The Oncologist, 2022, **27**, 30–39
https://doi.org/10.1093/oncolo/oyab003
Advance access publication 28 January 2022
Review Article

Early-stage Triple-negative Breast Cancer: Time to Optimize Personalized Strategies

Nour Abuhadra[1,*], Shane Stecklein[2], Priyanka Sharma[3], Stacy Moulder[4]

[1]Breast Medicine Service, Division of Solid Tumor Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[2]Department of Radiation Oncology, University of Kansas Medical Center, Kansas City, KS, USA
[3]Division of Medical Oncology, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, USA
[4]Eli Lilly and Company. Lilly Corporate Center, Indianapolis, IN, USA

*Corresponding author: Nour Abuhadra, MD, Breast Medicine Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Email: abuhadn@mskcc.org

Abstract

Triple-negative breast cancer (TNBC) accounts for approximately 15%-20% of breast cancers diagnosed worldwide, which amounts to almost 200 000 cases each year. Although historically TNBC is considered difficult to treat with a poor prognosis, there is emerging evidence showing excellent response rates in a subset of TNBC patients. Attempts to de-escalate chemotherapy in hormone-receptor-positive (HR+) and HER2-neu amplified breast cancer subtypes have been successful. At present, robust strategies to personalize therapy in early-stage TNBC do not exist, and despite excellent response rates in a subset of patients, all patients are exposed to the same several cycles of cytotoxic chemotherapy. Personalizing therapy in TNBC represents a challenge due to the scarcity of treatment options outside of cytotoxic chemotherapy and limited predictive and prognostic biomarkers to tailor treatment. Recent developments in understanding TNBC biology have sparked interest in exploring treatment optimization and personalization with the goal of achieving excellent response rates and long-term clinical outcomes, while simultaneously reducing physical, psychological, and financial toxicities for select patients. Here, we provide an update on the current evidence to support future studies examining de-escalating chemotherapy in patients with low-risk TNBC and adjuvant intensification strategies to improve outcomes for patients who are at high risk for systemic failure despite current standard-of-care treatments.

Key words: early stage; triple-negative breast cancer; de-escalation; personalization; biomarkers; immunotherapy; quality of life.

Implications for Practice

De-escalation efforts have been successful in hormone-receptor-positive and HER2-positive breast cancer. There is a growing interest in exploring the de-escalation of chemotherapy in triple-negative breast cancer. While there are limitations to achieving this due to the lack of biomarkers and limited treatment options, there have been some recent successes that could guide de-escalation in this patient population. Here, we provide an updated summary on the current status of personalized therapy in triple-negative breast cancer and comment on future directions.

Introduction

Triple-negative breast cancer (TNBC), which is defined by the lack of expression of estrogen receptor (ER) and progesterone receptor (PR) and absence of HER2 overexpression and/or gene amplification accounts for 15%-20% of all breast cancers diagnosed worldwide each year.[1] TNBC is associated with poor long-term outcomes compared with other breast cancers.[2] Treatment personalization guided by clinical and genomic tumor characteristics has become standard of care in patients with early-stage hormone-receptor positive (HR+) and HER2-neu amplified (HER2+) breast cancer, thus successfully de-escalating and escalating therapy in appropriate patients.[3-6]

Unlike HR+ and HER2+ breast cancer, TNBC is complicated by the (1) scarcity of treatment options outside of cytotoxic chemotherapy more recently immunotherapy in a subset of patients, and (2) limited predictive and prognostic biomarkers to tailor treatment. Although historically TNBC is considered difficult to treat with a poor prognosis, a substantial number of patients (~30%-50%) achieve pathologic complete response (pCR) with neoadjuvant chemotherapy (NACT).[7,8] Pathologic complete response is an excellent surrogate for disease-free survival (DFS) and overall survival (OS) in TNBC and can serve as a useful surrogate for treatment optimization.[7-9] Although not used in daily clinical practice, there is evidence to support the predictive and prognostic role of immune-related markers in TNBC including tumor immune infiltration as well as immune-related molecular signatures correlated with response.[10-15] While these markers have been informative, they are lacking in discriminatory ability to choose specific regimens in an unselected patient population. Despite these limitations, the recent progress

Received: March 25, 2021. Editorial Acceptance: September 7, 2021.

in understanding TNBC biology has sparked interest in exploring treatment optimization and personalization with the goal of achieving excellent long-term clinical outcomes, while reducing physical, psychological and financial toxicities for select patients. Here, we provide an update on the current evidence to support future studies examining de-escalating chemotherapy in patients with low-risk TNBC and adjuvant intensification strategies to improve outcomes for patients who are at high risk for systemic failure despite current standard-of-care treatments.

Pathologic Complete Response: Standard NACT and De-escalation Strategies

Chemotherapy for early-stage TNBC is increasingly being applied in the neoadjuvant setting due to the ability to monitor for disease response, the prognostic value of pCR and alternative treatment strategies for patients with residual disease.[16,17] Meta-analyses of prospective trials have demonstrated that attaining pCR with NACT in TNBC is associated with excellent prognosis with 92% 5-year event-free survival (EFS) and 87% 10-year EFS.[18] There is also evidence to support that the excellent prognosis associated with pCR is independent of the regimen used that led to a pCR.[19,20] Others have demonstrated similar outcomes with or without adjuvant chemotherapy in patients who attain pCR.[21] Taken together, these data suggest that personalized treatment in TNBC based on neoadjuvant response could be an effective strategy to decrease toxicity and healthcare costs at no detriment to long-term patient outcomes.

Combination therapy with an anthracycline and cyclophosphamide followed by a taxane (AC-T) is considered standard of care for patients with stage I-III TNBC and 30%-40% of patients will achieve pCR with this regimen. Though anthracyclines are a pillar of breast cancer chemotherapy, these agents are associated with considerable long-term toxicities including the risk of secondary leukemia and cardiotoxicity.[22,23] The toxicity associated with anthracyclines has supported the initiative to explore anthracycline-sparing regimens, particularly in TNBC where patients typically present at a younger age.

Similar to anthracyclines, platinum agents damage DNA and have shown synergistic activity when given in combination with taxanes in both preclinical models and increased pCR when combined with anthracyclines/taxanes in TNBC clinical trials.[24-26] The efficacy of anthracycline-free neoadjuvant carboplatin/taxane chemotherapy regimens (CbT) in TNBC has been evaluated in 3 contemporary studies with reported pCR rates of 46%-55% with 12-18 weeks of CbT in unselected TNBC patients.[19,20,25] A recent randomized study of 100 patients also demonstrates that 18 weeks of CbT yields pCR rates similar to CbT followed by AC but with a more favorable toxicity profile.[26] Long-term follow-up of WGS-ADAPT and a neoadjuvant trial by Sharma et al show that patients who attain a pCR with carboplatin/taxane regimens have an excellent 3-year recurrence-free survival (>90%) and overall survival (>94%) without adjuvant anthracycline, suggesting that pCR accurately identifies patients at low risk of recurrence who can avoid anthracyclines and their associated toxicities.[19,20]

Furthermore, a recent study that assessed patient-reported toxicities during various chemotherapy regimens for breast cancer patients noted that longer chemotherapy regimens, such as anthracycline-based regimens followed by paclitaxel, had a higher incidence of patient-reported major toxicities.[27] Carboplatin/taxane regimens are well tolerated with favorable safety profile as 90% of patients can complete prescribed NACT and a very small proportion of patients demonstrated disease progression during NACT (<5%).[20] Taken together, these data suggest that there may be a role for carboplatin-taxane NACT as a potential treatment de-escalation strategy in TNBC. However, there is insufficient evidence to support replacing anthracyclines with platinum-based therapy; anthracyclines have robust clinical data demonstrating long-term efficacy in patients with TNBC[28,29] while the data on long-term outcomes with platinum-based therapy remain premature at this time.[30-33] Ultimately, early de-escalation strategies will need to be guided by pCR to allow for salvage adjuvant treatment when necessary. Therefore, the NACT regimen chosen must have established pCR rates as well as long-term outcomes data.

Emerging Role for Immunotherapy

Several phase III trials have evaluated the role of immune checkpoint blockade when given concurrently with standard NACT in TNBC. The I-SPY 2 trial first demonstrated that the addition of pembrolizumab to NACT substantially improved pCR rates from 22% to 60%.[34] However, the GeparNuevo trial failed to demonstrate an improvement in pCR with the addition of durvalumab to standard NACT, although an underpowered subgroup analysis suggested an improvement in pCR in patients who started durvalumab 2 weeks before NACT.[35] The recent results from KEYNOTE-522 demonstrate that the addition of pembrolizumab to carboplatin/paclitaxel and AC/EC chemotherapy significantly improved pCR from 51.2% to 64.8% representing an absolute difference of 13.6% ($P < .001$) in patients with Stage II or III TNBC.[36] Following surgery, all patients in this trial were treated with maintenance pembrolizumab or placebo for up to 1 year. The greatest magnitude of benefit for the addition of pembrolizumab was seen in patients with Stage III disease (absolute increase in pCR of 25%) with lower absolute benefit in those with Stage IIA (pCR of 73.1% vs 62.1%, for an absolute difference of 11.0%) or IIB disease (pCR 56.2% vs 48.4%, for an absolute difference of 7.8%). Similarly, patients with lymph node–positive disease were observed to have a greater pCR benefit with pembrolizumab versus placebo, with an absolute pCR difference of 20.6% (64.8% and 44.1%). In comparison, those with the node-negative disease did not receive the same magnitude of benefit with the addition of pembrolizumab, with an absolute pCR difference of 6.3% (64.9% vs 58.6%). More than 80% of KEYNOTE-522 patients were considered to have PD-L1-positive disease (based on a combined positive score ≥1 by PD-L1 IHC 22C3 pharmDx assay); however, the benefit of pembrolizumab was noted regardless of PD-L1 expression. Patients with PD-L1-positive status achieved a high pCR rate in both arms (pCR 55% in chemotherapy arm and 68% in pembrolizumab arm), and a numerically higher delta for pCR improvement was noted in those with PD-L1-negative disease compared with those with PD-L1 positive disease (delta of 18% compared with 14%).[36]

Conversely, the addition of atezolizumab to chemotherapy (carboplatin and nab-paclitaxel) failed to significantly improve pCR rates compared with chemotherapy alone in the NeoTRIP trial. The pCR rates were not significantly different between the 2 study arms: 43.5% with atezolizumab versus

40.8% with chemotherapy alone. A multivariate analysis showed that the only variable associated with pCR rate was PD-L1–positive status according to immunohistochemistry ($P < .0001$).[37] The results available from this study are still preliminary, but there are subtle differences between the KEYNOTE-522 and NeoTRIP studies; the type of checkpoint inhibitor as well as the chemotherapy backbone differ, and the assays used to evaluate PD-L1 expression were also different. An important consideration is that while both studies evaluated pCR as an important early endpoint, this may not be the endpoint of interest with regards to immunomodulation in the early-stage setting for TNBC. Similarly, PD-L1 expression may not be as relevant a predictive marker of response in early-stage disease as it is in metastatic disease.[38] Interestingly, the recent Impassion031 trial demonstrated that the addition of atezolizumab to a standard anthracycline/taxane-based chemotherapy did significantly improve pCR rates (58% vs 41%) regardless of PD-L1 status, although the pCR difference was slightly greater in the PD-L1 positive (defined as PD-L1-expressing tumor-infiltrating immune cells ≥1% subgroup) with an acceptable safety profile.[39] The key difference between the NeoTRIP and IMpassion031 is the inclusion of anthracycline in the chemotherapy backbone, the positive results in Impassion031 supports data from the metastatic setting,[40] suggesting that anthracycline induction leads to an upregulation of immune-related genes, thereby priming the tumor microenvironment for a more favorable response to immunotherapy. This highlights the significance of the chemotherapy backbone selected when combining chemotherapy and immunotherapy.

These data highlight that we still lack biomarkers to select patients for the addition of immunotherapy—this is imperative as these regimens have substantially increased toxicity (eg, KEYNOTE-522: ~78% incidence of grade 3 or higher adverse events). Furthermore, long-term outcomes in patients treated with immunotherapy have yet to mature. Ultimately, the role of immunotherapy in the neoadjuvant setting continues to evolve, but represents an important potential tool toward the goal of individualizing treatment.

Predictive Biomarkers of Response to NACT in TNBC

Tumor-infiltrating Lymphocytes

In TNBC, the tumor immune microenvironment plays an important role in prognosis and response to NACT.[41] Stromal and intratumoral lymphocytes (sTIL and iTIL) are reproducible biomarkers and multiple studies have confirmed their prognostic value in TNBC.[11,42] The association between increasing TIL in pretreatment tumor tissue and higher pCR rates has been observed with different NACT regimens across several trials and appears to be independent of the type or duration of NACT (Table 1).[10,11,20] Seminal trials where TIL has predicted higher pCR rates (with anthracycline-based chemotherapy) include GeparDuo and GeparTrio, where pCR rates in patients with HR- lymphocyte predominate breast cancer (LPBC) were 43% and 52%, respectively (of note, this includes patients with HER2+ disease who did not receive anti-HER2 therapy).[51] In the GeparSixto trial, which compared platinum to non-platinum NACT, 28% of patients in the TNBC subgroup had lymphocyte predominate-TNBC (LP-TNBC) and these patients experienced very high pCR rates of 74% when treated with the anthracycline/platinum/taxane regimen.[24] Interestingly, the absolute pCR rate in LP-TNBC was much higher with the platinum regimen compared with non-platinum regimen (74% vs 43%). These data suggest

Table 1. Major studies demonstrating association between TIL and pCR.

Author, publication year	Country	Number of TNBC pts	TIL location	Definition of high TIL	NACT regimen	pCR rate (overall)	pCR (high TIL)
Ono et al 2012[43]	Japan	92	sTIL	TIL score high if sum was 3-5	Anthracycline-based	32%	37%
Miyashita et al 2014[44]	Japan	110	sTIL and iTIL	Median TIL used as cutoff	Anthracycline-based	29%	41%
Denkert et al 2015[11]	Germany	314	sTIL	TIL involving 60% of either tumor stroma or cell nests	GeparSixto (PM/PMCb)	40%	60%
Hida et al 2016 [45]	Japan	48	sTIL and iTIL	Cutoff >50%	Anthracycline and taxane	43%	63%
Herrero-Vicent et al 2017[46]	Spain	164	sTIL	LPBC >40%	Anthracycline and taxane	37%	87%
Cerbelli et al 2017[47]	Italy	54	sTIL	Continuous, also LPBC >50%	AC > T	35%	50%
O'Loughlin et al 2018[48]	Ireland	75	sTIL	Increments of 10%, LPBC >50% stromal TIL	Anthracycline/taxane Anthracycline/taxane/carboplatin	46%	89%
Denkert et al 2018[49]	Germany	906	sTIL	LPBC >60%	GeparDuo, GeparTrio, GeparQuattro, GeparSixto, GeparSepto	36%	50%
Asano et al 2018 [50]	Japan	61	sTIL	Cutoff >10%	FEC	46%	54%

Abbreviations: AC, anthracycline/cyclophosphamide; AD, anthracycline/docetaxel; ACT, AC followed by taxane; FEC, fluorouracil/epirubicin/cyclophosphamide; iTIL, intratumoral TIL; LPBC, lymphocyte-predominant breast cancer; NR, not reported ; NACT, neoadjuvant chemotherapy; pCR, pathologic complete response; PM, paclitaxel/nonpegylated liposomal doxorubicin; PMCb, paclitaxel/nonpegylated doxorubicin/carboplatin; sTIL, stromal TIL; TNBC, triple-negative breast cancer; TIL, tumor-infiltrating lymphocytes.

that neoadjuvant carboplatin may be especially beneficial in TIL-enriched TNBC. Similarly, the BrighTNess trial showed that tumors with higher inferred CD8+ T-cell infiltration derived greater benefit from carboplatin.[52]

A pooled analysis of 9 adjuvant clinical trials (including 2148 TNBC patients) confirmed the prognostic role of sTIL in early-stage TNBC patients where for each 10% increment in sTIL there was 17% improvement in DFS and 16% improvement in OS. This pooled analysis also demonstrated excellent survival outcomes for TNBC patients with ≥ 30% sTIL with 3-year distant disease-free survival (DDFS) of 97% and OS of 99%.[42] Recent retrospective work has also shown good survival outcomes in patients with early-stage high sTIL TNBC even in the absence of adjuvant chemotherapy. Park et al conducted a retrospective analysis of systemically untreated Stage I TNBC patients with 98% 5-year overall survival in patients with high sTIL (using a cutoff of >30%).[53] Another retrospective study on systemically untreated TNBC patients demonstrated an improvement in invasive disease-free survival at 5 years in patients with high sTIL (using a cutoff of 50%) compared with low sTIL.[54] Of note, in both studies, the median age was higher than expected for an average TNBC population which highlights an inherent selection bias of the retrospective nature where older patients may have been less likely to have been recommended (or accepted) cytotoxic chemotherapy. These data are still intriguing as it suggests a subset of early-stage TNBC patients may have excellent outcomes even without chemotherapy, though further prospective research would be needed to confidently identify these patients. Furthermore, a recent prospective study demonstrated that in early-stage TNBC, there was a significant difference in EFS between high sTIL/pCR and high sTIL/with residual disease (RD), highlighting that while high sTIL is an important biomarker, it may not be sufficient independently and emphasizes the need for an integrated approach when incorporating sTIL into personalized treatment strategies.[55]

With the growing interest in using TIL to select patients for de-escalation, these data highlight that TIL will need to be judiciously integrated into any selection strategy for de-escalation efforts to be successful. This also underscores that the first steps of any de-escalation strategy will need to be less toxic chemotherapy and/or for a shorter duration. Many are interested in foregoing chemotherapy; however, more data are needed to safely select candidates for this approach. While there are many clinical and investigative benefits to NACT as compared with adjuvant therapy, ultimately it is well established that there is no difference in long-term recurrence or mortality outcomes between neoadjuvant and adjuvant chemotherapy. Therefore, in the event of suboptimal pCR rates on de-escalation trials, adjuvant chemotherapy (with chemotherapy that was omitted in the neoadjuvant setting) represents a potential opportunity for salvage.

BRCA and Homologous Recombination Deficiency

The prevalence of BRCA mutations (including both germline mutations and somatic genetic aberrations) is reported in up to 20%-30% of unselected TNBC patients.[56] Poly(ADP-ribose) polymerase (PARP) inhibitors exploit this deficiency through synthetic lethality and have emerged as a therapeutic strategy in these patients.[57] These agents have demonstrated efficacy in patients with *BRCA*-mutant metastatic breast cancer, prompting investigators to evaluate their role in the neoadjuvant setting. In unselected TNBC patients, the addition of veliparib to platinum-based chemotherapy failed to increase the pCR rate.[52] In another study, the addition of olaparib to paclitaxel was not superior to carboplatin/paclitaxel in patients with HER2-negative breast cancer with a *BRCA1/2* mutation.[58] However, early phase II data using single-agent neoadjuvant talazoparib demonstrated an excellent pCR rate of 53% in patients with germline *BRCA* pathogenic variants.[59] A single-arm pilot study with neoadjuvant Niraparib also demonstrated antitumor activity in patients with localized HER2-negative breast cancer with a BRCA1/2 mutation. The tumor response rate was 90.5% (including 2 complete responses and 17 partial responses, n = 21) as assessed by MRI but pCR rates have not yet been reported.[60] Survival outcomes from these studies are pending validation of these findings in larger cohorts and may represent an opportunity to de-escalate neoadjuvant treatment to a chemotherapy-free targeted regimen in carefully selected patients.

Furthermore, approximately 50%-60% of TNBCs will exhibit homologous recombination deficiency (HRD) due to genetic or epigenetic inactivation of one or more HR pathway genes.[61] The presence of HRD is associated with vulnerability to DNA damaging agents like anthracyclines and platinum chemotherapy agents.[62] PARP inhibitors are also known to induce synthetic lethality in cells that harbor HRD. In the BrighTNess trial, higher rates of pCR were observed in HRD+ patients across all treatment arms. Interestingly, patients treated with platinum-based therapy had higher rates of pCR in both HRD+ and HRD- subsets.[63] Thus, HRD status may also play a role in personalizing therapy in TNBC pending validation in larger studies.

Immune-Related Molecular Signatures

Expression-based signatures and genomic predictors are increasingly incorporated into clinical practice to predict benefits from chemotherapy.[64,65] Lehman et al identified molecular subtypes of TNBC and Masuda et al went on to demonstrate that chemotherapy responsiveness varied between the 7 subtypes with the highest pCR rate note in the basal-like 1 (BL1) subtype. Conversely, basal-like 2 (BL2) and luminal androgen receptor (LAR) had the lowest pCR rates (0% and 10%, respectively).[64,66] There are ongoing trials evaluating anti-androgen therapy as a treatment strategy in early-stage LAR subtype of TNBC with data in the metastatic setting demonstrating clinical activity in this subgroup of patients.[67] Others have shown that multiple distinct immune signatures are associated with response to NACT in TNBC as well as a diverse set of proliferation-associated and proliferation independent signatures.[65] While informative, these findings have not yet been integrated into routine clinical practice but there is ongoing interest in integrating these findings into personalization strategies.

Residual Disease: Adjuvant Treatment Intensification

The risk of disease recurrence after anthracycline/taxane chemotherapy ranges from approximately 10% in patients with stage I disease and up to 25%-50% in patients with stage III disease.[68] These high rates of disease recurrence after standard chemotherapy have driven several trials aimed at investigating adjuvant treatment intensification. Given that capecitabine is known to have activity in metastatic TNBC,

several trials have investigated adjuvant treatment intensification with this agent.

The phase III CBCSG010 trial randomized patients with early-stage TNBC treated with upfront surgery to 3 cycles of capecitabine/docetaxel followed by 3 cycles of capecitabine/epirubicin/cyclophosphamide (XT-XEC) or control treatment with 3 cycles of docetaxel followed by 3 cycles of 5-fluorouracil/epirubicin/cyclophosphamide (T-FEC). The primary endpoint was DFS. At a median follow-up of 67 months, patients randomized to the XT-XEC arm had a superior DFS (86.3% vs 80.4% for T-FEC, $P = .044$), though there was no significant difference in OS (93.3% for XT-XEC vs 90.7% for T-FEC, $P = .19$).[69] SYSUCC-001 was another trial of adjuvant capecitabine in early-stage TNBC patients who had received anthracycline/taxane chemotherapy predominately in the adjuvant setting (93% of patients). Randomization was between metronomic capecitabine (650 mg/m^2 BID) for 1 year or observation. This study showed significant improvements in 5-year DFS (82.8% for capecitabine vs 73.0% for observation, $P = .03$) and 5-year DDFS (85.8% for capecitabine vs 75.8% for observation, $P = .02$), though there was no significant improvement in overall survival (85.5% for capecitabine vs 81.3% for observation, $P = .22$).[70] The CIBOMA/GEICAM trial randomized patients with early-stage TNBC who had been treated with a standard anthracycline and taxane chemotherapy, mostly in the adjuvant setting, to receive no further adjuvant therapy or oral capecitabine for 8 cycles. In the entire study group, capecitabine failed to show any significant improvement in DFS or OS. However, initial randomization was stratified by the presence or absence of a basal-like subtype (defined by cytokeratin 5/6 and/or EGFR expression by immunohistochemistry) and in a preplanned analysis, capecitabine was found to be associated with improved 5-year DFS (82.6% for capecitabine vs 72.9% for observation, $P = .02$) and OS (89.5% for capecitabine vs 79.6% for observation, $P = .007$) in patients with non-basal TNBC.[71] Furthermore, the ECOG-ACRIN EA1131 assessed adjuvant platinum compared with adjuvant capecitabine in basal subtype TNBC with residual disease after standard NACT. In this trial, platinum agents did not improve the 3-year iDFS in patients with basal subtype TNBC compared with capecitabine (42% vs 49%); additionally, grade 3-4 toxicities were more common in the platinum-arm.[72] These studies generally show that adjuvant capecitabine has activity in TNBC when used as an adjunct after standard anthracycline/taxane chemotherapy, but that there is no benefit in biologically unselected patients. Though the CIBOMA/GEICAM did achieve a significant OS benefit in non-basal-like TNBC, current clinical practice does not discriminate between basal and non-basal TNBC, so the results of this trial are difficult to apply in practice.

The association of pCR with favorable long-term survival outcomes in TNBC has been observed in numerous clinical trials. A recent meta-analysis of 25 neoadjuvant trials in TNBC showed that patients who achieve a pCR have substantially better 5-year event-free survival (EFS; 85% for pCR vs 50% for non-PCR) and OS (92% for pCR vs 58% for non-pCR).[73] These data allow us to cautiously reassure patients who have complete responses that outcomes are generally excellent, but also identify patients who are likely to benefit from treatment intensification in the adjuvant setting. The CREATE-X trial randomized patients with localized HER2-negative breast cancer who failed to achieve a pathologic complete response to neoadjuvant anthracycline and/or taxane-containing chemotherapy to observation or adjuvant capecitabine. No significant difference was observed in patients with hormone receptor-positive disease, but TNBC patients randomized to the capecitabine arm had improved 5-year DFS (69.8% for capecitabine vs 56.1% for observation) and OS (78.8% vs 70.3%).[43] A meta-analysis of 12 randomized trials (including CREATE-X) of 15 457 TNBC patients, shows that capecitabine in addition to standard systemic therapy is associated with an 18% improvement in DFS and a 22% improvement in OS.[44] Based on these data, current guidelines suggest that TNBC patients who receive neoadjuvant anthracycline/taxane-based chemotherapy and have residual breast or nodal disease should be offered adjuvant capecitabine.

Current approaches to intensifying treatment for higher-risk patients are based on detecting viable residual breast or nodal disease at the time of definitive surgery. While these patients collectively are at higher risk of disease recurrence compared with patients who achieve a pathologic complete response, the residual disease is an imperfect predictor of systemic failure. Recent work has shown that TNBC patients who exhibit plasma circulating tumor DNA (ctDNA) and/or circulating tumor cells (CTCs) after definitive treatment are significantly more likely to develop recurrent disease and die of TNBC compared with patients with undetectable ctDNA. In a preplanned secondary analysis of the BRE12-158 trial, Radovich et al examined blood samples taken from 196 TNBC patients who had residual disease after neoadjuvant chemotherapy. ctDNA and CTCs were observed in 63.4% and 40.7% of patients, respectively. The presence of ctDNA was associated with inferior DDFS (hazard ratio [HR] = 2.99, 95% confidence interval [CI] = 1.38-6.48, $P = .006$), DFS (HR = 2.67, 95% CI = 1.28-5.57, $P = .009$), and OS (HR = 4.16, 95% CI = 1.66-10.42, $P = .002$). OS at 24 months was 80% for ctDNA- patients versus 57% for ctDNA+ patients. CTCs alone were not predictive for DDFS, DFS, or OS, but when used in combination with ctDNA showed an improvement in sensitivity to detect recurrences (79% with ctDNA alone vs 90% with ctDNA and CTCs) and improved stratification of outcomes, particularly between the ctDNA-/CTC- versus ctDNA+/CTC+ cohorts.[45] This suggests that ctDNA and CTCs may be reliable markers of systemic minimal residual disease and that this paradigm could be used to optimize adjuvant treatment intensification strategies by focusing on patients who are particularly high-risk of systemic failure. This finding has important implications for stratifying future post-neoadjuvant therapy trials in TNBC. Ongoing clinical trials utilizing residual disease to intensify treatment or attainment of pCR to de-escalate the intensity of therapy are summarized in Table 2.

Morbidity, Financial, and Social Burdens of Therapy

Chemotherapy is often feared by patients due to the side effects associated with treatment; however, the costs for administering therapy have also become a major burden for both the United States healthcare system as well as the patients it serves.[46] Financial toxicity is not frequently disclosed, and can be materially and psychologically debilitating for patients.[47] Financial hardships induced by the cost of cancer care worsen patient psychological stress and financial insolvency has been identified as a risk factor for early mortality in cancer patients.[48,49]

The cost of chemotherapy extends beyond the financial implications, and while chemotherapy is administered with the goal of prolonging DFS, the quality of that survivorship is

Table 2. Ongoing clinical trials exploring escalation and de-escalation in TNBC.

Trial number	Phase	Description	Primary outcome measure	Status
Studies evaluating escalation in the setting of residual disease				
NCT04595565	III	SASCIA: Postneoadjuvant Study Evaluating Sacituzumab Govitecan, an Antibody Drug Conjugate in Primary HER2-negative Breast Cancer Patients With High Relapse Risk After Standard Neoadjuvant Treatment	iDFS	Recruiting
NCT02954874	III	S1419: A Randomized, Phase III Trial to Evaluate the Efficacy and Safety of MK-3475 (Pembrolizumab) as Adjuvant Therapy for Triple Receptor-Negative Breast Cancer With >/= 1cm Residual Invasive Cancer or Positive Lymph Nodes (ypN1mi, ypN1-3) After Neoadjuvant Chemotherapy	iDFS	Recruiting
NCT02926196	III	A-BRAVE-Trial :Adjuvant Treatment for High-risk Triple Negative Breast Cancer Patients With the Anti-PD-l1 Antibody Avelumab:	DFS	Active, not recruiting
NCT02445391	III	EA1131: A Randomized Phase III Post-operative Trial of Platinum Based Chemotherapy vs. Capecitabine in Patients With Residual Triple-Negative Basal-Like Breast Cancer Following Neoadjuvant Chemotherapy	iDFS	Recruiting
NCT03818685	II	BreastImmune03: A Multicenter, Randomised, Open-label Phase II Study to Evaluate the Clinical Benefit of a Post-operative Treatment Associating Radiotherapy + Nivolumab + Ipilimumab Versus Radiotherapy + Capecitabine for Triple Negative Breast Cancer Patients With Residual Disease After Neoadjuvant Chemotherapy	DFS	Recruiting
NCT03487666	II	OXEL: A Pilot Study of Immune Checkpoint or Capecitabine or Combination Therapy as Adjuvant Therapy for Triple Negative Breast Cancer With Residual Disease Following Neoadjuvant Chemotherapy	Immune activation measured by changes in peripheral immunoscore	Recruiting
NCT04437160	II	A Multicenter, Randomised, Open-label Phase II Study to Evaluate the Efficacy and Safety of Adjuvant Chemotherapy for Triple Negative Breast Cancer Patients With Residual Disease After Platinum-based Neoadjuvant Chemotherapy	RFS	Recruiting
NCT03756298	II	ATOX-2018: Randomized, Phase II Trial to Evaluate the Efficacy and Safety of Atezolizumab Plus Capecitabine Adjuvant Therapy Compared with Capecitabine Monotherapy for TNBC With Residual Invasive Cancer After Neoadjuvant Chemotherapy.	5-year iDFS	Recruiting
NCT03542175	I	A Phase I Study of Rucaparib Administered Concurrently With Postoperative Radiotherapy in Patients With Triple Negative Breast Cancer With an Incomplete Pathologic Response Following Neoadjuvant Chemotherapy	MTD	Recruiting
Studies evaluating de-escalation with alternative regimens in the setting of pathologic complete response				
NCT03150576	II/III	Randomised, Phase II/III, 3 Stage Trial to Evaluate the Safety and Efficacy of the Addition of Olaparib to Platinum-based Neoadjuvant Chemotherapy in Breast Cancer Patients With TNBC and/or gBRCA.	pCR	Recruiting
NCT01372579	II	Phase II Neoadjuvant Trial With Carboplatin and Eribulin Mesylate in Triple Negative Breast Cancer Patients	pCR	Active, not recruiting
NCT04664972	II	Comparing TP (Docetaxel + Cisplatin) and TAC (Docetaxel + Doxorubicin + Cyclophosphamide) in Neoadjuvant Therapy for Operable Triple Negative Breast Cancer	pCR	Recruiting
NCT04138719	II	Clinical Study of Nab-paclitaxel Plus Carboplatin Versus Nab-paclitaxel Plus Epirubicin in the Neoadjuvant Therapy for Triple Negative Breast Cancer	pCR	Recruiting
NCT04427293	I	BRE-03: Window of Opportunity Trial of Preoperative Lenvatinib Plus Pembrolizumab in Early-Stage Triple-Negative Breast Cancer	Effectiveness on infiltration of CD8+ tumor infiltrating lymphocytes. (Secondary outcome: pCR)	Recruiting

Abbreviations: iDFS, invasive disease-free survival; MTD, maximum tolerated dose; pCR, pathologic complete response; RFS, recurrence-free survival; TNBC, triple-negative breast cancer.

frequently impacted by persistent or late effects of therapy in breast cancer survivors. Younger women face the risk of premature menopause which is shown to be associated with poorer quality of life (QoL), decreased sexual functioning, infertility, psychosocial distress related to fertility concerns and uncertainty about the late effects of premature menopause. One case–control study of long-term breast cancer survivors found that breast cancer survivors had significantly decreased handgrip strength, elevated lipids as well as decreased psychological and social functioning.[50] A survey-based study suggested that a history of adjuvant systemic therapy was associated with poorer functioning on several QoL domains including physical functioning, bodily pain, social functioning, and general health.[74] Women who receive chemotherapy are also at risk for a post-traumatic stress syndrome and thus a lower QoL experience.[75] Interestingly, a cross-sectional study of 105 long-term breast cancer survivors has shown that patients diagnosed later in life (age >65 years) showed significantly worse QoL outcomes in the physical domain, while those who received diagnoses at a younger age (27-44 years) showed worse QoL outcomes in the psychosocial domain.[76]

Conclusions

Individualizing treatment represents a space in breast cancer research where optimal therapy and patient well-being intersect. The widespread uptake of personalized strategies in the HR+ and HER2+ populations suggests that there would be a similar uptake in TNBC. These efforts have been successful in HR+ and HER2+-positive breast cancer in part due to the availability of alternative treatment strategies including hormonal and targeted therapies. While personalizing neoadjuvant and adjuvant systemic therapy backbones and identifying patients who will benefit from treatment intensification has been slower in TNBC, there is a growing body of evidence now available to support potential approaches to individualizing chemotherapy. Accurate risk stratification is crucial to identify patients at low risk in whom de-escalated or alternate strategies might be appropriate. There has been a tremendous effort in identifying predictive biomarkers in TNBC (including TIL, molecular subtyping, germline mutations) and these biomarkers will need to be integrated into the design of future trials as selection or stratification criteria. Large randomized studies will be required to discern the benefits and safety of potential de-escalation strategies in TNBC, though the predictive power of pCR as the endpoint of interest and escalating treatment for patients with residual disease after experimental deintensification represents a safe, efficient, and feasible approach to answer questions of de-escalation. Multiple large, randomized prospective trials have identified anthracycline-sparing regimens with equal efficacy to anthracycline-containing regimens and there are neoadjuvant data on immunotherapy and targeted therapies that will shift the landscape and enrich the opportunities for chemotherapy-sparing regimens. As our understanding of TNBC evolves, it is exceedingly clear that the heterogenous nature of TNBC requires a personalized approach to improve patient outcomes while only administering therapy that is necessary. In conclusion, there are different strategies for personalization that will need to be explored that rely on a combination of clinical risk and biomarker-driven strategies. Patients with low clinical risk selected based on favorable biomarkers represent one approach, alternatively, the combination of 2 biomarkers with robust predictive and prognostic power could be applied to an unselected population. The second challenge in de-escalation will be selecting the optimal regimen. This review has summarized anthracycline-sparing options as well as the possibility of single-agent targeted therapy (eg, PARPi) and the evolving role of immunotherapy in this space. Utilizing biology-driven individualized therapy in TNBC will decrease toxicity and cost of care while improving the length and quality of patient survival. The combination of effective treatment strategies and a conscientious approach to patient QoL represents the cornerstone of optimal oncologic care. There is increasing awareness in the breast cancer community that we over treat many patients and the benefits of personalization are manifold.

Funding

None declared.

Conflict of Interest

Priyanka Sharma: Novartis, Puma Biotechnology, Merck, Seattle Genetics, Epic Sciences, Exact Sciences, AstraZeneca, Immunomedics (C/A), Cosmo Biosciences (RF [spouse]), Novartis, Celgene, Bristol-Myers Squibb, Merck (RF [institutional]); **Stacy Moulder:** Lilly Oncology (E). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Author Contributions

Conception/design: N.A. and S.M. **Collection and/or assembly of data:** N.A. and S.M. **Data analysis and interpretation:** N.A. **Manuscript writing:** All authors. **Final approval of manuscript:** All authors.

Data Availability

No new data were generated or analyzed in support of this research.

References

1. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406(6797):747-752. https://doi.org/10.1038/35021093
2. Carey LA, Cheang MCU, Perou CM. Chapter 29: Genomics, Prognosis, and Therapeutic Interventions. In: Harris JR, Lippman ME, Morrow M, Osborne CK. *Diseases of the Breast*, 5th edition. Lippincott Williams & Wilkins; 2014.
3. von Minckwitz G, Huang CS, Mano MS, et al.; KATHERINE Investigators. Trastuzumab Emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. 2019;380(7):617-628. https://doi.org/10.1056/NEJMoa1814017
4. Tolaney SM, Guo H, Pernas S, et al. Seven-year follow-up analysis of adjuvant Paclitaxel and Trastuzumab trial for node-negative, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. 2019;37(22):1868-1875. https://doi.org/10.1200/JCO.19.00066
5. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-Gene expression assay in breast cancer. *N Engl*

J Med. 2015;373(21):2005-2014. https://doi.org/10.1056/NEJMoa1510764
6. Cardoso F, van't Veer LJ, Bogaerts J, et al.; MINDACT Investigators. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375(8):717-729. https://doi.org/10.1056/NEJMoa1602253
7. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384(9938):164-172. https://doi.org/10.1016/S0140-6736(13)62422-8
8. Spring L, Greenup R, Niemierko A, et al. Pathologic complete response after Neoadjuvant chemotherapy and long-term outcomes among young women with breast cancer. *J Natl Compr Canc Netw*. 2017;15(10):1216-1223. https://doi.org/10.6004/jnccn.2017.0158
9. Prowell TM, Pazdur R. Pathological complete response and accelerated drug approval in early breast cancer. *N Engl J Med*. 2012;366(26):2438-2441. https://doi.org/10.1056/NEJMp1205737
10. Denkert C, Loibl S, Noske A, et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. *J Clin Oncol*. 2010;28(1):105-113. https://doi.org/10.1200/JCO.2009.23.7370
11. Denkert C, von Minckwitz G, Brase JC, et al. Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. *J Clin Oncol*. 2015;33(9):983-991. https://doi.org/10.1200/JCO.2014.58.1967
12. Loi S, Sirtaine N, Piette F, et al. Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. *J Clin Oncol*. 2013;31(7):860-867. https://doi.org/10.1200/JCO.2011.41.0902
13. Salgado R, Denkert C, Demaria S, et al.; International TILs Working Group 2014. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. *Ann Oncol*. 2015;26(2):259-271. https://doi.org/10.1093/annonc/mdu450
14. Dieci MV, Radosevic-Robin N, Fineberg S, et al.; International Immuno-Oncology Biomarker Working Group on Breast Cancer. Update on tumor-infiltrating lymphocytes (TILs) in breast cancer, including recommendations to assess TILs in residual disease after neoadjuvant therapy and in carcinoma in situ: a report of the International Immuno-Oncology Biomarker Working Group on Breast Cancer. *Semin Cancer Biol*. 2018;52(Pt 2):16-25. https://doi.org/10.1016/j.semcancer.2017.10.003
15. Adams S, Gray RJ, Demaria S, et al. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. *J Clin Oncol*. 2014;32(27):2959-2966. https://doi.org/10.1200/JCO.2013.55.0491
16. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol* 2018;19(1):27-39.
17. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol*. 2012;30(15):1796-1804. https://doi.org/10.1200/JCO.2011.38.8595
18. Yau C, van der Noordaa M, Wei J, et al. Abstract GS5-01: Residual cancer burden after neoadjuvant therapy and long-term survival outcomes in breast cancer: A multi-center pooled analysis. In: General Session Abstracts. *American Association for Cancer Research*. 2020:GS5-01-GS5-01.
19. Sharma P, López-Tarruella S, García-Saenz JA, et al. Pathological response and survival in triple-negative breast cancer following Neoadjuvant Carboplatin plus Docetaxel. *Clin Cancer Res*. 2018;24(23):5820-5829. https://doi.org/10.1158/1078-0432.CCR-18-0585
20. Gluz O, Nitz U, Liedtke C, et al. Comparison of neoadjuvant Nab-Paclitaxel+Carboplatin vs Nab-Paclitaxel+Gemcitabine in triple-negative breast cancer: randomized WSG-ADAPT-TN trial results. *J Natl Cancer Inst*. 2018;110(6):628-637. https://doi.org/10.1093/jnci/djx258
21. Spring LM, Fell G, Arfe A, et al. Pathologic complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: a comprehensive meta-analysis. *Clin Cancer Res*. 2020;26(12):2838-2848. https://doi.org/10.1158/1078-0432.CCR-19-3492
22. Muss HB, Berry DA, Cirrincione C, et al.; Cancer and Leukemia Group B Experience. Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B Experience. *J Clin Oncol*. 2007;25(24):3699-3704. https://doi.org/10.1200/JCO.2007.10.9710
23. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med*. 1979;91(5):710-717. https://doi.org/10.7326/0003-4819-91-5-710
24. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol*. 2014;15(7):747-756. https://doi.org/10.1016/S1470-2045(14)70160-3
25. Sharma P, López-Tarruella S, García-Saenz JA, et al. Efficacy of Neoadjuvant Carboplatin plus Docetaxel in triple-negative breast cancer: combined analysis of two cohorts. *Clin Cancer Res*. 2017;23(3):649-657. https://doi.org/10.1158/1078-0432.CCR-16-0162
26. Sharma P, Kimler BF, O'Dea A, et al. Randomized phase II trial of anthracycline-free and anthracycline-containing neoadjuvant carboplatin chemotherapy regimens in stage I-III triple-negative breast cancer (NeoSTOP). *Clin Cancer Res*. 2021;27(4):975-982. https://doi.org/10.1158/1078-0432.CCR-20-3646
27. Nyrop KA, Deal AM, Reeder-Hayes KE, et al. Patient-reported and clinician-reported chemotherapy-induced peripheral neuropathy in patients with early breast cancer: Current clinical practice. *Cancer*. 2019;125(17):2945-2954. https://doi.org/10.1002/cncr.32175
28. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet* 2012;379(9814):432-44.
29. Blum JL, Flynn PJ, Yothers G, et al. Anthracyclines in early breast cancer: the ABC Trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). *J Clin Oncol*. 2017;35(23):2647-2655. https://doi.org/10.1200/JCO.2016.71.4147
30. Valsecchi ME, Kimmey G, Bir A, Silbermins D. Role of Carboplatin in the treatment of triple negative early- stage breast cancer. *Rev Recent Clin Trials*. 2015;10(2):101-110. https://doi.org/10.2174/1574887110666150624101343
31. Loibl S, Weber KE, Timms KM, et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. *Ann Oncol*. 2018;29(12):2341-2347. https://doi.org/10.1093/annonc/mdy460
32. Poggio F, Bruzzone M, Ceppi M, et al. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis. *Ann Oncol*. 2018;29(7):1497-1508. https://doi.org/10.1093/annonc/mdy127
33. Sikov WM, Polley M-Y, Twohy E, et al. CALGB (Alliance) 40603: Long-term outcomes (LTOs) after neoadjuvant chemotherapy (NACT) +/- carboplatin (Cb) and bevacizumab (Bev) in triple-negative breast cancer (TNBC). *JCO* 2019;37(15_suppl):591-591.
34. Nanda R, Liu MC, Yau C, et al. Effect of Pembrolizumab plus Neoadjuvant chemotherapy on pathologic complete re-

sponse in women with early-stage breast cancer: an analysis of the ongoing phase 2 adaptively randomized I-SPY2 trial. *JAMA Oncol*. 2020;6(5):676-684. https://doi.org/10.1001/jamaoncol.2019.6650
35. Loibl S, Untch M, Burchardi N, et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. *Ann Oncol*. 2019;30(8):1279-1288. https://doi.org/10.1093/annonc/mdz158
36. Schmid P, Cortes J, Pusztai L, et al.; KEYNOTE-522 Investigators. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382(9):810-821. https://doi.org/10.1056/NEJMoa1910549
37. Gianni L, Huang C, Egle D, et al. Pathologic complete response to neoadjuvant treatment with or without atezolizumab in triple-negative, early high-risk and locally advanced breast cancer. NeoTRIPaPDL1 Michelangelo randomized study. *2019 San Antonio Breast Cancer Symposium* 2019.
38. Schmid P, Adams S, Rugo HS, et al.; IMpassion130 Trial Investigators. Atezolizumab and Nab-Paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379(22):2108-2121. https://doi.org/10.1056/NEJMoa1809615
39. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. *Lancet*. 2020;396(10257):1090-1100. https://doi.org/10.1016/S0140-6736(20)31953-X
40. Voorwerk L, Slagter M, Horlings HM, et al. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. *Nat Med*. 2019;25(6):920-928. https://doi.org/10.1038/s41591-019-0432-4
41. Stanton SE, Disis ML. Clinical significance of tumor-infiltrating lymphocytes in breast cancer. *J Immunother Cancer*. 2016;4:59. https://doi.org/10.1186/s40425-016-0165-6
42. Loi S, Drubay D, Adams S, et al. Tumor-infiltrating lymphocytes and prognosis: a pooled individual patient analysis of early-stage triple-negative breast cancers. *J Clin Oncol*. 2019;37(7):559-569. https://doi.org/10.1200/JCO.18.01010
43. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med*. 2017;376(22):2147-2159. https://doi.org/10.1056/NEJMoa1612645
44. van Mackelenbergh M, Seither F, Möbus V, et al. Abstract GS1-07: Effects of capecitabine as part of neo-/adjuvant chemotherapy. A meta-analysis of individual patient data from 12 randomized trials including 15,457 patients. In: *General Session Abstracts*. American Association for Cancer Research; 2020. p. GS1-07-GS1-07.
45. Radovich M, Jiang G, Hancock BA, et al. Association of circulating tumor DNA and circulating tumor cells after Neoadjuvant chemotherapy with disease recurrence in patients with triple-negative breast cancer: preplanned secondary analysis of the BRE12-158 randomized clinical trial. *JAMA Oncol*. 2020;6(9):1410-1415. https://doi.org/10.1001/jamaoncol.2020.2295
46. Yabroff KR, Dowling EC, Guy GP Jr, et al. Financial hardship associated with cancer in the United States: findings from a population-based sample of adult cancer survivors. *J Clin Oncol*. 2016;34(3):259-267. https://doi.org/10.1200/JCO.2015.62.0468
47. Bestvina CM, Zullig LL, Rushing C, et al. Patient-oncologist cost communication, financial distress, and medication adherence. *J Oncol Pract*. 2014;10(3):162-167. https://doi.org/10.1200/JOP.2014.001406
48. Ramsey SD, Bansal A, Fedorenko CR, et al. Financial insolvency as a risk factor for early mortality among patients with cancer. *J Clin Oncol*. 2016;34(9):980-986. https://doi.org/10.1200/JCO.2015.64.6620
49. Chino F, Peppercorn JM, Rushing C, et al. Out-of-pocket costs, financial distress, and Underinsurance in cancer care. *JAMA Oncol*. 2017;3(11):1582-1584. https://doi.org/10.1001/jamaoncol.2017.2148
50. Trudeau ME, Lickley L, Narod S, et al. Ten-year breast cancer survival - at what cost in human and physical terms? A case-control study of long-term survivors of breast cancer and their physical and functional well-being. *J Clin Oncol* 2004;22(14_suppl):8010.
51. Costa SD, Loibl S, Kaufmann M, et al. Neoadjuvant chemotherapy shows similar response in patients with inflammatory or locally advanced breast cancer when compared with operable breast cancer: a secondary analysis of the GeparTrio trial data. *J Clin Oncol*. 2010;28(1):83-91. https://doi.org/10.1200/JCO.2009.23.5101
52. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. *Lancet Oncol*. 2018;19(4):497-509. https://doi.org/10.1016/S1470-2045(18)30111-6
53. Park JH, Lee HJ, Lee SB, et al. Intrinsic prognostic impact of tumor-infiltrating lymphocytes in systemically untreated patients with early-stage triple-negative breast cancer. *Anticancer Res*. 2019;39(6):3111-3119. https://doi.org/10.21873/anticanres.13447
54. Leon-Ferre RA, Polley MY, Liu H, et al. Impact of histopathology, tumor-infiltrating lymphocytes, and adjuvant chemotherapy on prognosis of triple-negative breast cancer. *Breast Cancer Res Treat*. 2018;167(1):89-99. https://doi.org/10.1007/s10549-017-4499-7
55. Abuhadra N, Sun R, Litton JK, et al. Prognostic impact of high stromal tumor-infiltrating lymphocytes (sTIL) in the absence of pathologic complete response (pCR) to neoadjuvant therapy (NAT) in early stage triple negative breast cancer (TNBC). *JCO* 2020;38(15_suppl):583-583.
56. Gonzalez-Angulo AM, Timms KM, Liu S, et al. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. *Clin Cancer Res*. 2011;17(5):1082-1089. https://doi.org/10.1158/1078-0432.CCR-10-2560
57. Yap TA, Sandhu SK, Carden CP, de Bono JS. Poly(ADP-ribose) polymerase (PARP) inhibitors: exploiting a synthetic lethal strategy in the clinic. *CA Cancer J Clin*. 2011;61(1):31-49. https://doi.org/10.3322/caac.20095
58. Fasching PA, Link T, Hauke J, et al.; German Breast Group and Arbeitsgemeinschaft Gynäkologische Onkologie Breast. Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative breast cancer and homologous recombination deficiency (GeparOLA study). *Ann Oncol*. 2021;32(1):49-57. https://doi.org/10.1016/j.annonc.2020.10.471
59. Litton JK, Scoggins ME, Hess KR, et al. Neoadjuvant Talazoparib for patients with operable breast cancer with a Germline BRCA pathogenic variant. *J Clin Oncol*. 2020;38(5):388-394. https://doi.org/10.1200/JCO.19.01304
60. Han H, Liu MC, Hamilton E, et al. Abstract P3-11-03: Pilot neoadjuvant study of niraparib in *HER2* -negative, *BRCA* -mutated resectable breast cancer. In: Poster Session Abstracts. *American Association for Cancer Research*. 2020:P3-11-03-P3-11-03.
61. Chopra N, Tovey H, Pearson A, et al. Homologous recombination DNA repair deficiency and PARP inhibition activity in primary triple negative breast cancer. *Nat Commun*. 2020;11(1):2662. https://doi.org/10.1038/s41467-020-16142-7
62. Sharma P, Barlow WE, Godwin AK, et al. Impact of homologous recombination deficiency biomarkers on outcomes in patients with triple-negative breast cancer treated with adjuvant doxorubicin and cyclophosphamide (SWOG S9313). *Ann Oncol*. 2018;29(3):654-660. https://doi.org/10.1093/annonc/mdx821
63. Telli ML, Hellyer J, Audeh W, et al. Homologous recombination deficiency (HRD) status predicts response to standard neoadjuvant chemotherapy in patients with triple-negative or BRCA1/2 mutation-associated breast cancer. *Breast Cancer Res Treat*. 2018;168(3):625-630. https://doi.org/10.1007/s10549-017-4624-7
64. Masuda H, Baggerly KA, Wang Y, et al. Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer

molecular subtypes. *Clin Cancer Res*. 2013;19(19):5533-5540. https://doi.org/10.1158/1078-0432.CCR-13-0799
65. Stover DG, Bell CF, Tolaney SM. Chemotherapy considerations for triple negative breast cancer | Oncology CME. *American Journal of Hematology / Oncology®*. 2016;
66. Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest*. 2011;121(7):2750-2767. https://doi.org/10.1172/JCI45014
67. Traina TA, Miller K, Yardley DA, et al. Results from a phase 2 study of enzalutamide (ENZA), an androgen receptor (AR) inhibitor, in advanced AR+ triple-negative breast cancer (TNBC). *J Clin Oncol* 2015;33(15_suppl):1003-1003.
68. Metzger-Filho O, Sun Z, Viale G, et al. Patterns of Recurrence and outcome according to breast cancer subtypes in lymph node-negative disease: results from international breast cancer study group trials VIII and IX. *J Clin Oncol*. 2013;31(25):3083-3090. https://doi.org/10.1200/JCO.2012.46.1574
69. Li J, Yu K, Pang D, et al.; CBCSG010 Study Group. Adjuvant Capecitabine with Docetaxel and Cyclophosphamide Plus Epirubicin for triple-negative breast cancer (CBCSG010): an open-label, randomized, multicenter, Phase III trial. *J Clin Oncol*. 2020;38(16):1774-1784. https://doi.org/10.1200/JCO.19.02474
70. Wang X, Wang SS, Huang H, et al.; South China Breast Cancer Group (SCBCG). Effect of Capecitabine maintenance therapy using lower dosage and higher frequency vs observation on disease-free survival among patients with early-stage triple-negative breast cancer who had received standard treatment: The SYSUCC-001 randomized clinical trial. *JAMA*. 2021;325(1):50-58. https://doi.org/10.1001/jama.2020.23370
71. Lluch A, Barrios CH, Torrecillas L, et al.; GEICAM Spanish Breast Cancer Group; CIBOMA (Iberoamerican Coalition for Research in Breast Oncology); LACOG (Latin American Cooperative Oncology Group). Phase III trial of adjuvant Capecitabine after standard Neo-/Adjuvant Chemotherapy In Patients With Early Triple-Negative Breast Cancer (GEICAM/2003-11_CIBOMA/2004-01). *J Clin Oncol*. 2020;38(3):203-213. https://doi.org/10.1200/JCO.19.00904
72. Mayer IA, Zhao F, Arteaga CL, et al. Randomized phase III postoperative trial of platinum-based chemotherapy versus capecitabine in patients with residual triple-negative breast cancer following neoadjuvant chemotherapy: ECOG-ACRIN EA1131. *J Clin Oncol* 2021;JCO2100976.
73. Huang M, O'Shaughnessy J, Zhao J, et al. Association of pathologic complete response with long-term survival outcomes in triple-negative breast cancer: a meta-analysis. *Cancer Res*. 2020;80(24):5427-5434. https://doi.org/10.1158/0008-5472.CAN-20-1792
74. Ganz PA, Desmond KA, Leedham B, Rowland JH, Meyerowitz BE, Belin TR. Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. *J Natl Cancer Inst*. 2002;94(1):39-49. https://doi.org/10.1093/jnci/94.1.39
75. Amir M, Ramati A. Post-traumatic symptoms, emotional distress and quality of life in long-term survivors of breast cancer: a preliminary research. *J Anxiety Disord*. 2002;16(2):195-206. https://doi.org/10.1016/s0887-6185(02)00095-6
76. Cimprich B, Ronis DL, Martinez-Ramos G. Age at diagnosis and quality of life in breast cancer survivors. *Cancer Pract*. 2002;10(2):85-93. https://doi.org/10.1046/j.1523-5394.2002.102006.x