L, Baselga J, Eiermann W, *et al*. Feasibility and tolerability of sequential doxorubicin/paclitaxel followed by cyclophosphamide, methotrexate, and Fluorouracil and its effects on tumor response as preoperative therapy. *Clin Cancer Res* 2005; 11: 8715–8721.

19. Gianni L, Baselga J, Eiermann W, *et al*. Phase III trial evaluating the addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate and Áuorouracil, as adMuvant or primary systemic therapy: results of a randomized phase III European Cooperative Trial in Operable Breast Cancer (ECTO). *J Clin Oncol* 2009; 27: 2474–2481.

20. Mauri D, Pavlidis N and Ioannidis JP. Neoadjuvant ***versus*** adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst* 2005; 97: 188–194.

21. Mieog JS, Van der Hage JA and Van de Velde CJ. Neoadjuvant chemotherapy for operable breast cancer. *Br J Surg* 2007; 94: 1189–1200.

22. Haufmann M, Von MincNwitz G, Smith R, *et al*. Internacional expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: review and recommendations. *J Clin Oncol* 2009; 21: 2600–2608.

23. Bear HD, Anderson S, Brown A, *et al*. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from national surgical adjuvant breast and

bowel project protocol B-27. *J Clin Oncol* 2003; 21: 4165–4174.

24. Evans TRJ, Yellowlees A, Foster E, *et al*. Phase III randomized trial of doxorubicin and docetaxel ***versus*** doxorubicin and cyclophosphamide as primary medical therapy in women with breast cancer: an AngloCeltic cooperative oncology group study. *J Clin Oncol* 2005; 2: 2988–2995.
25. Bear HD, Anderson S, Smith RE, *et al*. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: national surgical adjuvant breast and bowel project protocol B-27. *J Clin Oncol* 2006; 24: 2019–2027.
26. Jones S, Holmes FA, O'Shaughnessy J, *et al*. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of us oncology research trial 9735. *J Clin Oncol* 2009; 27: 1177–1183.
27. Blum JL, Flynn PJ, Yothers G, *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* 2017; 35: 2647–2655.
28. Von Mincwitz G, Raab G, Caputo A, *et al*. Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German Breast Group. *J Clin Oncol* 2005; 23: 2676–2685.
29. Untch M, Konecny G, Ditsch N, *et al*. Dose-dense sequential epirubicin and paclitaxel as preoperative treatment of breast cancer: results of a randomized AGO study. *J Clin Oncol* 2002; 21: 133a.
30. Green MC, Buzdar AU, Smith T, *et al*. Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. *J Clin Oncol* 2005; 23: 5983–5992.
31. Sachelarie I, Grossbard ML, Chadha M, *et al*. Primary systemic therapy of breast cancer. *Oncologist* 2006; 11: 574–589.
32. Sikov WM, Berry DA, Perou CM, *et al*. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J Clin Oncol* 2015; 33: 13–21.
33. Seidman AD, Berry D, Cirrincione C, *et al*. CALGB 9840: phase III study of weekly paclitaxel via 1-hour infusion ***versus*** standard 3h infusion every third week in treatment of metastatic breast cancer, with trastuzumab for +ER-2 positive MBC and randomized for T in +ER-2 normal MBC. *J Clin Oncol* 2004; 23: 512a.
34. Sikov WM, Polley MY, Twohy E, *et al*. CALGB (Alliance) 40603: long-term outcomes (LTOs) after neoadjuvant chemotherapy (NACT) +/– carboplatin (Cb) and bevacizumab (Bev) in triple-negative breast cancer (TNBC). *J Clin Oncol* 2019; 37: 591–591.
35. Von Minckwitz G, Schneeweiss A, Loibl S, *et al*. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol* 2014; 15: 747–756.
36. Loibl S, Weber KE, Timms KM, *et al*. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. *Ann Oncol* 2018; 29: 2341–2347.
37. Castrellon AB, Pidhorecky I, Valero V, *et al*. The role of carboplatin in the neoadjuvant chemotherapy treatment of triple negative breast cancer. *Oncol Rev* 2017; 11: 324.
38. Alba E, Chacon JI, Lluch A, *et al*. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006-03, multicenter study. *Breast Cancer Res Treat* 2012; 136: 487–493.
39. Sharma P, Stecklein S, Kimler B, *et al*. Efficacy of neoadjuvant carboplatin/docetaxel chemotherapy in sporadic and BRCA-associated triple-negative breast cancer (TNBC). *J Clin Oncol* 2014; 32: 1022–1022.
40. Ando M, Yamauchi H, Aogi K, *et al*. Randomized phase II study of weekly paclitaxel with or without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA HER2-negative breast cancer. *J Clin Oncol* 2014; 32: 1017–1017.
41. Loibl S, O'Shaughnessy J, Untch M, *et al*. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. *Lancet Oncol* 2018; 19: 497–509.
42. Poggio F, Bruzzone M, Ceppi M, *et al*. Platinum-based neoadjuvant chemotherapy

in triple-negative breast cancer: a systematic review and meta-analysis. *Ann Oncol* 2018; 29: 1497–1508.

43. Sharma P, López-Tarruella S, García-Saenz JA, *et al*. Pathological response and survival in triple-negative breast cancer following neoadjuvant carboplatin plus docetaxel. *Clin Cancer Res* 2018; 24: 5820–5829.

44. Sharma P, Kimler BF, O'Dea A, *et al*. Results of randomized phase II trial of neoadjuvant carboplatin plus docetaxel or carboplatin plus paclitaxel followed by AC in stage I-III triple-negative breast cancer (NCT02413320). *J Clin Oncol* 2019; 37: 516–516.

45. Untch M, Jackisch C, Schneeweiss A, *et al*. Nab-paclitaxel *versus* solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto—GBG 69): a randomised, phase 3 trial. *Lancet Oncol* 2016; 17: 345–356.

46. Untch M, Jackisch C, Schneeweiss A, *et al*. NAB-Paclitaxel improves disease-free survival in early breast cancer: GBG 69–GeparSepto. *J Clin Oncol* 2019; 18: 01842.

47. Miller K, Wang M, Gralow J, *et al*. Paclitaxel plus bevacizumab *versus* paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007; 357: 2666–2676.

48. Brufsky AM, Hurvitz S, Perez E, *et al*. IBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol* 2010; 29: 4286–4293.

49. Munoz R, Shaked Y, Bertolini F, *et al*. Anti-angiogenic treatment of breast cancer using metronomic low-dose chemotherapy. *Breast* 2005; 14: 466–479.

50. Masuda N, Lee SJ, Im O, *et al*. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med* 2017; 376: 2147–2159.

51. Lluch A, Barrios C, Torrecillas L, *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: 203–213.

52. Wang X, Wang S, Huang H, *et al*. Phase III trial of metronomic capecitabine maintenance after standard treatment in operable triple-negative breast cancer (SYSUCC-001). *J Clin Oncol* 2020; 38: 507–507.

53. Venturini M, Paridaens R, Rossner D, *et al*. An open-label, multicenter study of outpatient capecitabine monotherapy in 631 patients with pretreated advanced breast cancer. *Oncology* 2007; 72: 51–57.

54. James AN, Kaufman B, Gelber R, *et al*. Olympia: a randomized phase III trial of olaparib as adjuvant therapy in patients with high-risk HER2-negative breast cancer (BC) and a germline BRCA1/2 mutation (gBRCAm). *J Clin Oncol* 2017; 67(Suppl. 5): 33.

55. Loibl S, Untch M, Burchardi N, *et al*. A randomised phase II study investigating durvalumab in addition to an anthracyclinetaxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. *Ann Oncol* 2019; 30: 1279–1288.

56. Schmid P, Cortes J, Pusztai L, *et al*.; for the KEYNOTE-522 Investigators. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med* 2020; 382: 810–821.

57. Gianni L, Huang C, Egle D, *et al*. Pathologic complete response to neoadjuvant treatment with or without atezolizumab in triple-negative, early high-risk and locally advanced breast cancer. NeoTRIPaPDL1 Michelangelo randomized study. *San Antonio Breast Cancer Symposium*, 10-14 December 2019, San Antonio, TX. Abstract GS3–04.

58. Goodman A. No improved pathologic complete response with atezolizumab in early triple-negative breast cancer. *The ASCO Post*, 2020.

59. Mittendorf EA, Zhang H, Barrios CH, *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* 2020; 396: 1090–1100.

60. ClinicalTrials. gov. US National Institutes of Health. I-SPY 2 trial: neoadjuvant and personalized adaptive novel agents to treat breast cancer, https://clinicaltrials.gov/ct2/show/NCT01042379.

61. Gerratana L, Basile D, Buono G, *et al*. Androgen receptor in triple negative breast cancer: a potential target for the targetless subtype. *Cancer Treat Rev* 2018; 68: 102–110.

62. ClinicalTrials. gov. Molecular testing and imaging in improving response in patients with stage I-III triple-negative breast cancer receiving chemotherapy MDACC breast moonshot initiative. ClinicalTrials.gov Identifier:

NCT02276443, https://clinicaltrials.gov/ct2/show/NCT02276443

63. Traina TA, Boyle LA, Arumov A, *et al*. Adjuvant enzalutamide for the treatment of early-stage androgen receptor-positive (AR+) TNBC. *J Clin Oncol* 2019; 37: 546–546.
64. Damodaran S, Litton JK and Hess KR. A phase-2 trial of neoadjuvantalpelisib and nab-paclitaxel in anthracycline refractory triple negative breast cancers with PIK3CA or PTEN alterations. In: *Proceedings of the 2019 San Antonio Breast Cancer Symposium*, San Antonio, TX. Philadelphia, PA: AACR, Cancer Research, 2020. Abstract OT2-06-01.
65. Gonzalez-Angulo AM, Akcakanat A, Liu S, *et al*. Open-label randomized clinical trial of standard neoadjuvant chemotherapy with paclitaxel followed by FEC *versus* the combination of paclitaxel and everolimus followed by FEC in women with triple receptor-negative breast cancer. *Ann Oncol* 2014; 25: 1122–1127.
66. Oliveira M, Saura C and Calvo I. *Primary results from FAIRLANE (NCT02301988), a double-blind placebo (PBO)-controlled randomized phase II trial of neoadjuvantipatasertib (IPAT) + paclitaxel (PAC) for early triple-negative breast cancer (eTNBC)*. Poster presented at 2018 American Association for Cancer Research Annual Meeting, Chicago, IL, 2018.
67. Oliveira M, Saura C, Nuciforo P, *et al*. FAIRLANE, a double-blind placebo-controlled randomized phase II trial of neoadjuvantipatasertib plus paclitaxel for early triple-negative breast cancer. *Ann Oncol* 2019; 30: 1289–1297.
68. Matsuda N, Wang X, Lim B, *et al*. Safety and efficacy of panitumumab plus neoadjuvant chemotherapy in patients with primary her2-negative inflammatory breast cancer. *JAMA Oncol* 2018; 4: 1207–1213.
69. Liu Y, Zhang X, Wang L, *et al*. 270P Apatinib added to taxanes and platinum neoadjuvant chemotherapy for patients with triple-negative and HER2-positive breast cancer: a multicenter, randomized, phase II, open-label trial. *Ann Oncol* 2020; 31: S346.
70. Sahota S and Vahdat LT. Sacituzumabgovitecan: an antibody-drug conjugate. *Expert Opin Biol Ther* 2017; 17: 1027–1031.
71. Bardia A, Tolaney SM, Loirat D, *et al*. ASCENT: a randomized phase III study of sacituzumabgovitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC). *Ann Oncol* 2020; 31: S1142–S1215.
72. ClinicalTrials.gov. Sacituzumab GovitecanIn TNBC (NeoSTAR). ClinicalTrials.gov Identifier: NCT04230109, https://clinicaltrials.gov/ct2/show/NCT04230109
73. Jacobo M, Huerta JG and Cravioto P. Interacciones entre el cáncer y el sistema inmunológico. *Revista Alergia, asma e inmunología* 2017; 26: 56–63.
74. Zgura A, Galesa L, Bratila E, *et al*. Relationship between tumor infiltrating lymphocytes and progression in breast cancer. *Maedica (Buchar) J Clin Oncol* 2018; 13: 317–320.
75. Kurozumi S, Matsumoto H, Kurosumi M, *et al*. Prognostic significance of tumour-infiltrating lymphocytes for oestrogen receptor-negative breast cancer without lymph node metastasis. *Oncol Lett* 2019; 17: 2647–2656.
76. Loi S, Druba D, Adams S, *et al*. Tumor-Infiltrating lymphocytes and prognosis: a pooled individual patient analysis of early-stage triple-negative breast cancers. *J Clin Oncol* 2019; 37: 559–569.
77. Dieci MV, Radosevic-Robin N, Fineberg S, *et al*. Update on tumor-infiltrating lymphocytes (TILs) in breast cancer, including recommendations to assess TILs in residual disease after neoadjuvant therapy and in carcinoma in situ: a report of the international immuno-oncology biomarker working group on breast cancer. *Semin Cancer Biol* 2018; 52: 16–25.
78. Dadiani M, Necula D, Kahana-Edwin S, *et al*. TNFR2+ TILs are significantly associated with improved survival in triple-negative breast cancer patients. *Cancer Immunol Immunother* 2020; 69: 1315–1326.
79. Denkert C, von Minckwitz G, Brase JC, *et al*. Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. *J Clin Oncol* 2015; 33: 983–991.
80. Park JH, Jonas SF, Bataillon G, *et al*. Prognostic value of tumor infiltrating lymphocytes in patients with early-stage triple-negative breast cancers (TNBC) who did not receive adjuvant chemotherapy. *Ann Oncol* 2019; 30: 1941–1949.
81. De Jong VMT, Wang Y, Opdam M, *et al*. Prognostic value of tumor infiltrating lymphocytes in young triple negative breast cancer patients who did not receive adjuvant systemic treatment; by the PARADIGM study group. *Ann Oncol* 2020; 31: S303.

82. Voutsadakis IA. Immune blockade inhibition in breast cancer. *Anticancer Res* 2016; 36: 5607–5622.

83. Muenst S, Schaerli AR, Gao F, *et al*. Expression of programmed death ligand 1 (PD-L1) is associated with poor prognosis in human breast cancer. *Breast Cancer Res Treat* 2014; 146: 15–24.

84. Wen WX and Leong C. Association of BRCA1- and BRCA2-deficiency with mutation burden, expression of PD-L1/PD-1, immune infiltrates, and T cell-inflamed signature in breast cancer. *PLoS One* 2019; 14: e0215381.

85. Cyprian FS, Akhtar S, Gatalica Z, *et al*. Targeted immunotherapy with a checkpoint inhibitor in combination with chemotherapy: a new clinical paradigm in the treatment of triple-negative breast cancer. *Bosn J Basic Med Sci* 2019; 19: 227–233.

86. Kassardjian A, Shintaku PI and Moatamed NA. Expression of immune checkpoint regulators, cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death-ligand 1 (PD-L1), in female breast carcinomas. *PLoS One* 2018; 13: e0195958.

87. Marra A, Viale G and Curigliano G. Recent advances in triple negative breast cancer: the immunotherapy era. *BMC Med* 2019; 17: 90.

88. ClinicalTrials.gov. Peri-Operative Ipilimumab+Nivolumab and Cryoablation *versus* standard care in women with triple-negative breast cancer. ClinicalTrials.gov Identifier: NCT03546686, https://clinicaltrials.gov/ct2/show/NCT03546686

89. ClinicalTrials.gov. Combination of nivolumab and ipilimumab in breast, ovarian and gastric cancer patients. ClinicalTrials.gov Identifier: NCT03342417, https://clinicaltrials.gov/ct2/show/NCT03342417

90. Wei L, Zhu S, Li M, *et al*. High indoleamine 2,3-dioxygenase is correlated with microvessel density and worse prognosis in breast cancer. *Front Immunol* 2018; 9: 724.

91. Chen H, Wu J, Zhang Z, *et al*. Association between BRCA status and triple-negative breast cancer: a meta-analysis. *Front Pharmacol* 2018; 9: 909.

92. Martínez de and Dueñas E. Tratamiento médico del cáncer de mama avanzado con mutación germinal de BRCA. *Revisiones en cáncer* 2015; 29: 187–195.

93. Caramelo O, Silva C, Caramelo F, *et al*. The effect of neoadjuvant platinum-based chemotherapy in BRCA mutated triple negative breast cancers -systematic review and meta-analysis. *Hereditary Cancer in Clinical Practice* 2019; 17: 11.

94. Litton JK, Scoggins M, Hess KR, *et al*. Neoadjuvanttalazoparib (TALA) for operable breast cancer patients with a BRCA mutation (BRCA+). *J Clin Oncol* 2018; 36: 508–508.

95. ClinicalTrials.gov. Talazoparib for neoadjuvant treatment of germline BRCA1/2 mutation patients with early human epidermal growth factor receptor 2 negative breast cancer. ClinicalTrials.gov Identifier: NCT03499353, https://clinicaltrials.gov/ct2/show/NCT03499353

96. Fasching PA, Jackisch C, Rhiem K, *et al*. GeparOLA: a randomized phase II trial to assess the efficacy of paclitaxel and olaparib in comparison to paclitaxel/carboplatin followed by epirubicin/cyclophosphamide as neoadjuvant chemotherapy in patients (pts) with HER2-negative early breast cancer (BC) and homologous recombination deficiency (HRD). *J Clin Oncol* 2019; 37(Suppl. 15): 506.

97. Wormser G, Dattwyler RJ, Shapiro ED, *et al*. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the infectious diseases society of America. *Clin Infect Dis* 2006; 43: 1089–1134.

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