Seminars in Oncology 47 (2020) 201–208

Contents lists available at ScienceDirect

Seminars in Oncology

journal homepage: www.elsevier.com/locate/seminoncol

Early stage triple negative breast cancer: Management and future directions

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ARTICLE INFO

Article history:
Received 1 May 2020
Revised 5 May 2020
Accepted 5 May 2020

Keywords:
Triple negative breast cancer
Neoadjuvant chemotherapy
Complete pathologic response
Systemic chemotherapy

ABSTRACT

Triple negative breast cancer is the most aggressive kind of breast cancer with high risk of recurrences and poor outcomes. Systemic chemotherapy has significantly improved long term outcomes in early stage patients; however, metastatic recurrences still develop in a significant number of patients. Anthracycline and taxane based chemotherapy regimens are standard of care for early stage patients. Neoadjuvant treatment is preferred due to the ability to assess pathologic responses providing important prognostic information and guidance in adjuvant therapy decisions. Carboplatin addition to the anthracycline and taxane backbone is associated with a significant improvement in pathologic complete response but is associated with more toxicity. Understanding the immune microenvironment of triple negative disease is an exciting field and immune checkpoint inhibitors have shown great promise in further improving response rates in early stage patients. Patients with residual disease after neoadjuvant chemotherapy have a significantly higher risk of recurrence compared to those with complete responses. Adjuvant capecitabine for these high-risk patients have shown significant improvement in long term outcomes and is routinely used in this setting.

Given the heterogeneity within triple negative tumors, molecular subtypes with variable genomic makeup and chemo sensitivities have been identified and will likely aid in further clinical developmental therapeutics.

Introduction

Triple negative breast cancer (TNBC) defined as lack of estrogen, progesterone and HER2 (human epidermal growth factor receptor 2) [1-3] expression comprises about 15% of breast cancers [4] and is associated with worst outcomes compared to other breast cancers [5]. TNBC is usually associated with a higher pathologic grade, higher prevalence in young African American women [5-9] and has a strong correlation with BRCA pathogenic mutation [8,10-13]. Despite the advances in systemic therapies, 25%–30% of early stage patients develop metastatic disease within 3–5 years of diagnosis [7,14-17].

TNBC is a heterogenous disease and gene expression profiling has identified multiple subtypes within TNBCs. Lehmann et al [18] reported two basal-like (BL1 and BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL) and luminal androgen receptor (LAR) subtypes, which were later revised and limited to four distinct subtypes (BL1, BL2, M, and LAR types) [19]. Similarly, Burstein et al [20] reported four subtypes as luminal/androgen receptor, mesenchymal, basal-like/immune-suppressed, and basal-like/immune-activated. These subtypes have been shown to have distinct genomic phenotypes and variable sensitivity to chemotherapy with higher response rates seen in BL1 tumors and lowest in BL2, luminal/androgen receptor and M types. Genomic profiling of TNBC and investigating subtype-specific responses to chemotherapy have created a platform for further clinical trials with novel and targeted therapies. However, these subtypes are not currently used in routine clinical practice due to complexity of genomic analysis. Further studies are needed to validate and standardize therapies based on molecular subtypes.

Principles of surgery and radiation for TNBC are the same as in all other breast cancers and there are no TNBC-specific recommendations for local management. Systemic chemotherapies have evolved over time with improvement in responses and patient outcomes. Novel combinations have also been evaluated and exciting new developmental therapeutics are currently underway. This review will focus on systemic therapies and summarize the current management strategies with future developments for early stage TNBC.

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https://doi.org/10.1053/j.seminoncol.2020.05.006
0093-7754/

Table 1
Selected neoadjuvant clinical trials and pathologic responses in TNBC

Study	Total N	TNBC N	Tumor size	Chemotherapy regimen	pCR (%)	pCR (%) in TNBC
Anthracycline and Taxanes						
GeparDuo [36] von Minckwitz et al, 2005	913	261	T2-T3	AC-T versus AT	14.3% versus 7% ($P<$ 0.001)	22.8% ($P=$ 0.0001)
GeparTrio [108] Huober et al, 2010	2072	351	T2-T4	TAC	20.5%	38.9% ($P<$ 0.0001)
GeparQuattro [109] von Minckwitz et al, 2010	1421	326	T1-T4	EC-T versus EC-TX versus EC-T-X	22.3% versus 19.5% versus 22.3% ($P=$ 0.298)	17.6% versus 14.4% versus 17.5%
PREPARE [34] Untch et al, 2011	733	145	T2-T4	EPtx-CMF versus EC-Ptx	18.7% versus 13.2% ($P=$ 0.04)	44.6% versus 30.4 ($P=$ 0.12)
I-SPY 1 [33] Esserman et al, 2012	221	53	≥ 3cm	AC-T	27%	35%
EORTC 10994/ BIG 1-00 trial [110] Bonnefoi et al, 2014	1212	221	T2-T4	FEC versus T-ET	18%	31%
Platinum agents						
GeparSixto GBG66 [49] Von Minckwitz et al, 2014	588	315	T1-T4	APtx/Bev/Cb versus APtx/Bev	43.7% versus 36.9% ($P=$ 0.068)	53.2% versus 36.9% ($P=$ 0.005)
CALGB 40603 [51] Sikov WM et al, 2015	443		T1-T4	Cb and/or Bev/Ptx-AC versus Ptx-AC		Cb: 60% versus 44% ($P=$ 0.0018) Bev: 59% versus 48% ($P=$ 0.0089)
*GEICAM 2006-03 [111] Alba et al, 2012	94		T1-T4	EC-TCb versus EC-T		30% versus 35% ($P=$ 0.61)
Ando et.al [52], 2014	181	75	T1-T4	Cb/Ptx-CEF versus Ptx-CEF	31.8% versus 17.6% ($P=$ 0.01)	61.2% versus 26.3% ($P=$ 0.003)
Zhang et al [98], 2016	91		T1-T4	Cb/Ptx versus EPtx		38.8% versus 14% ($P=$ 0.014)
WSG-ADAPT-TN [112] Gluz et al, 2018	336		T1-T4	nabP/Cb versus nabP/Gem		45.9% versus 28.7% ($P=$ 0.002)
Immune checkpoint Inhibitors						
KEYNOTE-522 [87] Schmid et al, 2020	602		T2-T4	Pembro/Cb/Ptx-AC versus Cb/Ptx-AC		64.8% versus 51.2% ($P<$ 0.001)
**NeoTRIPaPDL1 [88] Gianna et al, 2019	280		T1-T4	Atezo/Cb/nabP versus Cb/nabP		43.5% versus 40.8% ($P=$ 0.66)
I-SPY 2 [86] Nanda et al, 2020PMID:32053137	250	114	T2-T4	Pembro/Ptx- AC versus Ptx-AC	44% versus 17% (est)	60% versus 22% (est)
PARP inhibitors						
I-SPY 2 [95] Rugo et al, 2016	116	60	T2-T4	Ptx/Cb/Vel-AC versus Ptx-AC	33% versus 22% (est)	51% versus 26% (est)
BrighTNess [101] Loibl et al, 2018	634		T2-T4	Ptx/Cb/Vel-AC, Ptx/Cb-AC versus Ptx-AC		Cb/Vel: 53% versus 31% ($P<$ 0.0001) Cb: 58% versus 31% ($P<$ 0.0001)

A = Doxorubicin; C = cyclophosphamide; T = Docetaxel; E = epirubicin; X = capecitabine; Ptx = paclitaxel; M = methotrexate; F = 5-flourourachil; Bev = bevacizumab; Cb = carboplatin; nabP = nab-paclitaxel; Gem = Gemcitabine; Pembro = pembrolizumab; est = estimated; Atezo = atezolizumab; Vel = veliparib.
*basal like (TNBC, CK5/6+ or EGFR+).
**AC, EC or FEC in adjuvant setting.

Neoadjuvant approach

Despite the unfavorable prognosis, TNBCs are highly sensitive to chemotherapy and systemic chemotherapy remains the mainstay of treatment [21-23]. It is well established that the long-term outcomes are equivalent between adjuvant and neoadjuvant chemotherapy (NACT) approaches. Early Breast Cancer Trialist's Collaborative Group reported 15-year outcomes of a meta-analysis including 10 randomized controlled clinical trials (RCTs) comparing neoadjuvant versus adjuvant chemotherapy [24]. No significant difference between NACT and adjuvant chemotherapy was noted for distant recurrence (15-year risk 38•2% *v*38•0%, *P*= 0•66), breast cancer mortality (34•4% *v*33•7%, *P*= 0•31), or all-cause mortality (40•9% *v*41•2%, *P*= 0•45). Local recurrence rates were higher with NACT (21.4% *v*15.9%, *P*= 0.0001), however, some trials did not have patients undergo surgery after NACT which may have impacted local recurrence rates.

NACT helps downsize the tumor and increases rates of breast conservation surgery [25,26], but more importantly, it allows assessment of pathologic responses providing important prognostic information and aides in adjuvant treatment decisions.

Pathologic complete response

Pathologic complete response (pCR) is defined as absence of invasive cancer on pathologic evaluation in both breast and regional lymph nodes after neoadjuvant therapy. Several neoadjuvant studies have shown pCR to be predictive of improved long-term outcomes whereas a high burden of residual disease post NACT is predictive of early recurrences and mortality [22,27-31]. The Collaborative Trials in Neoadjuvant Breast Cancer International working group reported a pooled analysis of 12 neoadjuvant clinical trials [27] which showed improved event free survival and overall survival (OS) with pCR. This association was particularly strong in TNBC patients (event free survival: HR 0.24, 95% CI 0.18–0•33; OS: HR 0.16, 95% CI 0.11–0.25). Given the available data, pCR is an acceptable surrogate for long-term outcomes and is routinely used as an endpoint in neoadjuvant clinical trials.

TNBC patients have higher response rates to chemotherapy compared to non-TNBCs given their higher proliferation and chemosensitivity [22,31]. The pCR rates in TNBC ranges from 30%–40% with standard anthracycline and taxane based regimens [31-36]. Many novel agents and combination chemotherapy

regimens have been studied and are being investigated to further maximize pCR rates and improve patient outcomes. Table 1 summarizes some of the NACT trials and pCR rates in TNBC.

Systemic chemotherapy

Anthracycline and Taxane based Regimens

Most guidelines recommend anthracycline and taxane based chemotherapy for TNBC in the neoadjuvant or adjuvant setting. Early Breast Cancer Trialist's Collaborative Group meta-analysis [37] of 123 RCTs reported a one-third reduction in breast cancer mortality at 10 years in patients treated with anthracycline, taxane and an alkalyting agent compared to no chemotherapy regardless of breast cancer subtype. Furthermore, in a meta-analysis of 10 RCTs [38], dose dense chemotherapy showed a significantly improved disease-free survival (DFS: HR 0.81; 95% CI 0.75–0.88, $P< 0.001$) and overall survival (OS: HR 0.85; 95% CI 0.77–0.93, $P< 0.001$), particularly in hormone receptor-negative patients. Given the risk of cardiotoxicity and secondary cancer with anthracycline based regimens, nonanthracycline regimens have been studied to assess efficacy in breast cancer. Jone SE et al [39]. reported 5 year outcomes with adjuvant TC (docetaxel 75 and cyclophosphamide 600 mg/m² every 3 weeks x 4 cycles) compared to AC (doxorubicin 60 and cyclophosphamide 600 mg/m² every 3 weeks x 4 cycles) in a phase III RCT, with TC showing significantly improved DFS and a trend towards OS (DFS 86% *v*80%, $P= 0.015$; OS 90% *v*87%, $P= 0.13$). However, no taxane was given in the AC arm. The ABC trials (USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49) [40] compared 6 cycles of TC to several AC and taxane (TaxAC) based regimens in patients with HER2 negative breast cancer. TaxAC was associated with a significant improvement in 4 year invasive DFS (90.7% *v*88.2%, $P= 0.04$) as well as recurrence free survival (RFS; HR 1.51; 95% CI 1.20–1.90, $P< 0.001$) compared to TC and this benefit was most evident in hormone receptor-negative (HR-) and node positive patients. Taken altogether, these data have established anthracycline and taxane based chemotherapy as standard of care in TNBC patients. For patients with small TN tumors (≤1 cm), observation or TC chemotherapy alone can be considered given the overall good prognosis and low risk of recurrence with very early stage disease [41-48].

Platinum Agents

Preclinical and clinical studies have suggested increased sensitivity to DNA-damaging agents such as platinum drugs in TNBC due to intrinsic defects in DNA repair mechanisms. Platinum drugs have been studied in multiple NACT trials and have shown improvement in pCR rates as shown in Table 1. In the GeparSixto GBG 66 study [49], patients with stage II–III TNBC breast cancer were randomized to receive paclitaxel (80 mg/m^2 once a week), nonpegylated liposomal doxorubicin (20 mg/m^2 once a week) and bevacizumab (15 mg/kg intravenously every 3 weeks) with or without carboplatin (AUC 1.5 once a week [AUC 2 for first 329 patients]). Carboplatin addition was associated with a significant improvement in pCR rates (53.2% *v*36.9%, $P= 0.005$) as well as improved DFS (HR 0.56, 95% CI 0.34–0.93; $P= 0.022$) [50]. CALGB 40603 [51] evaluated the effect of adding carboplatin (AUC 6 every 3 weeks) and/or bevacizumab (10 mg/kg every 2 weeks) to weekly paclitaxel (80mg/m^2 weekly x 12) followed by dose-sense AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 weeks x 4 cycles) in 443 stage II–III TNBC patients. Both carboplatin (60% *v*44%, $P= 0.0018$) and bevacizumab (59% *v*48%, $P= 0.0089$) were associated with a significant improvement in pCR breast, however only carboplatin improved pCR breast/axilla (54% *v*41%, $P= 0.0029$). In both trials, however, significant myelosuppression and other nonhematologic toxicities were observed with carboplatin requiring not only dose reductions but treatment discontinuation (48% and 20%, respectively). Of note, these trials were not powered to demonstrate long-term survival benefit. Ando et al [52] reported similar pCR rates with carboplatin (AUC 5 every 3 weeks) added to weekly paclitaxel (80 mg/m² weekly) followed by cyclophosphamide, epirubicin, and 5-fluorouracil (CEF 500/100/500 mg/m^2 every 3 weeks x 4 cycles) NACT in TNBC patients (pCR 61.2% *v*26.3%, $P= 0.003$). In this study, carboplatin addition was also associated with a significantly improved DFS and OS in TNBC patients (DFS: HR 0.22, 95% CI 0.06–0.82, $P= .015$; OS: HR 0.12, 95% CI 0.01–0.96, $P= .046$) [53]. Carboplatin use without anthracycline has also been studied and has demonstrated impressive response rates. Sharma et al [54] reported pCR rate of 55% in a single arm study of stage I-III TNBC patients treated with carboplatin and docetaxel (AUC 6 and 75 mg/m² respectively) for 6 cycles. These patients also had significantly improved 3-year DFS and OS compared to non-pCR patients (90% *v*66%, $P= 0.0001$ and 94% *v*79%, $P= 0.001$, respectively). A recent meta-analysis of 11 RCTs including 8 NACT trials in TNBC showed a significant improvement in pCR with carboplatin (40% *v*27%, $P< .0001$) [55]. Several ongoing trials are evaluating various schedules and chemotherapy combinations of platinum agents in early stage TNBC as shown in Table 2.

Despite the added toxicity, given significant improvement in pCR rates, it is reasonable to consider platinum addition to standard NACT particularly in high risk TNBC patients.

Role of Platinum agents in BRCA mutation

Germline BRCA1/2 mutations are more prevalent in TNBC compared to other breast cancers and occur in about 10%–15% of TNBCs with BRCA1 being more common than BRCA2 mutation [56-59]. BRCA1 and 2 genes are involved in double-stranded DNA break repair by homologous recombination and hence the impaired DNA repair pathway in BRCA1/2 mutated cancers makes them more susceptible to chemotherapy agents that damage or interfere with the DNA repair process. Such agents include platinum and poly ADP ribose polymerase (PARP) inhibitors.

Clinical efficacy of platinum agents in BRCA-mutated TNBC has been shown in some early metastatic studies with response rates up to 50%–60% [60,61], however, its role in neoadjuvant space remains unclear. The high pCR seen with carboplatin in the neoadjuvant study reported by Sharma et al [54] was independent of BRCA mutation status, with pCR being 59% in BRCA-mutated and 56% in BRCA-wild type patient ($P= 0.83$). In GeparSixto GBG 66 trial [49], carboplatin addition was not associated with an improved pCR rate in BRCA-mutated patients. In contrast, patients without BRCA mutations had a higher pCR with carboplatin (55% *v*36.4%, $P= 0.004$) and improved DFS (85.3% *v*73.5%, $P= 0.04$) [62]. Currently, the decision to add platinum agent in the neoadjuvant setting for early stage TNBC patients is driven by burden of disease and not necessarily the BRCA mutation status. Ongoing research efforts are focusing on defining better molecular markers and assays for homologous recombination deficiency beyond germline BRCA testing to better identify subsets of TNBC patients with improved responses to DNA damaging agents.

Immune Checkpoint Inhibitors

Although initially thought to be immunologically quiescent, certain breast cancers have been shown to be more immunologically active using identification of tumor-infiltrating lymphocytes (TILs) as a surrogate marker for immune activation [63,64]. High TIL presence has been consistently demonstrated in TNBC [65-67]. The presence of TILs has been associated with improved outcomes

Table 2
Selected ongoing neoadjuvant clinical trials in TNBC

NCT number	Phase	Treatment intervention
Taxanes		
NCT04137653	III	Nab-Paclitaxel and Carboplatin versus Paclitaxel and Carboplatin in neoadjuvant TNBC
NCT02897050	II	Docetaxel(T) combined with metronomic cyclophosphamide/capecitabine (mCX) followed by fluorouracil /epirubicin/cyclophosphamide (FEC) versus T followed by FEC
Platinum agents		
PEARLY NCT02441933	III	Anthracyclines Followed by Taxane Versus Anthracyclines Followed by Taxane Plus Carboplatin as (Neo) Adjuvant Therapy in Patients With TNBC
NeoSTOP NCT02413320	II	Neoadjuvant Carboplatin Plus Docetaxel or Carboplatin Plus Paclitaxel Followed by Doxorubicin Plus Cyclophosphamide in Stage I-III TNBC
NCT03154749	II	TC (Docetaxel/Carboplatin) Versus EC-T (Epirubicin/Cyclophosphamide Followed by Docetaxel) as NACT for TNBC
NCT04083963	II	BRE-01: Phase 2 Trial of Neoadjuvant Weekly Carboplatin Plus Paclitaxel Followed by Doxorubicin and Cyclophosphamide in TNBC
Immune checkpoint inhibitors		
NSABP B-59/GBG 96-GeparDouze NCT03281954	III	Atezolizumab or Placebo with paclitaxel and carboplatin followed by doxorubicin and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC) in Patients with TNBC Followed by Adjuvant Continuation of Atezolizumab or Placebo
IMpassion 031 NCT03197935	III	Randomized Study to Investigate the Efficacy and Safety of Atezolizumab versus Placebo in Combination with Neoadjuvant Anthracycline/Nab-Paclitaxel-Based Chemotherapy in TNBC
NeoPACT NCT03639948	II	Neoadjuvant Pembrolizumab And Carboplatin Plus Docetaxel in TNBC
NCT04243616	II	Study of PD-1 Inhibition with Cemiplimab in Locally Advanced Hormone Receptor (HR) Positive HER2 Negative or TNBC Patients Undergoing Standard NACT
NCT04213898	I/II	SHR-1210 (anti- PD1 inhibitor) Combined with Albumin-bound Paclitaxel and Epirubicin Neoadjuvant for TNBC
NCT03356860	I/II	A Phase IB/II Study of Durvalumab Combined with Dose-dense EC following Paclitaxel in a Neoadjuvant Setting for Patients with Locally Advanced Luminal B HER2(-) or TNBC
NCT02489448	I/II	Neoadjuvant MEDI4736 Concomitant with Weekly Nab-paclitaxel and Dose-dense AC for Stage I-III TNBC
NCT04331067	I/II	Cabiralizumab* in Combination with Nivolumab and paclitaxel/Carboplatin NACT in Patients with Localized TNBC
PARP inhibitors		
PARTNER NCT03150576	II/III	Evaluate the Safety and Efficacy of the Addition of Olaparib to Platinum-based NACT in Patients with TNBC and/or gBRCA.
NCT03329937	I	Evaluate the Antitumor Activity and Safety of Niraparib as Neoadjuvant Treatment in Localized, HER2-negative, BRCA-mutant Breast Cancer Patients
Androgen receptor antagonists		
NCT02689427	II	Enzalutamide and Paclitaxel Before Surgery in Treating Patients with Stage I-III Androgen Receptor-Positive TNBC
NCT02676986	II	Study of Short-term Preoperative Treatment with Enzalutamide (Alone or in Combination with Exemestane) in Patients with Primary Breast Cancer (HR+ and TNBC)

* Anticolony stimulating factor 1 receptor (CSF1R) antibody.

and responses to chemotherapy [68-70]. PD-1 and its ligands, PD-L1 and PD-L2, interact to down regulate the activation of T cells in cancer, and therapies targeted against the PD-1 axis have shown remarkable clinical responses in many cancers including breast cancer [71-79].

Given the modest responses with immune checkpoint inhibitors monotherapy in early metastatic trials [80-82] and the potential synergy between chemotherapy and immune therapy, combination strategies have been explored to improve patient outcomes. The practice changing IMpassion 130 trial [83] showed significantly improved outcomes with atezolizumab, an anti-PD-L1 antibody (840 mg IV days 1 and 15) in combination with nab-paclitaxel (100 mg/m² days 1,8 and 15 of every 28 day cycle) in metastatic TNBC patients particularly those with PD-L1 positive tumors (PFS: 7.5 m *v*5 m, HR 0.62, 95% CI 0.49–0.78, $P<$ 0.001; OS: 25 m *v*15.5 m, HR 0.62, 95% CI 0.45–0.86). Recent results from KEYNOTE-355, a phase III trial showed significant improvement in PFS with pembrolizumab, an anti-PD1 antibody, in combination with chemotherapy in patients with PD-L1+ metastatic TNBC [84].

Given promising data in advanced setting, immune checkpoint inhibitors have also been explored in the neoadjuvant setting. Phase 1b, KEYNOTE-173 study [85] of neoadjuvant pembrolizumab (200 mg every 3 weeks) plus chemotherapy (taxane with or without carboplatin, followed by AC) for locally advanced TNBC showed pCR rate of 60% (range 49%–71%) with PD-L1 positivity associated with a higher pCR rate ($P=$ 0.012). In the ongoing phase II I-SPY2 trial [86], pembrolizumab (200 mg every 3 weeks) addition to standard anthracycline and taxane based NACT (weekly paclitaxel 80 mg/m² weekly x 12 followed by 4 cycles of doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² every 2–3 weeks) was associated with a significant improvement in estimated pCR in all breast cancer subtypes with the highest difference being in TNBC (60% *v*22%). KEYNOTE-522 [87], a phase III RCT, 1175 patients with stage II–III TNBC were randomized to receive pembrolizumab (200 mg every 3 weeks) or placebo with paclitaxel (80 mg/m² weekly x 12) and carboplatin (AUC 5 every 3 weeks or AUC 1.5 every week x 12) followed by four cycles of doxorubicin (60 mg/m²) or epirubicin (90 mg/m²) plus cyclophosphamide (600 mg/m²) with or without pembrolizumab. Addition of pembrolizumab was associated with a significant improvement in pCR (64.8% *v*51.2%, $P<$ 0.001) with the effect being much more pronounced in patients with PD-L1 positive tumors (68.9% *v*54.9%) compared to PD-L1 negative (45.3% *v*30.3%). Interestingly, the NeoTRIPaPDL1 trial [88] did not show a significant improvement in pCR with neoadjuvant atezolizumab (1200 mg) combined with carboplatin (AUC 2) and nab-paclitaxel (125 mg/m² days 1 and 8 every 3 weeks x 8 cycles) for TNBC patients (43.5% *v*40.8%, OR 1.11, 95% CI, 0.69–1.79). PD-L1-positivity predicted treatment benefit with atezolizumab compared with PD-L1 negativity (OR 2.08; 95% CI 1.64–2.65, $P<$ 0.0001). The risk of immune mediated adverse events is significant and requires close monitoring and early intervention.

Immune checkpoint inhibitors are being investigated in multiple ongoing trials in all subtypes of breast cancers in both metastatic and early stage setting. None of the agents are currently approved in neoadjuvant or adjuvant setting, however FDA review is awaited given the promising results and significant pCR improvement in KEYNOTE-522 trial.

Table 3
Selected ongoing adjuvant clinical trials in TNBC

NCT number	Phase	Treatment Intervention
Platinum agents		
NCT02445391	III	Platinum Based Chemotherapy or Capecitabine in Treating Patients with Residual TN Basal-Like Breast Cancer Following NACT
NCT04297267	II	Gemcitabine Plus Cisplatin in the Treatment of Patients with Non-pCR TNBC Following standard NACT
Immune checkpoint inhibitors		
S1418/BR006 Keynote-242 NCT02954874	III	Pembrolizumab as Adjuvant Therapy for TNBC with residual cancer after NACT
IMpassion 030 NCT03498716	III	Atezolizumab In Combination with Adjuvant Anthracycline/Taxane-Based Chemotherapy Versus Chemotherapy Alone in Patients with Operable TNBC
NCT02926196	III	Adjuvant Treatment for High-risk TNBC Patients with Avelumab
PHOENIX DDR/Anti-PD-L1 trial NCT03740893	II	A Pre-surgical Window of Opportunity and Post-surgical Adjuvant Biomarker Study of DNA Damage Response (DDR) Inhibition and/or Anti-PD-L1 Immunotherapy in Patients with NACT Resistant Residual TNBC
PARP inhibitors		
OlympiA NCT02032823	III	Efficacy and Safety of Olaparib Versus Placebo as Adjuvant Treatment in Patients With gBRCA1/2 Mutations and High Risk HER2 Negative Primary Breast Cancer Who Have Completed Definitive Local Treatment and Neoadjuvant or Adjuvant Chemotherapy
Therapeutic vaccine		
GLORIA Trial NCT03562637	III	Adagloxad Simolenin (OBI 822)/OBI 821 versus placebo Treatment for High Risk Early Stage TNBC Patients with Residual Invasive Disease Following NACT

PARP Inhibitors

BRCA-mutated tumors have shown increased responses to PARP inhibition in preclinical and clinical studies [89-98]. OlympiAD [99], a phase III RCT showed significantly improved PFS with olaparib monotherapy compared to non-platinum chemotherapy (7 m *v*4.2 m, HR 0.58 95% CI 0.43–0.8, $P< 0.001$) in germline BRCA-mutated metastatic HER2 negative breast cancer patients. EMBRACA trial [100], another phase III RCT showed significant improvement in PFS with talazoparib compared to physician's choice chemotherapy (8.6 m *v*5.6 m, HR 0.54, 95% CI 0.41–0.71, $P< 0.001$) in germline BRCA-mutated metastatic breast cancer patients.

PARP inhibitors have also been investigated in early stage TNBC patients. In the adaptive neoadjuvant I-SPY2 trial [95], the addition of veliparib and carboplatin to standard anthracycline and taxane based chemotherapy improved estimated pCR from 26% to 51%. However, it is unclear if veliparib contributed to the improved pCR given the similar pCR rates seen with carboplatin alone in GeparSixto [49] and CALGB 40603 [51] trials. Given these results, the phase III BrighTNess trial [101] was conducted which showed significantly improved pCR with the addition of carboplatin-veliparib (53% *v*31%, $P< 0.0001$) and carboplatin (58% *v*31%, $P< 0.0001$) to standard neoadjuvant chemotherapy, however there was no significant difference between the two interventional arms.

A phase II RCT of adjuvant cisplatin with or without rucaparib in TNBC with residual disease post NACT showed similar 2-year DFS in both arms (58.3% *v*63.1%, $P= 0.43$) [102]. OlympiA (NCT02032823) is an ongoing phase III trial assessing the role of adjuvant olaparib in BRCA-mutated HER2 negative breast cancer patients. There are several PARP inhibitors currently under investigation for both metastatic and early stage BRCA-mutated and/or TNBC. Select ongoing trials for early stage TNBC patients are mentioned in Tables 2 and 3. The clinical efficacy of PARP inhibitors for early stage TNBCs regardless of BRCA mutation status remains unclear and they are not used in routine clinical practice in neoadjuvant or adjuvant setting.

Adjuvant therapy for residual disease

Lack of pCR after NACT has been recognized as a crucial prognostic marker and is used for tailoring adjuvant therapy. Given the poor outcomes in patients with residual disease after NACT, several systemic therapeutic approaches have been studied in adjuvant setting.

Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) trial [103] randomized HER2-negative breast cancer patients with residual disease post NACT to capecitabine (1250 mg/m^2 twice daily for up to 8 cycles) or placebo. Adjuvant capecitabine was associated with a significant improvement in 5-year DFS and OS (74.1% *v*67.6%, $P= 0.01$ and 89.2% *v*83.6%, $P= 0.01$, respectively). This improvement was even more pronounced in TNBC patients with DFS of 69.8% *v*56.1% (HR 0.58, 95% CI 0.39–0.87) and OS improved to 78.8% *v*70.3% (HR 0.52, 95% CI 0.3–0.9). Hematologic and nonhematologic adverse events were much more frequent with capecitabine use with hand-foot syndrome being the most significant.

Despite significant dose reductions and discontinuations, adding capecitabine in adjuvant setting for patients with residual disease after NACT is very reasonable due to no other standard adjuvant treatments available. Several ongoing trials are exploring adjuvant chemotherapy and novel agents for TNBC with residual disease. Some of them are summarized in Table 3.

Future directions

The genomic landscape of TNBC is rapidly evolving and several promising clinical trials are ongoing in efforts to improve clinical outcomes. Several molecular pathways serve as potential therapeutic targets and are currently under investigation with some showing favorable responses in advanced setting. Androgen receptor (AR) positivity have been reported in ~20% of TNBC patients [104] and is a potential target for anti-androgen therapy. Favorable responses to AR inhibitors have been reported in advanced AR+ TNBC patients [105-107] with clinical trials ongoing in early stage patients as well. Some of the other targeted therapies under investigation include agents against Phosphatidylinositol 3-kinase (PI3K/mTOR), Mitogen-activated protein kinase (MAPK/ERK), Histone deacetylase (HDAC) inhibitors and vaccines. Given the heterogeneity of TNBC, understanding the molecular landscape of the disease and targeting tumor-specific alterations would be the most effective approach towards personalized medicine and improved long-term outcomes.

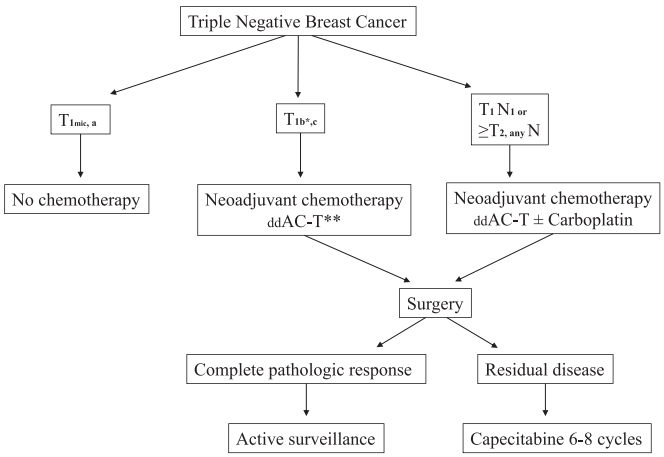

Fig. 1. Treatment recommendations for early stage TNBC.
Footnotes: *For T1b tumors, consider chemotherapy if patient is a good candidate. Neoadjuvant approach is preferred. For small T1b tumors, surgery first can be considered followed by active surveillance versus adjuvant TC (taxane and cyclophosphamide). Dd = dose dense; AC = doxorubicin and cyclophosphamide; T = paclitaxel. **Anthracycline and taxane based regimens of treating physicians' choice.
Chemotherapy recommendations are in accordance with NCCN guidelines.

Conclusions

Systemic chemotherapy significantly reduces the risk of local and distant recurrence in early stage TNBC patients; however, metastatic disease develops in a significant number of patients due to the aggressive nature of this disease. This review summarizes the current clinical practices and management of early stage TNBC patients (Fig. 1). Patients with very early stage disease (<1 cm, N0) where benefit of chemotherapy is unclear can certainly have surgery upfront to fully assess the burden of disease and decide if active surveillance would be reasonable. For all others, systemic chemotherapy is usually warranted. Neoadjuvant approach is preferred for pathologic response assessment, prognostic information and tailoring adjuvant treatment accordingly. Anthracycline and taxane based regimens are considered standard of care for early stage TNBC patients. Addition of carboplatin to the standard regimen is associated with a significant improvement in pCR, albeit at the cost of added toxicity. However, for patients with larger tumors or nodal involvement, carboplatin use is very reasonable. Patients with residual disease after NACT have a significantly higher risk of recurrence compared to patients achieving pCR. Adjuvant capecitabine in patients with residual disease post-NACT is associated with a significant improvement in PFS and OS and is routinely used in clinical practice. Many chemotherapy and novel agents have been evaluated in neoadjuvant clinical trials to assess pCR benefits with multiple trials ongoing. Immune checkpoint inhibitors have shown promise in early stage patients with significant improvement in pCR with pembrolizumab added to anthracycline, taxane and carboplatin containing neoadjuvant regimen in the KEYNOTE-522 trial. These results could be practice changing and FDA review is highly anticipated. Exciting future avenues for treating TNBC will involve harnessing information from the genomic molecular profiling of various subtypes within this disease and overcoming the complexities to construct new therapeutic options.

Declaration of Competing Interest

None.

Acknowledgments

This publication was supported by the National Center for Research Resources, the National Center for Advancing Translational Sciences, and the Office of the Director, National Institutes of Health, through Grant Number KL2TR001438. Its contents are solely the responsibility of the author/authors and do not necessarily represent the official views of the NIH.

Dr. Jame Abraham, MD, FACP, Cleveland Clinic provided his expert opinion and feedback to this review article.

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