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BREAST CANCER (AS ZIMMER, SECTION EDITOR)

# Emerging Therapeutics for Patients with Triple-Negative Breast Cancer

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## Abstract

**Purpose of review** Triple negative breast cancer (TNBC) accounts for approximately 10–15% of all breast cancers and it is associated with a poor prognosis. However, recent new effective treatment strategies have improved its outcomes. The aim of this review is to provide an overview on the emerging therapeutics for TNBC, describing both previously approved therapies that are currently being repurposed, as well as new target therapies that may improve patient outcomes.

**Recent findings** Emerging therapies are forthcoming in TNBC's treatment landscape, including new post-neoadjuvant chemotherapy strategies, PARP inhibitors, immune checkpoint inhibitors, and antibody-drug conjugates. Combination of different therapies such as AKT/PI3K/mTOR-inhibitors, other immunotherapeutic agents, CDK-inhibitors, antiandrogens, antiangiogenics, and histone deacetylase inhibitors is under clinical investigation.

**Summary** The treatment landscape for TNBC is gradually evolving towards a more personalized approach with promising expectations.

**Keywords** Triple-negative breast cancer, · Breast cancer, · New treatments, · New therapies, · PARP inhibitors, · Immunotherapy

## Introduction

Triple-negative breast cancer (TNBC) accounts for about 10–15% of newly diagnosed breast cancers (BC) and is associated with worse overall survival (OS) compared to other BC subtypes (5-year OS of 76.5% versus 94% for luminal BC) [1]. More than 30% of patients with TNBC eventually develop metastatic disease and relapses often occur during the first 2–3 years from diagnosis [2, 3].

This prognosis reflects an intrinsic aggressive behavior since TNBC is often associated with high histological grade and high proliferation index (ki67) [4] as well as the lack of actionable oncogenic targets, namely hormone receptors and human epidermal growth factor receptor-2 (HER2) [5].

For many years, chemotherapy has been the only available systemic treatment option for TNBC, but, recently, a deeper understanding of genomic and molecular characteristics of TNBC has led to the introduction of new target therapies. TNBC is no longer considered a single entity since different subtypes have been identified, depending on different protein expressions, genomic alterations, and/or mRNA signatures [6].

Lehmann et al. evaluated gene expression profiles of TNBC and identified six subtypes: two basal-like, immunomodulatory, mesenchymal, mesenchymal stem–like, and luminal androgen receptor (LAR) subtypes [7]. Another classification, proposed by Burnstein et al. distinguishes four different subtypes with its own characteristics and prognosis: LAR, mesenchymal, basal-like immunosuppressed, and basal-like immune-activated [8]. Each molecular subtype showed different degrees of sensitivity to targeted therapies [7]. Thus far, these classifications have no direct implications in clinical practice. However, molecular analyses of TNBC are leading towards a more tailored approach in clinical trials.

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The aim of this review is to provide an overview on the emerging therapeutics for TNBC treatment, describing both previously approved therapies which are currently being evaluated in different scenarios (i.e., therapies approved in the metastatic setting, under evaluation in the early setting), and new therapies that may improve patient outcomes (Fig. 1).

## Current Treatment Strategy for TNBC

### Early Setting

The standard of care is represented by dose-dense anthracycline-based chemotherapy followed by a taxane [9]. While clinical data suggest that TNBC is particularly sensitive to platinum salts and support the use of platinum-based chemotherapy in the advanced setting [10, 11], the use of carboplatin in the neoadjuvant setting is still a matter of debate [12–14]. Platinum-based neoadjuvant regimens are associated with higher pathological complete response (pCR) rates [12]. However, there is no conclusive data on long-term outcome benefit, although some adjuvant data recently became available for anthracycline-free platinum-containing regimens [15–17].

### Advanced Setting

In current clinical practice, a proposed treatment algorithm for advanced TNBC relies on the *BRCA* mutational status and PD-L1 expression [3]. In the presence of a germline *BRCA* mutation, platinum-based chemotherapy or PARP inhibitors (PARPi) represent first-line treatment options. In case of PD-L1 expression (defined as PD-L1≥1% on immune cells with the SP142 assay, Ventana), first-line treatment with atezolizumab and nab-paclitaxel should be considered. For *BRCA*-wild-type TNBC without PD-L1 expression, chemotherapy is the first-line treatment option [3]. Sequential single-agent chemotherapy represents the optimal approach, while combinations should be reserved for patients with high disease burden, rapid clinical progression or visceral crisis. Anthracyclines or taxanes are recommended first-line options, provided patients did not progress on these regimens in the early setting. Other treatment options exist and their choice depends on patients preferences, comorbidities and safety profile [10]. Inclusion in clinical trials should be considered at any disease stage, where available.

## Repurposing Previously Approved Therapies into New Settings

### Chemotherapy in the Post-neoadjuvant Setting

The CREATE-X study showed that the use of adjuvant capecitabine in HER2-negative BC without pCR after neoadjuvant

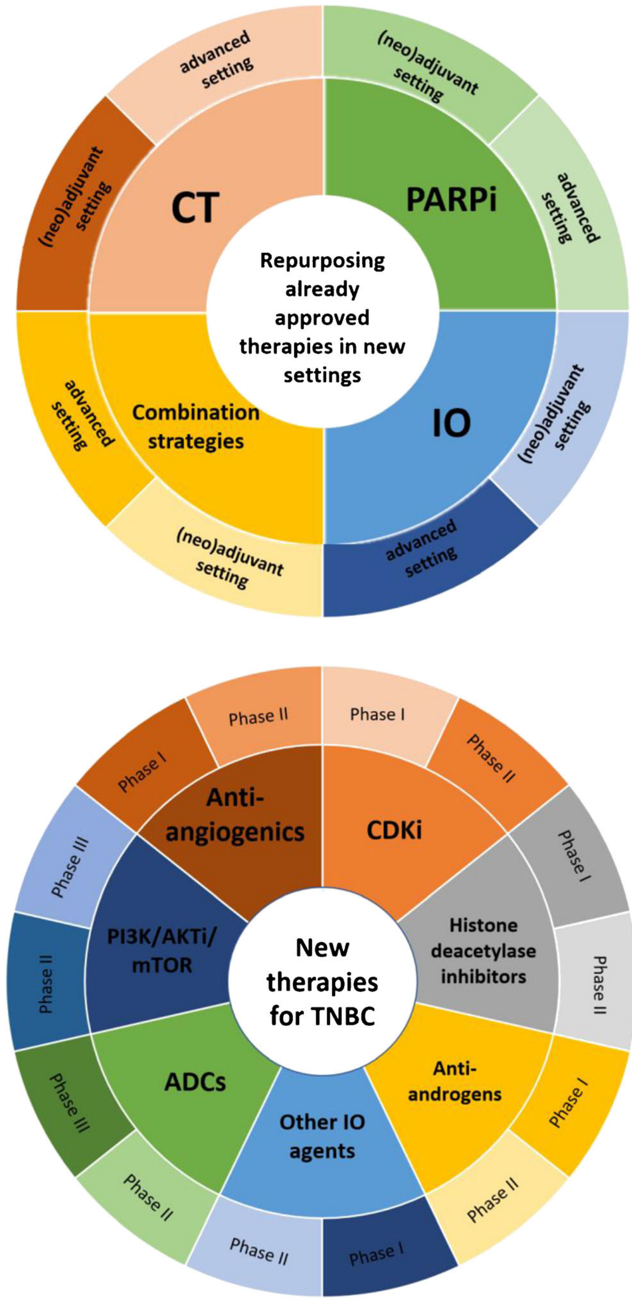


**Fig. 1** Emerging therapeutics for triple-negative breast cancer. CT: chemotherapy, PARPi: PARP-inhibitors, IO: immunotherapy, CDKi: cyclin-dependent kinase inhibitors, ADCs: antibody-drug conjugates, AKTi: AKT inhibitors, TNBC: triple-negative breast cancer

chemotherapy (NAC) provided a statistically significant disease-free survival (DFS) and OS benefit, which was more prominent in the TNBC subgroup [18••]. In a large meta-analysis, (neo)adjuvant capecitabine was able to decrease the risk of a DFS event by 21% in TNBC [19]. Based on these data, adjuvant capecitabine is nowadays considered a standard option for patients with residual disease after NAC, according to European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines [9, 20].

Additionally, data from two randomized phase III trials of adjuvant capecitabine in TNBC were recently presented [21, 22]. In these trials, patients were not selected for residual disease as in CREATE-X. Both studies concluded that adjuvant capecitabine improved DFS rates without significant OS benefit [21, 22].

Besides capecitabine, other post-neoadjuvant strategies are being evaluated for TNBC with residual disease after NAC. Examples are platinum-based chemotherapy vs. capecitabine in patients with ≥1cm residual TNBC after NAC (NCT02445391) or cisplatin plus gemcitabine as post-neoadjuvant treatment for non-pCR TNBC after standard NAC (NCT04297267).

## PARP Inhibitors in BRCA-Mutated TNBC and Beyond

Approximately 11% of patients affected by TNBC are carriers of a germline pathogenic variant in *BRCA1* or *BRCA2* (g*BRCA*) [23]. *BRCA* genes code for proteins involved in the repair of double-strand DNA breaks through homologous recombination repair (HRR) [24]. Therefore, *BRCA*-mutated cells are unable to use HRR pathway and rely on complementary DNA repair processes, which involve poly ADP-ribose polymerase (PARP) proteins. As a consequence, the use of PARP inhibitors (PARPi) induces cell death because of accumulation of unrepaired DNA damages, a concept known as "synthetic lethality" [25–27]. Two PARPi (olaparib and talazoparib) have been approved in monotherapy as treatment options for advanced g*BRCA*-mutated HER2-negative BC [28••, 29••], based on data from OlympiAD and EMBRACA trial which showed a significant PFS improvement compared to chemotherapy of investigator's choice (HR 0.58, 95% CI 0.43-0.80 and HR 0.54; 95% CI 0.41-0.71, respectively).

Recently, final OS results from OlympiAD trial were published. No statistically significant OS improvement was observed (HR 0.90, 95%CI 0.66-1.23, in all patients; HR 0.93, 95%CI 0.62-1.43 in TNBC patients) [30]. Of note, the trial was not powered for OS, and crossover after the end of the study can significantly confound OS analysis. Interestingly, olaparib-treated patients who had not received prior chemotherapy in the advanced setting showed a 7.9 months longer median OS compared to control arm, suggesting a larger benefit of olaparib in earlier lines. This hypothesis should be confirmed in further studies [30]. Similarly, the final analysis from the EMBRACA trial showed no significant OS benefit with talazoparib vs standard chemotherapy (HR 0.85, 95%CI 0.67–1.07) [31].

Gradually, the use of PARPi is evolving, and while PARPi monotherapy is being evaluated in HRR-deficient BC beyond g*BRCA*, new combination strategies with chemotherapy, immunotherapy, antibody-drug conjugates (ADCs), target therapy (such as ATR-inhibitors, BET-inhibitors) and radiotherapy are under evaluation in BC patients with or without a g*BRCA* mutation [32]. In a phase III study, patients with metastatic g*BRCA*-mutated TNBC received carboplatin and paclitaxel with or without veliparib. The addition of the PARPi significantly increased PFS (HR 0.71, 95%CI 0.57–0.88), with a durable benefit, compared to controls [33].

Particularly, the combination of PARPi and chemotherapy is being studied in the treatment of *BRCA*-wild type (WT) BC [34]. It should be considered that up to 10% of g*BRCA*-WT TNBC have pathogenic mutations leading to homologous recombination deficiency (HRD), resulting thus in a *BRCA*-like phenotype despite the *gBRCA*-WT status (*BRCA*ness) [35]. In a phase II window clinical trial enrolling untreated TNBC, HRD was identified even in 69% of patients using a mutational-signature-based assay [36]. Recently, a randomized phase II study of cisplatin with or without veliparib in three groups of metastatic TNBC (*gBRCA* mutant carriers, *gBRCA*-WT but *BRCA*-like and non-*BRCA*-like) was presented. In the *BRCA*-like group, the addition of veliparib was associated with significantly improved PFS with a trend towards OS benefit, while the non-*BRCA*-like group did not benefit from the addition of veliparib [37].

Another strategy under evaluation is the combination of PARPi with immunotherapy. The rational is that the emergence of neoantigens following PARPi-induced DNA-damage can stimulate antitumoral immune response and improve response to immune checkpoint inhibitors (ICIs) [38, 39]. In the I-SPY 2 trial, the addition of olaparib and durvalumab to standard NAC for stage II/III HER2-negative BC was associated with a significantly improved pCR rate in a small TNBC cohort (47% vs 27%) [40].

Despite most recent studies on PARPi aiming to broaden their indications in BC treatment, maintenance data in the advanced setting is lacking and some challenges remain in the evaluation of their long-term safety profile, the interaction in combination with other therapies, and the overcoming of resistance mechanisms.

The ongoing phase III study OlympiA is evaluating olaparib in the adjuvant setting for *gBRCA*- HER2-negative BC and will shed further light on the role of PARPi in the early setting of *gBRCA*-BC (NCT02032823).

## Immunotherapy

TNBC represents the optimal BC subtype for ICIs, since it is characterized by higher genomic instability compared to other BC subtypes [6, 41]. Moreover, stromal tumor-infiltrating lymphocytes (sTILs) in TNBC have demonstrated a strong prognostic value as well as a predictive value for response to NAC in the early setting [42, 43], while in the advanced setting, there are data for higher benefit of single-agent checkpoint inhibition [44–46]. Main randomized clinical trials testing ICI in TNBC are summarized in Table 1.

Immunotherapy alone in TNBC has low response rates, especially in later lines of therapy [56–59] and combination

**Table 1** Randomized clinical trials on immune check-point inhibitors (ICIs) for triple-negative breast cancer. *TNBC* triple-negative breast cancer, *AC* doxorubicine-cyclophosphamide, *EC* epirubicine-cyclophosphamide, *pCR* pathological complete response, *OR* odds ratio, *CI* confidence interval, *mPFS* median progression-free survival, *HR* hazard ratio, *mOS* median overall survival, *CPS* combined positive score. *ITT* intention to treat, *EFS* event-free survival

| Study | Study design | Treatment | Setting /study population | N (TNBC) | Main outcomes |
|---|---|---|---|---|---|
| Early setting | | | | | |
| Keynote-522 [47•] | Phase 3 | Pembrolizumab or placebo + carboplatin and paclitaxel followed by AC/EC; Adjuvant pembrolizumab or placebo after surgery | Neoadjuvant and adjuvant settings | 602 | pCR: 64.8% in pembrolizumab arm vs 51.2% in control arm; treatment difference of 13.6% (95% CI, 5.4–21.8; $p$<0.001)<br>18 months EFS: 91.3% vs. 85.3% (HR of 0.63; 95% CI, 0.43–0.93) |
| NeoTRIPaPDL1 Michelangelo [48] | Phase 3 | Carboplatin and nab-paclitaxel +/- atezolizumab, followed by AC/EC | Neoadjuvant setting | 280 | pCR: 43.5% in atezolizumab arm vs 40.8% in control arm, OR=1.11 (95% CI 0.69–1.79) |
| GeparNuevo [49] | Phase 2 | Durvalumab or placebo + nab-paclitaxel followed by standard EC | Neoadjuvant setting | 117 | pCR: 53.4% in durvalumab arm vs 44.2% in control arm, OR=1.45 (95% CI 0.80-2.63) $p$=0.224<br>In the window-cohort (durvalumab/placebo alone given 2 weeks before nab-paclitaxel): pCR: 61.0% in durvalumab arm vs 41.4% in control arm, OR = 2.22 (95% CI 1.06-4.64), $p$=0.035 |
| I-SPY 2 (pembrolizumab arm) [50] | Phase 2 | Paclitaxel +/- pembrolizumab followed by AC | Neoadjuvant setting | 250 (114) | pCR: 44% vs 17% in HER2-negative population;<br>pCR: 60% vs 22% in TNBC cohort |
| I-SPY 2 (durvalumab and olaparib arm) [40] | Phase 2 | Paclitaxel +/- durvalumab and olaparib followed by AC | Neoadjuvant setting | 372 | In all patients:<br>pCR: 37% in durvalumab arm vs 22% in control arm<br>In TNBC subgroup:<br>pCR: 47% in durvalumab arm vs 27% in control arm |
| Advanced setting | | | | | |
| Impassion130 [51••, 52] | Phase 3 | Atezolizumab or placebo + nab-paclitaxel | 1st line | 902 | In all patients:<br>mPFS: 7.2 mo in atezolizumab arm vs 5.5 mo in control arm, HR 0.80; 95% CI 0.69–0.92, $p$=0.002<br>mOS: 21.0 mo in atezolizumab arm vs 18.7 in control arm, HR 0.86, 95% CI 0.72–1.02, $p$=0.08<br>In PD-L1+ population:<br>mPFS: 7.5 mo in atezolizumab arm vs 5.0 mo in control arm, HR 0.62, 95% CI 0.49–0.78; $P$<0.001<br>mOS: 25 mo in atezolizumab arm vs 18 mo in control arm, HR 0.71, 95%CI 0.54–0.94 |
| Keynote-119 [53] | Phase 3 | Pembrolizumab monotherapy | ≥2nd line | 622 | In PD-L1 CPS≥10 group:<br>mOS: 12.7 mo in pembrolizumab arm vs 11.6 mo in control arm (HR 0.78, 95%CI 0.57–1.06)<br>In PD-L1 CPS≥1 group:<br>mOS: 10.7 mo in pembrolizumab arm vs 10.2 mo in control arm (HR 0.86, 95%CI 0.69–1.06)<br>In all patients:<br>mOS: 9.9 mo in pembrolizumab arm vs 10.8 mo in control arm (HR 0.97, 95%CI 0.82–1.15) |
| KEYNOTE-355 [54] | Phase 3 | Pembrolizumab or placebo + chemotherapy (taxanes or carboplatin + gemcitabine) | 1st line | 847 | In PD-L1 CPS≥10 group:<br>mPFS= 9.7 vs. 5.6 months; HR=0.65 (95% CI, 0.49–0.86)<br>In PD-L1 CPS≥1 group:<br>mPFS= 7.6 vs. 5.6 months; HR=0.74 (95% CI, 0.61–0.90)<br>In ITT population: |

**Table 1** (continued)

| Study | Study design | Treatment | Setting /study population | N (TNBC) | Main outcomes |
|---|---|---|---|---|---|
| | | | | | mPFS= 7.5 vs. 5.6 months; HR=0.82 (95% CI, 0.69–0.97) |
| SAFIRO2-Immuno [55] | Phase 2 | Durvalumab vs chemotherapy as mantainance therapy after induction chemotherapy | 1st or 2nd line | 199 (75) | In all patients:<br>mPFS: 2.7 mo in durvalumab arm vs 4.6 mo in control arm (HR = 1.40; $p$=0.047)<br>In TNBC subgroup (predefined subgroup analysis):<br>HR for PFS 0.87 (95% CI 0.54–1.42)<br>In PD-L1+ group (predefined subgroup analysis):<br>HR for PFS 0.75 (95%CI 0.38–1.49) |

treatments have demonstrated more activity in metastatic TNBC.

The anti-PD-L1 antibody atezolizumab in combination with nab-paclitaxel has been proven superior to nab-paclitaxel alone in previously untreated, PD-L1-positive, advanced TNBC patients and is currently standard of care, as reported above [51••]. Surprisingly, a recent press-release reporting results from the IMpassion-131 trial about the combination of atezolizumab with paclitaxel in the same setting did not confirm the positive findings of IMpassion-130: further data are awaited to better understand the reason of this discrepancy.

Anti-PD1 antibody pembrolizumab in combination with chemotherapy (taxanes [paclitaxel or nab-paclitaxel] or carboplatin plus gemcitabine) was evaluated in the phase III KEYNOTE-355 trial, where 847 metastatic TNBC patients were randomized to receive first-line therapy with chemotherapy plus pembrolizumab or placebo [54]. The co-primary endpoints were PFS and OS in the PD-L1-positive population (combined positive score [CPS] ≥10 and ≥1) and in the overall population, with a hierarchical testing for PFS. The predefined significance threshold for PFS was met in the CPS≥10 population. OS data were still immature. In Keynote-119, pembrolizumab alone failed to prove superiority to investigator's choice of chemotherapy in pre-treated metastatic TNBC patients [53]. As an exception, pembrolizumab alone is approved by US Food and Drug Administration (FDA) for patients with treatment-refractory, mismatch repair deficient tumors (<2% of TNBC cases), based on the efficacy results of tumor-agnostic basket trials [60, 61]. Altogether, in the metastatic setting, immunotherapy seems to provide benefit to a subgroup of TNBC patients selected on PD-L1 expression and the benefit seems larger when combined with chemotherapy in first-line. However, many questions related to ICIs in metastatic TNBC, such as more precise predictive biomarkers and comparative data on the optimal chemotherapy partner, remain unanswered.

Ongoing studies (Table 2) are trying to expand the benefits of immunotherapy in TNBC patients, both anticipating its use in earlier disease settings (adjuvant and neoadjuvant) and going beyond PD-L1 positivity (e.g., TILs enrichment, tumor mutational burden [TMB]) [46, 62].

The addition of ICIs to chemotherapy in the neoadjuvant setting has shown conflicting results (Table 1). In the GeparNuevo trial, the addition of durvalumab to NAC did not significantly improve pCR rates in the ITT population, although in the window cohort (induction durvalumab prior to chemotherapy), better pCR rates were attained [49]. Also the addition of atezolizumab to neoadjuvant nab-paclitaxel plus carboplatin showed no pCR improvement, albeit the trial's primary endpoint was EFS, yet to be reported [48]. Conversely, the adaptive phase 2 trial I-SPY2 met its primary endpoint of improved pCR by adding pembrolizumab to NAC [50]. KEYNOTE-522 confirmed this benefit in phase III setting by demonstrating a significant increase in pCR rates by the addition of pembrolizumab to neoadjuvant platinum-containing taxane-anthracycline regimen (51.2% to 64.8%) with an early trend towards EFS benefit [47•]. The pCR benefit was irrespective of PD-L1 status.

Furthermore, in the post-neoadjuvant and adjuvant setting, ICIs could represent a treatment option for TNBC, which is being explored in ongoing trials (Table 2).

## New Target Therapies in TNBC Treatment

### Antibody-Drug Conjugates

Novel ADCs are opening new horizons in TNBC. Sacituzumab-govitecan is an ADC composed of a topoisomerase I inhibitor (SN-38), which is an active metabolite of irinotecan, and an anti-Trop2 monoclonal antibody, linked together by a cleavable protein. Trop-2 is a trophoblast cell-surface antigen which is expressed on the surface of many epithelial cancer cells, including TNBC, and its activation induces cell growth. Sacituzumab-govitecan has been evaluated in a phase I/II study in patients with advanced epithelial

**Table 2** Ongoing phase II and III randomized trials with immunotherapy in triple-negative breast cancer

| NCT number | Phase | Experimental treatment | Status |
|---|---|---|---|
| Early setting | | | |
| NCT03639948 | II | Pembrolizumab + Carboplatin + Docetaxel | Recruting |
| NCT03289819 | II | Pembrolizumab + Nab-Paclitaxel followed by Pembrolizumab + epirubicin and cyclophosphamide | Active, not recruiting |
| NCT04373031 | II | Pembrolizumab + IRX-2 + cyclophosphamide followed by pembrolizumab + pacliataxel followed by IRX-2, pembrolizumab + doxorubicine and cyclophosphamid | Not yet recruiting |
| NCT04443348 | II | Pembrolizumab + carboplatin + paclitaxel + cyclophosphamide and doxorubicine + preoperative radiation therapy | Not yet recruiting |
| NCT02883062 | II | Atezolizumab + carboplatin + paclitaxel | Active, not recruiting |
| NCT03756298 | II | Adjuvant atezolizumab + capecitabine | Recruiting |
| NCT03546686 | II | Nivolumab + ipilimumab followed by adjuvant nivolumab | Recruiting |
| NCT03872505 | II | Durvalumab + carboplatin + paclitaxel + preoperative radiation therapy | Not yet recruiting |
| NCT03356860 | II | Durvalumab + paclitaxel + epirubicin and cyclophosphamide | Recruiting |
| NCT04188119 | II | Avelumab + aspirin | Not yet recruiting |
| NCT03036488 | III | Pembrolizumab + carboplatin + paclitaxel + anthracycline andcyclophosphamide followed by pembrolizumab | Active, not recruiting |
| NCT02954874 | III | Adjuvant pembrolizumab | Recruiting |
| NCT03281954 | III | Atezolizumab + doxorubicin and cyclophosphamide + paclitaxel + carboplatin followed by atezolizumab | Recruiting |
| NCT03197935 | III | Atezolizumab + doxorubicin + cyclophosphamide + nab-paclitaxel followed by atezolizumab | Active, not recruiting |
| NCT03498716 | III | Atezolixumab + paclitaxel followed by dose-dense doxorubicin/epirubicin + cyclophosphamide | Recruiting |
| NCT02926196 | III | Adjuvant avelumab | Recruiting |
| Advanced setting | | | |
| NCT02768701 | II | Pembrolizumab + single-dose cyclophosphamide | Active, not recruiting |
| NCT03121352 | II | Pembrolizumab + carboplatin + nab-paclitaxel | Completed |
| NCT02755272 | II | Pembrolizumab + carboplatin/gemcitabine | Recruiting |
| NCT03164993 | II | Atezolizumab + pegylated liposomal doxorubicin + cyclophosphamide | Recruiting |
| NCT03206203 | II | Atezolizumab + carboplatin | Recruiting |
| NCT03464942 | II | Atezolizumab + Stereotactic Ablative Body Radiotherapy | Recruiting |
| NCT03853707 | I/II | Atezolizumab + ipatasertib + capecitabine | Recruiting |
| NCT04408118 | II | Atezolizumab + bevacizumab + paclitaxel | Not yet recruiting |
| NCT04434560 | II | Nivolumab + ipilimumab before brain metastasectomy | Not yet recruiting |
| NCT03789110 | II | Nivolumab + ipilimumab | Recruiting |
| NCT03606967 | II | Durvalumab + nabpaclitaxel + neoantigen vaccine | Not yet recruiting |
| NCT03616886 | II | Durvalumab + paclitaxel + carboplatin + oleclumab | Recruiting |
| NCT03167619 | II | Durvalumab + olaparib | Recruiting |
| NCT03742102 | I/II | Durvalumab + paclitaxel + immune-modulating agents (selumetinib, danvatirsen, oleclumab and capivasertib) | Recruiting |
| NCT03971409 | II | Avelumab + binimetinib, utomilumab, or anti-OX40 antibody PF-04518600 | Recruiting |
| NCT02819518 | III | Pembrolizumab + nab-paclitaxel or paclitaxel or carboplatin/gemcitabine | Active, not recruiting |
| NCT03125902 | III | Atezolizumab + paclitaxel | Active, not recruiting |
| NCT03371017 | III | Atezolizumab + carboplatin + gemcitabine or capecitabine | Recruiting |

cancer. Overall, 108 metastatic, heavily pre-treated TNBC patients received sacituzumab-govitecan, with durable objective responses (33.3% objective response rate (ORR) with a median duration of response of 7.7 months) [63••]. Based on this data, the FDA recently granted accelerated approval to sacituzumab-govitecan for pre-treated metastatic TNBC patients. A phase III study (ASCENT study) comparing sacituzumab-govitecan with single-agent chemotherapy of physician's choice was terminated early because of compelling efficacy and results are expected soon [64]. The availability of this new treatment option has the potential to change the treatment landscape of TNBC, since it is under evaluation as single agent and in combination in several settings in TNBC.

Another ADC being evaluated in TNBC treatment is ladiratuzumab-vedotin, an anti-LIV1 antibody combined with a microtubule-disrupting agent (MMAE) through a cleavable linker [65]. LIV-1 is a protein expressed on several cancer cells, including TNBC. In a phase I/II study of ladiratuzumab-vedotin in combination with pembrolizumab, 32 patients with first-line TNBC were enrolled in the dose-expansion phase. The combination was tolerable and showed encouraging clinical activity (ORR of 54%) [65].

The HER2-targeted ADC trastuzumab-deruxtecan has shown promising signs of efficacy in an early-phase trial of HER2-low BC (defined as HER2 immunohistochemistry 1+, or 2+ without HER2 amplification per ASCO/CAP guidelines) [66, 67]. Approximately 17% of HER2-low BC are TNBC [68]. A phase III trial in HER2-low BC with trastuzumab-deruxtecan vs. chemotherapy of investigator's choice is ongoing [69].

## PI3K/AKT/mTOR Pathway Inhibitors

The PI3K/AKT/mTOR pathway is often activated in TNBC, mainly due to activating mutations of PI3K catalytic subunit *PIK3CA*, *AKT1* or loss of function of PTEN [70, 71]. AKT is a key effector in PI3K/AKT/mTOR pathway and mediates cell proliferation and survival. Capivasertib, a pan-AKT inhibitor, was evaluated in a randomized phase II trial, in combination with paclitaxel, as first-line treatment for patients with metastatic TNBC [72]. Addition of capivasertib resulted in significantly improved PFS and OS, compared to placebo (HR 0.74, 95%CI 0.50-1.08 and HR 0.61, 95%CI 0.37-0.99, respectively) and benefits were more pronounced in patients *with PIK3CA/AKT1/PTEN*-altered tumors. These results are consistent with those of the LOTUS trial, a phase II study evaluating the AKT inhibitor ipatasertib in combination with paclitaxel as first-line treatment for metastatic TNBC. The trial showed an increase in median PFS (from 4.9 to 6.2 months in the ITT population, and from 4.9 to 9.0 months in the *PIK3CA*/*AKT1*/*PTEN* altered population) and a trend towards improved OS, supporting the role of AKT inhibitors in TNBC [73]. Phase III studies testing capivasertib, ipatasertib, and alpelisib (CAPItello-290 [NCT03997123], IPATunity130 [NCT03337724] and EPIK-B3 [NCT04251533]) in addition to (nab)-paclitaxel for metastatic TNBC are ongoing.

In a phase II trial, neoadjuvant ipatasertib with 12 weekly paclitaxel did not increase pCR rates compared to placebo/paclitaxel [74]. Nonetheless, MRI-assessed responses, a secondary endpoint, favored ipatasertib/paclitaxel, especially in the *PIK3CA*/*AKT1*/*PTEN*-altered population. Importantly, gastrointestinal adverse events (AE), especially diarrhoea, seem to dominate the toxicity profile of AKT inhibitors [72–74].

Other drugs targeting the PI3K/AKT/mTOR pathway are being evaluated in TNBC such as mTOR- and dual inhibitors, and combinations with immunotherapy (NCT02616848, NCT04177108).

## Cyclin-Dependent Kinase (CDK) Inhibitors

Targeting the cellular machinery responsible for cell cycle regulation has already been proven beneficial in luminal BC, with diverse CDK4/6-inhibitors (CDK4/6i) showing markedly survival benefit in combination with endocrine therapy [75]. In TNBC, the loss of the tumor suppressor retinoblastoma (Rb), an in vitro biomarker of sensitivity to CDK4/6i, is a common event, especially in basal-like TNBC, explaining the observed lower activity of CDK4/6i in vitro in TNBC compared with luminal models [7, 76, 77]. Moreover, targeting CDK4/6 with palbociclib has actually been shown to antagonize the cytotoxic effect of paclitaxel in Rb-positive TNBC cell lines, possibly due to the lower sensitivity to the cytotoxic effect upon tumor cell cycle arrest. While in unselected TNBC, CDK4/6i alone or in combination with chemotherapy does not seem to be a venue worth exploring, there is a phase II trial ongoing with abemaciclib in Rb-positive metastatic TNBC (NCT03130439). Combinations with antiandrogens and PI3K-inhibitors are discussed later.

Trilaciclib, an intravenous CDK4/6i, was tested in a phase II trial where 102 metastatic TNBC patients were randomized to either chemotherapy alone (carboplatin plus gemcitabine) or to two different schedules of the same chemotherapy and trilaciclib [78]. The primary objective was to show an improvement in myelotoxicity-related endpoints in favor of the trilaciclib arms, since the drug can arrest hematopoietic progenitor cells at G0/G1 and thereby preserve them from the cytotoxic effect, which could be translated into an enhanced chemotherapy dose-intensity and anti-tumor immunity. The trial failed to show a superiority for the trilaciclib arms in terms of severe neutropenia incidence and duration. However, there was an important benefit in the secondary OS endpoint (median OS in the chemotherapy arm of 12.6 vs. 20.1 months in the trilaciclib plus chemotherapy arms combined). A potential explanation for this survival benefit might be an enhanced anti-tumor lymphocyte immunity with trilaciclib, as seen by an increment in T cell production of IFN-$\gamma$, and this warrants further studies.

With dinaciclib, a small-molecule inhibitor of CDK1/2/5/9, disappointing results were initially reported from a phase I study combining dinaciclib with epirubicin in TNBC [79]. In the preclinical setting, the inhibition of CDK1 in TNBC xenograft models resulted in synthetic lethality and block in tumor dissemination for models overexpressing MYC, an oncogene overexpressed in approximately 70% of TNBC and associated with poor prognosis [80]. Moreover, MYC-driven TNBC models are associated with an increased PD-1 expression on sTILs. Based on these preclinical data, a phase I study was conducted with dinaciclib and pembrolizumab in metastatic TNBC [81]. Preliminary efficacy analysis showed an ORR of 16.7% and a CBR of 46.7%. Interestingly, at an exploratory analysis, MYC expression correlated with treatment response. Further studies are needed to establish the role of MYC as a possible predictive biomarker.

## Antiandrogens

Androgen receptor (AR) positivity occurs in about 24% of TNBC and is associated with a lower recurrence risk [82], supporting the hypothesis that AR-driven TNBC represent a distinct subtype. There is significant overlap between AR positivity and LAR TNBC subtype, which is enriched in lobular histology and frequently correlated with *PIK3CA* and *AKT1* alterations [83, 84]. Bicalutamide and enzalutamide have been tested in phase II trials and shown proof-of-efficacy in AR-positive TNBC patients [85, 86]. Enzalutamide is also being evaluated in a phase III trial, both as single agent and combined with paclitaxel vs paclitaxel monotherapy in patients selected by a genomic signature for AR-driven disease [87].

AR-expression in TNBC tends to be associated with expression of Rb, a biomarker of sensitivity to CDK4/6i [88]. This supports the hypothesis of increased efficacy by combining androgen blockade with CDK4/6i as palbociclib. Results from a phase II study combining bicalutamide with palbociclib for AR-positive TNBC showed that this combination was safe and efficacious, with 11/33 patients progression-free at 6 months [89]. Additionally, antiandrogens combined with PIK3CA-inhibitors are under evaluation in AR and PTEN-positive metastatic BC (NCT03207529).

## Other Immunotherapeutic Approaches

### Purinergic Pathway Antagonists

The purine nucleoside adenosine exerts multiple immunosuppressive functions in the tumor micro-environment [90]. The ecto-enzyme CD73 is responsible for generating adenosine from a by-product of ATP, whilst adenosine receptors (A2R) initiate the adenosine intracellular signaling pathway. It has been shown that CD73 overexpression in TNBC is associated with lower sTILs and worse prognosis, whereas by the same time CD73 and A2R blockade inhibits BC cells growth and migration [91–93]. Therefore, compounds targeting the purinergic pathway are currently under clinical development in TNBC: oleclumab, an anti-CD73 monoclonal antibody, given together with durvalumab plus chemotherapy, is being compared with durvalumab plus chemotherapy in 2 phase I/II trials [94, 95]. An oral A2R inhibitor is also being studied in metastatic TNBC (NCT03207867).

### Anti-cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA4)

The combination of anti-PD1 nivolumab with anti-CTLA4 ipilimumab is currently being tested for TNBC in two phase II trials (NCT03789110, NCT03668119) [62]. Eligibility is restricted to patients with hypermutated tumors (TMB ≥10 mutations/megabase), a rare event in BC (5% of cases) [96]. These trials are expected to clarify the role of dual ICI and to provide a prospective evaluation of TMC as predictive biomarker in TNBC.

### Innate Immune Activators

Imprime-PGG is an intravenously administered, yeast-derived beta-glucan, which is currently being evaluated in combination with ICIs for metastatic TNBC [97]. Imprime-PGG acts as a pathogen-associated molecular pattern activating the innate immune response against tumor cells by enhancing antigen presentation and T cell activation [98]. Imprime-PGG was evaluated in a phase II study (Imprime-1), where it was administered as first-line therapy in combination with pembrolizumab in patients with metastatic TNBC [97]. ORR was 13.6% and median OS was 13.7 months [97].

### Angiogenesis Inhibition

By decreasing neovessel permeability and tumor interstitial pressure, antiangiogenic drugs facilitate chemotherapy delivery and exert synergistic effects with various chemotherapy agents [99]. Nevertheless, despite increasing median PFS in metastatic HER2-negative BC, the addition of bevacizumab, a monoclonal antibody against circulating vascular endothelial growth factor (VEGF) to chemotherapy never showed an OS benefit [100]. Together with a low cost-effectiveness and an increased rate of bleeding, thromboembolic and cardiovascular AE, bevacizumab's approval for HER2-negative metastatic BC was revoked by the FDA in 2010, albeit the drug is still available for combination with paclitaxel as first-line therapy in Europe [99].

Nonetheless, different combinations with antiangiogenic agents may play a future role in the care of TNBC patients. Antiangiogenics have immunomodulatory properties and are able to increase lymphocytic infiltration into the tumor, hereby enhancing antitumor immune responses [101]. A phase II single-arm trial with 57 HER2-negative BC patients has explored the combination of bevacizumab, weekly paclitaxel and nivolumab in first-line [102]. The study met its primary endpoint, showing an ORR of 75.4% (83.3% in 18 patients with TNBC) [103]. A similar trial focusing on TNBC patients is ongoing (NCT04408118).

The angiogenesis pathway deeply interacts with DNA repair mechanisms, since tumor hypoxia induces DNA damage, genomic instability, and, ultimately, cell death. Therefore, antiangiogenics combined with DNA-repair inhibitors and/or ICIs might provide another synergistic approach [104, 105]. In a phase II study, cediranib, a pan-VEGF receptor tyrosine kinase inhibitor, was administered with olaparib in patients with advanced solid tumors including TNBC and resulted in objective responses in 14% of heavily pretreated metastatic TNBC. Toxicity profile was manageable, with gastrointestinal symptoms and hypertension among the most common AE [106].

### TRK Inhibitors

Although extremely rare in unselected BC (<1% of cases), neurotrophic tyrosine receptor kinase (NTRK) oncogene fusions are described in ductal TNBC with secretory features and ETV6-NTRK3 fusions are pathognomonic in the rare secretory subtype that can present as TNBC [107]. These fusions can be efficiently targeted by the tropomyosin kinase protein (TRK) inhibitors larotrectinib and entrectinib. [108] In this sense, patients with NTRK fusion-positive TNBC are eligible for treatment with TRK inhibitors, based on efficacy data coming from various tumor-agnostic basket trials [109].

### Histone Deacetylase Inhibitors

The acetylation of histone proteins induces the activation of genes mediating cell growth and proliferation, and histone deacetylases (HDAC) are often overexpressed in malignancies [110]. Thus far, HDAC inhibitors have shown limited activity as single agent in BC, and combination strategies are currently being tested. Entinostat, an oral HDAC inhibitor, in combination with atezolizumab was evaluated in a phase II study for patients with advanced TNBC. The combination did not improve PFS compared to placebo and was more toxic [111]. Therefore, the role of HDAC inhibitors in TNBC is yet to be defined.

### Other Strategies

Several trials are evaluating further approaches in advanced TNBC (including, but not limited to, interleukin-7, NKTR-214, bispecific antibodies, STAT3-inhibitors, NOTCH-inhibitors, CXCR4-antagonists) whose results are eagerly awaited.

## Conclusions

Recent evidence has introduced new therapies which have modified the treatment landscape from chemotherapy as only available treatment to a more personalized approach for TNBC: atezolizumab is now a standard of care for first-line advanced TNBC with PD-L1-positive tumors, PARPi are approved for *BRCA*-mutated advanced TNBC and recently sacituzumab-govitecan was FDA-approved for previously treated metastatic TNBC. Ongoing studies aim to broaden treatment indications for immunotherapy, PARP inhibitors, and ADC in TNBC, both anticipating their use in earlier disease settings (adjuvant and neoadjuvant) and going beyond the current limitations of PD-L1 positivity and *gBRCA* mutation for immunotherapy and PARPi, respectively. Several other target therapies are currently being evaluated, reflecting a promising evolution towards a more subtype-based approach in TNBC.

## Declarations

**Conflict of Interest** Elisa Agostinetto has no potential conflicts of interest.

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• Of importance
•• Of major importance

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