Optimal Systemic Treatment for Early Triple-Negative Breast Cancer

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Keywords

Triple-negative breast cancer · Early breast cancer · Guidelines · Treatment

Abstract

Background: Approximately 10–15% of all breast tumors are triple-negative breast cancer (TNBC). TNBC have a higher risk of relapse and distant metastases compared to other subtypes. The optimal systemic management of TNBC according to national and international guidelines is discussed herein. **Summary:** Anthracycline/taxane-based chemotherapy for patients with TNBC either in the neoadjuvant (NACT) or the adjuvant setting is considered standard of care. Exceptions are small tumors and a low-risk histology, in which chemotherapy can be spared. Dose-dense therapy is more effective in preventing recurrence and increasing survival. The use of nab-paclitaxel instead of a solvent-based taxane can lead to higher pathological complete response (pCR) rates and better outcomes. Platinum agents are effective in increasing pCR when added to anthracycline/taxane-based chemotherapy at the cost of increased toxicity. Long-term outcome data are lacking. In patients without a pCR, capecitabine leads to improved outcomes. **Key Messages:** The standard treatment approach of TNBC is anthracycline/taxane-based chemotherapy, preferably within the NACT

setting. Dose-dense schedules as well as platinum should be considered in the NACT setting. For patients without a pCR, capecitabine is an option to improve the outcome. The role of nab-paclitaxel is under debate. In case of immunogenic tumors, checkpoint inhibitors are promising new agents that merit further investigation.

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Introduction

Triple-negative breast cancer (TNBC) accounts for approximately 10–15% of all newly diagnosed breast tumors and is characterized by a lack of expression of the estrogen (ER), progesterone (PgR), and human epidermal growth factor 2 receptors (HER2) [1]. The recently updated guidelines define a tumor sample as ER/PgR negative if <1% of the tumor cell nuclei are immunoreactive [2]. However, a new category, i.e., ER/PgR low, has been implemented, which is biologically very much like TNBC [3]. TNBC is typically diagnosed at a younger age [4]. At diagnosis, the majority of TNBC patients present with stage T2 or T3 and have involved lymph nodes and positive lymph vascular invasion [5]. The locoregional relapse rate appears to be similar to those of other molecular subgroups, but TNBC is associated with higher rates of dis-

tant metastases [6], especially visceral ones, with a lower prevalence of bone metastases [7]. Most TNBC tend to have an aggressive course and a worse prognosis, with a high mortality rate [6].

Lately, there has been major progress in understanding TNBC, with the assertion that the use of standard markers is not enough to account for the complexity and heterogeneity of TNBC. Histopathological characterization is necessary to identify those subtypes with a better prognosis, such as adenoid cystic or metaplastic subtypes that might be treated with a less aggressive approach [8]. As highlighted by gene expression profile analyses, for the additional subclassification of TNBC, immune markers, androgen receptors, stem cells, basal markers, and the mesenchymal phenotype should be considered. In particular, based on the Vanderbilt classification, 4 molecular subtypes can be identified, with different histopathologies, gene expression profiles, prognoses, and treatment responses [9]. The treatment options for early TNBC are limited. Anthracycline/taxane-based chemotherapy is still the fulcrum of the therapy in the early setting. However, some steps forward have been made in recent years. Studies have shown that the addition of platinum can lead to higher pCR rates and might be considered in selected patients (Tables 1, 2). Furthermore, in case of residual disease after NACT, capecitabine has demonstrated efficacy in improving patient outcomes [10]. In an attempt to exploit the molecular diversity of TNBC, several agents have been tested targeting specific structures or signaling pathways essential for cell proliferation, invasion, and angiogenesis. Checkpoint, PARP, and AKT inhibitors are among the most important agents under investigation, with encouraging preliminary efficacy results. Adherence to guidelines when treating patients with TNBC improves outcomes [11]. In this review the optimal treatment approach for early TNBC defined by the most recognized international [12–15] and German national [16] guidelines are presented (Table 1), and studies leading to these recommendations are discussed (Table 2).

Predictive Biomarkers in Early TNBC

BRCA1/2 are tumor suppressor genes that encode proteins involved in the repair of DNA double-strand breaks through the homologous recombination repair pathway. Members of the PARP family of enzymes are central to the repair of DNA single-strand breaks. Fifteen to twenty percent of unselected TNBC have a *gBRCA* mutation (m) [17]. TNBC patients without *gBRCA*m have a somatic mutation in the homologous recombination signaling pathway (BRCAness). *gBRCA*m and BRCAness statuses are associated with an increased sensitivity to chemother-

apy and with better outcomes [17, 18]. Cells with *gBRCA*m are sensitive to PARP inhibition due to the synthetic lethality mechanism, resulting in an incapacity for DNA repair [19]. As *gBRCA*m is associated with a higher pathological complete response (pCR) rate and a prognostic impact in patients with TNBC [20], assessment of the *gBRCA* status should be considered in the early setting.

The results of studies with checkpoint inhibitors [21] have shown the importance of immune marker assessment in TNBC. TNBC are highly immunogenic as reflected by high levels of stromal tumor-infiltrating lymphocytes (TIL). TIL have a predictive and prognostic role, especially in TNBC [22]. In the early setting PD-L1 positivity on immune cells leads to higher pCR rates; in the advanced setting it leads to improved outcomes. Based on the results of IMpassion 130, the FDA approved the combination of nab-paclitaxel plus atezolizumab as first-line therapy for metastatic PD-L1+ TNBC. PD-L1 testing on immune cells is recommended in patients with advanced TNBC to consider this combination therapy.

As PD-L1 is a dynamic marker and differences exist in the types of assay used and in PD-L1 assessment, additional predictive biomarkers are under investigation. A high tumor mutational burden is associated with a higher neoantigen burden and increased T-cell infiltration. Recently, it was shown that hypermutated breast cancers, like tumors with a mismatch repair deficiency, seem to benefit from PD-1 inhibitor therapy independently of the underlying mutational process [23]. Further investigation is needed.

Management of TNBC: Evidence So Far

Despite it being a very heterogeneous disease, the treatment of patients with early TNBC is still founded on the administration of anthracycline/taxane-based chemotherapy. In a meta-analysis including women with hormone receptor (HR)-negative breast cancer treated in trials of non-taxane-based chemotherapy versus none, adjuvant chemotherapy reduced the 10-year risk of recurrence and breast cancer mortality [24]. In a retrospective analysis of patients enrolled into 3 randomized trials of anthracycline/taxane-based chemotherapy, dose-dense anthracycline/taxane-based chemotherapy lowered the rate of recurrence and death by more than 50% compared to low-dose anthracycline-based chemotherapy in HR-negative, node-positive breast cancer [25]. A meta-analysis using data of 100,000 women showed a reduced breast cancer mortality in patients receiving anthracycline/taxane-based chemotherapy. Proportional risk reductions were little affected by HR status [26].

Table 1. International and national guidelines and treatment recommendations

Guidelines	Recommendations	LoE
<i>Neoadjuvant setting</i>		
ASCO (2016) [14]	– Not applicable	
NCCN (V 1.2020) [13]	– Preferred option over adjuvant treatment if T ≥2 or N ≥1 – Regimens recommended in the adjuvant setting may be considered in the NACT setting; weekly paclitaxel or docetaxel + carboplatin are further recommended regimens for patients with TNBC – Several studies have shown improved pCR rates with incorporation of platinum; their routine use is not recommended for most patients (including <i>BRCA</i> mutation carriers) but might be considered in selected patients (such as those for whom achieving better local control is necessary)	2A
ESMO (2015) [12]	– Addition of a platinum compound (carboplatin) to NACT allows for an increase in the pCR rate, particularly in those carrying deleterious <i>BRCA1/2</i> or <i>RAD</i> mutations or in patients with a family history of breast/ovarian cancer; the effect of those compounds on long-term outcomes is unknown	IB
AGO (V 1.2019) [16]	– If chemotherapy is indicated NACT should be preferred over adjuvant therapy: Conventionally dosed AT-based CT Dose-dense CT (AT-based including a weekly schedule) NACT platinum-containing CT (irrespective of <i>BRCA</i> status)	AGO GoR + AGO GoR ++ AGO GoR +
St. Gallen International Consensus (2019) [15]	– Preferred initial approach in women with stage II or III TNBC (AC/T CT +/- platinum) – Platinum-based CT: against the routine inclusion of platinum in women already slated to receive A-, T-, and alkylator-based regimens; in favor of their inclusion among women with known, deleterious <i>g BRCA1/2</i> mutations (limited data, opinion not unanimous) – Dose-dense treatment: preferred approach for AT-based neo/adjuvant CT regimens – Neoadjuvant trials demonstrate that addition of an anti-PDL1 (durvalumab) or anti-PD1 (pembrolizumab) agent to standard CT improves the rate of pCR in TNBC	Expert opinion
<i>Adjuvant setting</i>		
ASCO (2016) [14]	– TNBC patients with T >5 mm N0 are considered at high risk and are therefore candidates for CT – Patients with early-stage, HER2-negative breast cancer with residual disease following standard AT-based NACT may be offered up to 6–8 cycles of adjuvant capecitabine – Platinum salts should not be routinely administered until efficacy data become available	Evidence quality: intermediate
NCCN (V 1.2020) [13]	– The use of a platinum agent is not recommended; if included in an A-based regimen, the optimal sequence of chemotherapy and choice of T agent is not established – In patients with residual disease after NACT with A-, T- and alkylator-based CT: capecitabine; if indicated, it should follow completion of radiotherapy	2A
ESMO (2015) [12]	– CT is recommended in the vast majority of TNBC (exception: secretory juvenile, apocrine, or adenoid cystic carcinomas); CT is usually administered for 12–24 weeks – The use of dose-dense schedules (with G-CSF) should be considered in highly proliferative tumors – The use of platinum compounds is not recommended for routine use (independently of <i>gBRCA1/2</i> status)	IA IB No LoR
AGO (V 1.2019) [16]	– Capecitabine containing regimen in the postneoadjuvant setting: generally in non-pCR (up to 8 courses) – Platinum-containing regimen	AGO GoR - AGO GoR + AGO GoR +
St. Gallen International Consensus (2019) [15]	– The adjuvant approach is typically used in stage I tumors: Stage T1cN0 or higher: AC/T CT is the preferred regimen for many women Stage T1ab (≤1 cm) N0: preference for a TC regimen without A (majority of panelists) T1a (≤0.5 cm) N0: CT on a case-by-case basis – Women with TNBC and residual tumor after NACT should consider capecitabine in the adjuvant setting – Dose-dense treatment: preferred approach for AT-based neo/adjuvant chemotherapy regimens	
A, anthracycline; ASCO, American Society of Clinical Oncology; C, cyclophosphamide; CT, chemotherapy; ESMO, European Society for Medical Oncology; g, germline; G-CSF, granulocyte colony-stimulating factor support; GoR, grade of recommendation; LoE, level of evidence; T, taxane; V, version.		

Based on this evidence, guidelines recommend the use of chemotherapy for patients with TNBC either in the neoadjuvant (NACT) or in the adjuvant setting, with the possible exception of small tumors and a low risk histology. Due to discordant results, the use of nab-paclitaxel is still under debate [27–30]. Arbeitsgemeinschaft Gynäko-

logische Onkologie (AGO) guidelines recommend the use of nab-paclitaxel instead of paclitaxel in the NACT setting [16]. Conversely, National Comprehensive Cancer Network (NCCN) guidelines state that nab-paclitaxel may substitute soluble taxanes due to medical necessity (e.g., hypersensitivity) [13].

Table 2. Key studies on treatment options for early TNBC

Study	Arm	Cohort	Primary endpoint	Further key results
<i>Nab-paclitaxel</i> GeparSepto [27–29]	nP 125 mg/m ² w for 12 w (before study amendment, 150 mg/m ²) → EC vs. P 80 mg/m ² w for 12 w → EC	cT2-cT4a–d or cT1c high-risk	pCR overall cohort 38 vs. 29% (OR = 1.53; 95% CI 1.20–1.95, <i>p</i> < 0.001); TNBC 48 vs. 26%, <i>p</i> < 0.001	4-years DFS 84.0 vs. 76.3% (HR = 0.66; 95% CI 0.51–0.86, <i>p</i> = 0.002); TNBC: 68.6 vs. 77.0% (HR = 0.66; 95% CI 0.42–1.05, <i>p</i> = 0.077)
	P 90 mg/m ² for 3 q4w for 4 cycles → A(E)C or FEC vs. nP 125 mg/m ² for 3 q4w for 4 cycles → A(E)C or FEC	HER2- (TNBC or luminal B-like)	pCR overall cohort 22.5 vs. 18.6% (OR = 0.77; 95% CI 0.52–1.13, <i>p</i> = 0.19)	Overall: 5-year EFS 68.1 vs. 75.6% (HR = 0.83; 95% CI 0.60–1.14, <i>p</i> = 0.245); TNBC: 61.0 vs. 63.5% (HR = 0.76; 95% CI 0.47–1.23, <i>p</i> = nr)
<i>Platinum agents</i>				
GEICAM/2006-3 [46]	EC (E 90 mg/m ² , cyclophosphamide 600 mg/m ² for 4 cycles) followed either by D 100 mg/m ² for 4 cycles (EC-D) or DCb (D 75 mg/m ² + Cb AUC 6 for 4 cycles; EC-DCb)	Basal-like BC	pCR (ypT0) EC-D 35% (95% CI 21–49) vs. EC-DCb 30% (95% CI 17–43), <i>p</i> = 0.606	RR 70 vs. 77%, <i>p</i> = 0.445
GeparSixto [48]	P 80 mg/m ² + nonpegylated liposomal doxorubicin 20 mg/m ² w for 18 weeks (+ Bev 15 mg/kg in TNBC and trastuzumab 6 mg/kg [initial dose 8 mg/kg] q3w and lapatinib 750 mg daily simultaneously with all cycles in HER2-positive) +/- Cb AUC 1.5 w for 18 weeks	Stage II–III, TNBC, and HER2-positive BC	pCR (ypT0 ypN0) Cb 43.7% vs. no Cb 36.9% (OR = 1.33; 95% CI 0.96–1.85, <i>p</i> = 0.107)	TNBC: pCR Cb 53.2% vs. no Cb 36.9%, (<i>p</i> = 0.005) HER2+: pCR Cb 32.8% vs. no Cb 36.8% (<i>p</i> = 0.581) DFS (HR = 0.56; 95% CI 0.34–0.93, <i>p</i> = 0.022)
UMIN000003355 [47]	P 80 mg/m ² w for 12 w + Cb AUC5 q3w for 4 courses → CEF (500 mg/m ² , 100 mg/m ² , 500 mg/m ²) q3w for 4 courses P 80 mg/m ² w for 12 w → CEF (500 mg/m ² , 100 mg/m ² , 500 mg/m ²) q3w for 4 courses	Stage II/IIIA HER2–	pCR (ypT0/is ypN0) PCb-CEF vs. P-CEF (31.8 vs. 17.6%, one-sided <i>p</i> = 0.01)	pCR TNBC 61.2 vs. 26.3 %, <i>p</i> = 0.003
CALGB 40603 [49]	P 80 mg/m ² w for 12 weeks (+/- Cb AUC 6 q3w for 4 cycles and/or Bev 10 mg/kg q2w for 9 cycles) → dd AC	Stage II–III noninflammatory TNBC	pCR (ypT0/is): Cb-containing therapy 60 vs. 46% (OR = 1.76, <i>p</i> = 0.0018); Bev containing therapy 59% vs. 48% (OR = 1.58, <i>p</i> = 0.0089)	LTO with Cb (EFS HR = 0.99; 95% CI 0.70–1.40) or Bev (EFS HR = 0.91; 95% CI 0.64–1.29).
GeparOcto [54]	E 150 mg/m ² q2w → P 225 mg/m ² q2w → C 2,000 mg/m ² q2w for 3 cycles each (ddEPC) vs. P 80 mg/m ² w + nonpegylated iposomol doxorubicin 20 mg/m ² w + Cb AUC 1.5 w (TNBC only) for 18 weeks (PM[Cb])	cT1c-cT4a–d TNBC, HER2+, or luminal B-like if N+	pCR (ypT0/is ypN0) overall cohort: 48.3 vs. 48.0% (OR = 0.99; 95% CI 0.77–1.28, continuity corrected χ^2 -test <i>p</i> = 0.979)	TNBC OR = 5.39; 95% CI 3.20–9.07, <i>p</i> < 0.001
GeparX [53]	nP 125mg/m ² w for 12 w +/- denosumab → EC +/- denosumab TNBC: +carboplatin w AUC 2	cT1c high-risk or cT2-cT4a–d	Overall pCR (ypT0 ypN0) +/- denosumab: 41.0 vs. 42.8%, <i>p</i> = 0.582; pCR nP 125 mg/m ² weekly vs. day 1, 8 q22: 44.9 vs. 39.0%, <i>p</i> = 0.062	pCR nP 125 mg/m ² weekly vs. day 1, 8 q22 TNBC: 60.4 vs. 50.0%, <i>p</i> = 0.056
TBCRC 030 [61]	Cisplatin 75 mg/m ² q3w for 4 cycles vs. P 80 mg/m ² w for 12 w	TNBC, T1>1.5 cm, stage II–III	RCB 0/1 26.4 vs. 22.1% RCB 2/3 73.6 vs. 76.5%	pCR 15.3 vs. 11.8% HRD+ 69.6 vs. 73.5% HRD– 30.4 vs. 26.5%

Table 2 (continued)

Study	Arm	Cohort	Primary endpoint	Further key results
<i>Checkpoint inhibitors</i>				
GeparNuevo [65]	Window phase (2 weeks before the start of nP): durvalumab 0.75 g i.v. /placebo; nP 125 mg/m ² w for 12 weeks + durvalumab 1.5 g i.v. → EC q2w vs. nP 125 mg/m ² w for 12 weeks + placebo q4w → EC q2w	TNBC; cT1b–cT4a–d	pCR (ypT0 ypN0) 53.4 vs. 44.2% (OR = 1.45; 95% CI 0.82–2.84, <i>p</i> = 0.182)	pCR window cohort: 61.0 vs. 41.4% (OR = 2.22; 95% CI 1.06–4.64, <i>p</i> = 0.035; interaction <i>p</i> = 0.048); pCR with durvalumab in PD–L1+ vs. PD–L1–: 54.3 vs. 30.0%, <i>p</i> = 0.048
NeoTrip [70]	Cb AUC 2 + nP 125 mg/m ² i.v. on day 1, 8 + q3w /– atezolizumab 1,200 mg i.v. q3w for 8 cycles → surgery → anthracycline regimen for 4 cycles	TNBC	5-year EFS (data pending)	pCR (ypT0/is ypN0) 43.5 vs. 40.8% (<i>p</i> = ns); PD–L1+ vs. PD–L1–: 51.9 vs. 48.0% (<i>p</i> = ns)
Keynote-173 [67]	<i>Cycle 1:</i> single pembrolizumab 200 mg administration on day 1 of cycle 1;	TNBC	Safety	Overall pCR (ypT0/Tis ypN0): 60% ORR: 100% in B/C, 90% in D/F, 80% in A, and 70% in E EFS rate at 12 months: 100% in B/C/E/F, 90% in D, and 80% in A EFS rate at 12 months: 100 and 88% for patients with and without pCR
	<i>Cycles 2–5:</i> pembrolizumab 200 mg with either: nP 125 mg/m ² qw (cohort A); nP 100 mg/m ² qw + Cb AUC6 q3w (cohort B); nP 125 mg/m ² qw + Cb AUC5 q3w (cohort C); nP 125 mg/m ² qw + Cb AUC2 qw (cohort D); P 80 mg/m ² qw + Cb AUC5 q3w (cohort E); P 80 mg/m ² qw + Cb AUC2 qw (cohort F) <i>Cycles 6–9:</i> AC q3w + pembrolizumab 200 mg			
Keynote-522 [68]	Pembrolizumab 200 mg/placebo q3w + P (80 mg/m ² w + Cb AUC 5 q3w/AUC 1.5 w for 4 cycles → pembrolizumab/placebo + AC for 4 cycles → surgery → pembrolizumab/placebo for 9 cycles	TNBC T1c N1–2, T2–4 N0–2	pCR (ypT0/Tis ypN0) 64.8 vs. 51.2% (95% CI 5.4–21.8, <i>p</i> = 0.00055) EFS (18 months) 91.3 vs. 85.3% (HR 0.63; 95% CI 0.43–0.93)	pCR PD–L1+ 68.9 vs. 54.9% pCR PD–L1– 45.3 vs. 30.3%
I-SPY 2 [66]	P weekly 80 mg/m ² for 12 w → AC q2–3w for 4 cycles vs. P weekly 80 mg/m ² for 12w + pembrolizumab 200 mg i.v. q3w for 4 cycles → AC q2–3w for 4 cycles	High-risk stage II–III	HER2– pCR 44 vs. 17% TNBC pCR 60 vs. 22%	mEFS overall cohort (explorative) 2.8 vs. 3.5
<i>PARP Inhibitors</i>				
I-SPY2 [51]	P 80 mg/m ² w for 12 weeks → AC for 4 cycles vs. P 80 mg/m ² + veliparib (50 mg b.i.d.) + Cb AUC 6 q3w for 12 weeks → AC for 4 cycles	Stage II–III, T >2.5 cm; HER2–	All HER2-negative: pCR (ypT0/Tis ypN0) VC 33% (23–43%) vs. control 22% (10–35%), probability of VC is superior to control 91%	pCR VC vs. control: HR+/HER2–: 14 vs. 19%; probability of VC is superior to control, i.e., 28% TNBC: pCR 51 vs. 26%, probability of VC is superior to control, i.e., 99%
BrightTNess [52]	Arm A: P 80 mg/m ² w for 12 w → AC q3 or q2 w vs. Arm B: P + Cb AUC 6 q3w, for 4 cycles → AC q3 or q2 w vs. Arm C: P, Cb, and veliparib (50 mg po b.i.d.) → AC q3 or q2	Stage II–III TNBC	pCR arm C vs. A 53 vs. 49.31%, <i>p</i> < 0.0001 pCR arm C vs. B 53 vs. 58%, <i>p</i> = 0.36	pCR in gBRCA1/2 mut: arm B vs. C: 50 vs. 57% arm A vs. arm C: 41 vs. 57% arm A vs. arm B: 41 vs. 50%

Table 2 (continued)

Study	Arm	Cohort	Primary endpoint	Further key results
GeparOla [74]	P weekly 80 mg/m ² for 12 w + olaparib po 100 mg b.i.d. → EC q2–3w vs. P weekly 80 mg/m ² for 12 w plus Cb (AUC2) → EC q2–3w	HER2-, cT2-cT4a-d or cT1c high-risk, known <i>t/gBRCA1/2</i> mutation, or HRD score high	pCR (ypT0/is ypN0): 55.1 vs. 48.6%	pCR (ypT0/is ypN0) TNBC: 56.0 vs. 59.3% <i>t/gBRCAmut</i> : 59 vs. 57.1% <i>t/gBRCAwt</i> : 51.7 vs. 37.5%
TALA [72]	Talazoparib 1 mg po daily for 6 months	Neoadjuvant setting, <i>gBRCA</i> mut	6 months RCB 0 overall cohort: 53%	6-month RCB 0/1: 63% 6-month RCB 0 TNBC cohort: 57%
<i>AKT inhibitors</i> FAIRLANE [78]	P 80 mg/m ² + ipatasertib 400 mg or placebo on days 1–21 q4w for 12 weeks	TNBC (T ≥ 1.5 cm, N0–2)	Overall pCR ipatasertib vs. placebo: 17 vs. 13% PTEN low cohort: 16 vs. 13%	pCR PIK3CA/AKT1/PTEN-altered tumors: 18 vs. 12%

AC, doxorubicin/cyclophosphamide; BC, breast cancer; Bev, bevacizumab; Cb, carboplatin; CEF, cyclophosphamide, epirubicin, 5-fluorouracil; CT, chemotherapy; D, docetaxel; dd, dose-dense; DFS, disease-free survival; EC, epirubicin /cyclophosphamide; EFS, event-free survival; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; g, germline; HRD, homologous recombination deficiency; LTO, long-term outcomes; mut, mutated; nP, nab-paclitaxel; nr, not reported; P, paclitaxel; po, per os; RCB, residual cancer burden; RR, response rate; t, tumor; VC, veliparib/carboplatin; w, weeks; wt, wild-type.

Treatment Setting

Administration of chemotherapy in the neoadjuvant setting is the preferred option as it permits prompt delivery of effective systemic therapy to downstage the tumor (aiming at more conservative surgery), to monitor the treatment response, and to identify chemotherapy-resistant tumors [31] that could benefit from non-cross-resistant therapy after surgery [10]. Moreover, TNBC obtained the highest pCR rate among all of the subtypes [32]. Even if TNBC is associated with a decreased 3-year disease-free survival (DFS) and overall survival (OS) [33], pCR is associated with improved outcomes [34]. In the rare event of progression under NACT [27], surgery should be promptly performed. The chemotherapy regimens used are the same in the neoadjuvant and adjuvant settings.

Postneoadjuvant Therapy

Patients without pCR have a substantial risk of relapse within the first 2–3 years. Several trials have been initiated to improve the outcomes by applying a non-cross-resistant drug after surgery.

The CREATE-X trial [10] is the first study investigating the use of capecitabine versus observation as a postneoadjuvant approach for patients without a pCR after anthracycline/taxane-based NACT. The trial was terminated early as the prespecified interim analysis met the primary endpoint, i.e., DFS, in favor of capecitabine (HR = 0.70; 95% CI 0.53–0.92; $p = 0.01$). Patients with TNBC derived the greatest benefit (HR = 0.58; 95% CI 0.39–0.87) even if a statistically significant interaction with HR status could not be shown. The CIBOMA/2004-01 [35] randomized node-positive or node-negative TNBC patients with tumors ≥ 1 cm treated with anthracycline/taxane-based chemotherapy in the (neo)adjuvant setting to capecitabine or observation after surgery, independently of pCR. The study failed to show a statistically significant increase in DFS by adding capecitabine. Recently, an individual patient data meta-analysis of capecitabine showed improved DFS and OS for TNBC patients when capecitabine was given in addition to other systemic treatments [36]. Similar results were found in 2 further trial level meta-analyses [37, 38].

Guidelines recommend the use of capecitabine in TNBC patients with residual disease after NACT. Of note, none of the patients received carboplatin as part of the (neo)adjuvant therapy. In patients aged ≥ 65 years, doses of 1,000 mg/m² orally twice daily should be considered to avoid toxicities leading to dose reductions [39].

Postneoadjuvant studies investigating the role of platinum agents alone (NCT02445391) or in combination

with a PARP inhibitor (rucaparib NCT01074970), olaparib (NCT02032823) avelumab (NCT02926196), and pembrolizumab (NCT02954874) are ongoing.

Dose-Dense and Dose-Intense Chemotherapy

According to the Goldie-Coldman [40] and Norton-Simon [41] hypotheses, outcomes can be improved by reducing the intervals between cycles and using chemotherapy sequentially at higher doses rather than concomitantly but at a lower dose. However, individual trial results have been discordant [42]. Recently, the EBCTCG conducted a meta-analysis of early breast cancer trials comparing 2-weekly dose-dense versus standard 3-weekly schedules and sequential versus concurrent administration of anthracycline/taxane-based chemotherapy [43]. With a median follow-up of 7.4 years a significant 3.4% absolute reduction in recurrence with dose intensification versus standard schedule chemotherapy was shown. The proportional reduction in recurrence was similar for ER-negative and ER-positive tumors. Additionally, the absolute 10-year breast cancer mortality rate was improved by 2.4%. Despite some limitations [44], these results suggest that especially in patients with high-risk breast cancer the dose-dense approach should be considered supported by granulocyte colony-stimulating factor.

European guidelines recommend the use of a dose-dense regimen in patients with high-risk breast cancer. NCCN guidelines list dose-dense anthracycline/taxane-based chemotherapy among the preferred options for HER2-negative tumors.

Role of Platinum Agents

TNBC is often associated with a deficiency in *BRCA*-driven DNA repair mechanisms, leading to a higher sensitivity to interstrand cross-linking agents damaging the DNA, such as platinum agents [45–47].

In the GeparSixto study, an increased pCR rate was seen in patients with TNBC when carboplatin (AUC 2) was added to anthracycline/taxane-based chemotherapy. Carboplatin was associated with a higher toxicity, but the frequency of grade 3–4 adverse events (AE) decreased when the dose was reduced to AUC 1.5 [48]. The pCR benefit translated into a significantly better DFS [17]. Similarly, in the CALGB 40603 study, the addition of either carboplatin or bevacizumab increased the pCR rate. However, patients assigned to either carboplatin or bevacizumab were less likely to complete the treatment without dose modifications due to AE [49]. Conversely to GeparSixto, the CALGB 40603 study did not show any improvement in outcomes by adding carboplatin or

bevacizumab [50]. Based on the I-SPY2 results [51], the BrighTNess trial investigated the use of carboplatin and velaparib in patients with stage II–III TNBC. Carboplatin increased the pCR rate compared to paclitaxel alone and independently by the use of velaparib. Grade 3–4 AE were more common in patients receiving carboplatin, whereas velaparib did not substantially increase toxicity [52]. Of note, 42% of patients required a reduction in the dose of carboplatin from AUC 6 to AUC 5. The recommended dose is therefore carboplatin AUC 1.5 weekly or AUC 5 q3w when given in addition to paclitaxel. The efficacy of carboplatin in TNBC was further confirmed in the GeparX study [53]. The GeparOcto study showed that an intense dose-dense regimen including high-dose cyclophosphamide was equally effective to the anthracycline/taxane-based regimen including conventionally dosed carboplatin and appeared to be more feasible [54].

Contrary to data obtained in the metastatic setting, the carboplatin effect was independent of *gBRCA* status. Patients with *gBRCA*m had in general a higher pCR rate compared to wild type ones, but the increase in pCR with the addition of carboplatin was more prominent in the wild type cohort [17, 18, 55–58]. One explanation of the different results could be the single versus combination therapy or the treatment setting.

Results of meta-analyses are consistent [59, 60]. Even though only a few small studies assessed the role of cisplatin [61], it seems to be as effective as carboplatin in increasing the pCR rate, but with a different safety profile [62, 63]. A head-to-head study of 4 cycles of weekly carboplatin (AUC 2) or cisplatin (25 mg/m²) and paclitaxel (80 mg/m²) showed similar pCR rates and outcomes for the 2 compounds. No significant differences were seen in terms of AE [64].

Many new trials have incorporated carboplatin as part of the standard regimen. Its use is recommended irrespectively of the *BRCA* status.

Checkpoint Inhibitors

Immunotherapy seems to be a very promising approach. In the GeparNuevo trial, the addition of durvalumab to anthracycline/taxane-based chemotherapy showed an increased pCR rate only in patients receiving durvalumab alone within the window phase. A priming effect of durvalumab has been hypothesized. In both arms, a significantly increased pCR was observed with higher stromal TIL, with a trend in PD-L1-positive tumors [65]. Encouraging results were also seen with pembrolizumab, which increased pCR rates in patients with early TNBC [66, 67]. The Keynote-522 trial showed a higher pCR rate especially for patients with stage III or node-positive disease, regardless of PD-L1 expression

[68] and an improved outcome [69]. Atezolizumab did not increase the pCR rate when added to carboplatin and nab-paclitaxel, with long term results pending [70]. None of these checkpoint inhibitors have been approved for use in the early breast cancer setting so far.

PARP Inhibitors

Two randomized phase III trials, i.e., OlympiAD [71] and EMBRACA [72], have shown efficacy of PARP inhibitors compared to treatment of the physician's choice in the metastatic setting, leading to investigations in the early setting. In the the BrightNess study, the use of veliparib seemed not to add benefit in terms of pCR when carboplatin was administered together with paclitaxel, with only minimally increased toxicities [51, 52]. Evidence from the metastatic setting where the addition of veliparib at 120 mg per os b.i.d. to paclitaxel and carboplatin was investigated in the BROCADE 3 study, showing increased progression-free survival compared to chemotherapy alone without altering the toxicity profile, might suggest exploration of higher veliparib doses in the early setting. Talazoparib has also shown activity when administered as neoadjuvant monotherapy [73]. The phase III study is ongoing (NCT03499353). Finally, in the neoadjuvant GeparOLA study, olaparib added to paclitaxel in HER2-negative early breast cancer with homologous recombination deficiency was well tolerated. pCR results are promising but need further confirmation [74]. Results of several ongoing trials (OlympiA NCT02032823, PARTNER NCT03150576, and Rucaparib NCT03542175) are pending.

AKT Inhibitors

In the metastatic setting both ipatasertib and capivasertib have shown promising activity especially in patients with PIK3CA/AKT1/PTEN altered tumors [75,

76]. In the adaptive phase II I-SPY2 trial, the AKT inhibitor MK-2206 plus standard NACT attained an estimated pCR rate of 40% compared to 22% with chemotherapy alone [77]. In the neoadjuvant FAIRLANE trial, the addition of ipatasertib to paclitaxel did not significantly increase the pCR rate. The overall response rate by MRI was numerically higher with ipatasertib. Notably, all patients with a complete response had PIK3CA/AKT1/PTEN altered tumors [78]. Further studies are warranted.

Conclusion

Anthracycline/taxane-based chemotherapy remains the preferred standard option for patients with early TNBC, but many promising agents are on the horizon. The use of carboplatin is recommended irrespectively of *BRCA* status. The role of PARP and AKT inhibitors in the early setting is still under investigation. The inclusion of checkpoint inhibitors in neoadjuvant therapy for high-risk patients is imminent. In patients with residual disease after NACT, adjuvant capecitabine is an option. *BRCA* status and immune marker assessment should be considered given their predictive and prognostic role.

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The authors declare no conflict of interests.

Author Contributions

J.F. and S.L. contributed equally to this paper.

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