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

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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.3,4

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.10-13 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...
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%).28 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 TNBC28,29 while the data on long-term outcomes with platinum-based therapy remain premature at this time.30-32 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.33 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).11,10,20 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).41 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.41 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

| 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 201241         | Japan   | 92                | sTIL        | TIL score high if sum was 3-5  | Anthracycline-based | 32%                | 37%           |
| Miyashita et al 201449   | Japan   | 110               | sTIL and iTIL | Median TIL used as cutoff      | Anthracycline-based | 29%                | 41%           |
| Denkert et al 201551     | Germany | 314               | sTIL        | TIL involving 60% of either tumor stroma or cell nests | GeparSixto (PM/PMCb) | 40%                | 60%           |
| Hida et al 201645        | Japan   | 48                | sTIL and iTIL | Cutoff >50%            | Anthracycline and taxane | 43%                | 63%           |
| Herrero-Vicent et al 201746 | Spain         | 164               | sTIL        | LPBC >40%              | Anthracycline and taxane | 37%                | 87%           |
| Cerbelli et al 201747    | Italy    | 54                | sTIL        | Continuous, also LPBC >50%  | AC > T       | 35%                | 50%           |
| O’Loughlin et al 201848  | Ireland  | 75                | sTIL        | Increments of 10%, LPBC >50% stromal TIL | Anthracycline/taxane | Anthracycline/taxane/carboplatin | 46% | 89% |
| Denkert et al 201849     | Germany  | 906               | sTIL        | LPBC >60%              | GeparDuo, GeparTrio, GeparQuattro, GeparSixto, GeparSepto | 36% | 50% |
| Asano et al 201850       | 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.44 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.46 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 noted 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).65,66 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.68 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,
suggested that adjuvant capecitabine has activity in TNBC when used as an adjunct after standard anthracycline/taxane chemotherapy, 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. Financial toxicity is not frequently disclosed, and can be materially and psychologically debilitating for patients. 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.

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 not necessarily consistent with the patient's psychosocial needs and quality of life.
### Table 2. Ongoing clinical trials exploring escalation and de-escalation in TNBC.

| Trial number       | Phase | Description                                                                 | Primary outcome measure | Status        |
|--------------------|-------|-----------------------------------------------------------------------------|--------------------------|---------------|
| 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-1 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

| Trial number       | Phase | Description                                                                 | Primary outcome measure | Status        |
|--------------------|-------|-----------------------------------------------------------------------------|--------------------------|---------------|
| 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 + Gsplatin) and TAC (Docetaxel + Doxorubicin + Cyclophosphamide) in Neoadjuvant Therapy for Operable Triple Negative Breast Cancer | pCR                     | Recruiting    |
| NCT04138719        | II    | Clinical Study of Nab-paclitxel Plus Carboplatin Versus Nab-paclitxel 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. 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. Women who receive chemotherapy are also at risk for a post-traumatic stress syndrome and thus a lower QoL experience. 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.

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.

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

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