Systemic Therapy De-Escalation in Early-Stage Triple-Negative Breast Cancer

Subjects: Oncology

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Early-stage triple negative breast cancer (TNBC) has been traditionally treated with surgery, radiation, and chemotherapy. The current standard of care systemic treatment of early-stage II and III TNBC involves the use of anthracycline-cyclophosphamide and carboplatin-paclitaxel with pembrolizumab in the neoadjuvant setting followed by adjuvant pembrolizumab per KEYNOTE-522. It is increasingly clear that not all patients with early-stage TNBC need this intensive treatment, thus paving the way for exploring opportunities for regimen de-escalation in selected subgroups. For T1a tumors (≤5 mm), chemotherapy is not used, and for tumors 6–10 mm (T1b) in size with negative lymph nodes, retrospective studies have failed to show a significant benefit with chemotherapy. In low-risk patients, anthracycline-free chemotherapy may be as effective as conventional therapy, as shown in some studies where replacing anthracyclines with carboplatin has shown non-inferior results for pathological complete response (pCR), which may form the backbone of future combination therapies.

Keywords: triple-negative breast cancer ; de-escalation ; targeted therapy ; BRCA mutations ; chemotherapy ; neo adjuvant treatment ; tumor infiltrating lymphocytes ; biomarkers ; immunotherapy

1. Introduction

Triple-negative breast cancer (TNBC) is a subtype of breast cancer that lacks estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. Approximately 10–15% of breast cancers are triple-negative. These are typically more aggressive and associated with a higher rate of relapse. In addition, they have a higher predisposition to involve visceral organs like the lungs, liver, and brain, leading to a significantly shorter survival than other subtypes [1]. Thus, there have been significant ongoing efforts to develop optimal treatment strategies to treat both early and advanced TNBC.

In the present era of molecular subtyping, great progress has been made in finding effective targeted therapies for most subtypes of breast cancer. As TNBC lacks receptor expression, such as ER/PR, the vast array of endocrine therapy agents, such as selective estrogen receptor modulators (SERMS) and aromatase inhibitors, are out of treatment focus. Therefore, the standard systemic treatment option for early-stage TNBC was, until recently, limited to (neo)adjuvant chemotherapy followed by surgery and radiation [2]. The approval of pembrolizumab (July 2021) in combination with carboplatin/paclitaxel and doxorubicin/cyclophosphamide in early TNBC in the neoadjuvant setting in KEYNOTE-522, with continuation of pembrolizumab in the adjuvant setting, shifts the standard of care regimen for early-stage TNBC towards an even more intensive chemotherapy backbone, now with an immune checkpoint inhibitor (ICI). However, immune related adverse events (irAEs) were observed in 43.6% of patients with this combination vs. 21.9% with chemotherapy alone. Some of these irAEs could be fatal and life-threatening [2] and, hence, this begs the question of whether patients need ICI or if it is possible to de-escalate treatment for select individuals.

De-escalation has been successfully accomplished in the surgical field for breast cancer. From Halsted's radical mastectomy described over 100 years ago with axillary lymph node dissection (ALND), which were profoundly morbid procedures, to the current standard-of-care of breast conservation therapy (BCT) with lumpectomy and/or sentinel lymph node biopsy (SLNB) [3], the field has made significant progress. Multiple trials have demonstrated that breast conservation therapy (BCT) i.e., lumpectomy with radiation, is at least equivalent to mastectomy alone in terms of survival outcomes [4]. In addition, neoadjuvant chemotherapy (NACT) has enabled more and more women to receive BCT [5]. Over the last five years, both an improved understanding of the subtypes of TNBC as well as identification of targeted therapies for mutations have contributed to a movement towards de-escalation of systemic therapy [6]. De-escalating therapy has multiple potential benefits, including reduced toxicity, improved quality of life, improved cost-effectiveness, and better compliance with therapy, while maintaining good clinical outcomes.

De-escalating systemic therapy has been attempted in several ways—to administer less toxic/less aggressive regimens in a (neo)adjuvant setting, to stratify patients by identifying low clinical or molecular risk subgroups in early TNBC to avoid aggressive regimens, or to decrease the duration of therapies [7]. In addition, several targeted therapies are under investigation for use in early TNBC, including anti-angiogenic agents, androgen receptor blockers, and epidermal growth factor receptor (EGFR) targeted agents; however, their use is currently limited to clinical trials [8].

2. Current Standard of Care of TNBC

The choice of treatment in early TNBC largely depends on the primary tumor size, number of lesions, and lymph node (LN) involvement. Current national and international guidelines recommend neoadjuvant or adjuvant chemotherapy for early TNBC with tumor size ≥ 1 cm and/or with LN involvement, especially with ≥1 ipsilateral LN with metastases > 2 mm. But when it comes to stage 1 TNBC, especially pT1N0M0, there are no clear data since most of these patients were excluded from definitive clinical trials [9].

There is discordance among major guidelines: National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology guidelines (ASCO), European Society for Medical Oncology (ESMO), St. Gallen International Expert Consensus, Dutch guidelines regarding the best clinical practice for early TNBC, which is described in **Table 1** [10][11][12][13][14][15]. Most of the guidelines recommend against adjuvant chemotherapy for T1aN0 TNBC and recommend systemic chemotherapy (neo/adjuvant) for T1cN0 TNBC. ESMO guidelines recommend adjuvant chemotherapy for pT1 tumors, with the possible exclusion of low-risk special histological subtypes and very early (T1aN0) tumors [12]. There is no consensus regarding systemic chemotherapy among these guidelines for T1bN0 TNBC, which makes decision making strenuous for clinicians and patients [10][11][12][13][14][15].

Table 1. Adjuvant/Neoadjuvant chemotherapy recommendations for stage I TNBC according to various international guideline.

Stage	AJCC Stage Definition	International Guideline	Recommendation
T1aN0M0	Tumor >1 mm but ≤ 5 mm in greatest dimension, no evidence of regional LN metastasis identified	NCCN [10]	No adjuvant therapy (category 2A). Adjuvant chemotherapy may be considered in patients with high-risk features (e.g., young patients with high grade histology) (category 2B)
		ASCO [11]	Should not routinely offer Neoadjuvant therapy
		St.Gallen [13]	No adjuvant chemotherapy
		Dutch [14][15]	No adjuvant chemotherapy
T1bN0M0	Tumor > 5 mm but </=10 mm in greatest dimension, no evidence of regional LN metastasis identified	NCCN [10]	Consider adjuvant chemotherapy (category 2A)
		ASCO [11]	Should not routinely offer neoadjuvant therapy
		St.Gallen [13]	Adjuvant chemotherapy
		Dutch [14][15]	No adjuvant chemotherapy
T1cN0M0	Tumor > 10 mm but </=20 mm in greatest dimension, no evidence of regional LN metastasis identified	NCCN [10]	Adjuvant chemotherapy (category 1)
		ASCO [11]	Offer neoadjuvant therapy
		St.Gallen [13]	Adjuvant chemotherapy
		Dutch [14][15]	Adjuvant chemotherapy recommended if tumor grade 3 or if >/=grade 2 and age </= 35 years

The mainstay for early-stage TNBC with tumor greater than 2 cm in size (T2 or more) (prior to KEYNOTE-522 data) was neoadjuvant chemotherapy (NACT) followed by definitive surgery with or without adjuvant treatment (if residual disease). NACT was also used for T1 tumors if upfront surgery would provide an inferior cosmetic outcome and downstaging was essential. NACT also provides additional benefit in patients with locally advanced breast cancer who are not candidates for breast-conserving surgery (BCS) and wish for breast conservation, or those who are unlikely to have a good cosmetic outcome with upfront BCS [10].

The most common chemotherapy regimen in the United States for use in a (neo) adjuvant setting for cT1N0 is anthracycline and cyclophosphamide (AC) given in dose-dense schedule followed by weekly paclitaxel or dose-dense

paclitaxel for a total of 4–5 months [11]. The rationale for using this regimen came from the meta-analysis carried out by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in 2012, which showed that anthracycline-based regimens had similar or even better outcomes over historical cyclophosphamide, methotrexate, and fluorouracil (CMF) regimen. In addition, adding taxanes was associated with a reduction in recurrence rate and breast cancer-specific mortality. This led anthracycline and taxane (AT)-based regimens to become the standard treatment for operable breast cancer [16].

Although AC followed by taxane is superior for high-risk patients, alternative therapies are considered for patients with early TNBC who cannot receive anthracyclines, for example, those with a history of cardiac disease or extensive cardiac comorbidities and those who are unwilling to accept the risks of anthracycline-based therapies. For such patients, taxane-based treatment is offered; the common regimen used is docetaxel and cyclophosphamide (TC) [17]. CMF is another alternative regimen that can be used for those who have extensive peripheral neuropathy or cardiac comorbidities preventing the use of taxanes and anthracyclines [16].

For patients who cannot complete the full treatment course of NACT, the remainder of the planned course of chemo is usually completed in the adjuvant setting after careful consideration of adjustments for toxicities. For patients who have completed the standard NACT, and if they have attained complete pathologic response (pCR), then further adjuvant chemotherapy is not required. However, if the patients did not achieve complete pCR after NACT, they have a higher risk of disease recurrence. For those patients, adjuvant capecitabine was recommended after the promising results of the CREATE-X trial. It showed that patients with HER2 negative breast cancer with residual disease after NACT who received adjuvant capecitabine had higher rates of five-year disease-free survival (DFS) and overall survival (OS) when compared to those who received no further treatment. Subgroup analysis suggested that the improvement in DFS was mainly due to the improvement in outcomes among patients with early TNBC with 5-year DFS of 69.8% with capecitabine vs. 56.1% in the control group (HR 0.58, 95% CI, 0.38 to 0.87) and 5-year OS of 78.8% vs. 70.3% in the capecitabine vs. the control group (HR 0.52, 95% CI, 0.30 to 0.90) [18]. Recently, a PARPi, olaparib, was approved for patients with Her 2 negative breast cancer with germline BRCA mutation who have residual disease after NACT, based on the positive findings from the OlympiA trial that showed 3 year-invasive DFS of 85.9% in olaparib vs. 77.1% in the control group (HR 0.58, 99.5% CI, 0.41 to 0.82) and 3-year distant DFS of 87.5% in olaparib vs. 80.4% in the control group (HR 0.57, 99.5% CI, 0.39 to 0.83) [19]. According to recently published data, olaparib also significantly improved the OS. The 3-year OS rate in the olaparib arm vs. placebo was 92% vs. 89.1% (HR 0.68; 98.5% CI, 0.47 to 0.97, p = 0.0009) [20]. This highlights the need for better personalized strategies in the neoadjuvant setting to improve pCR, so that additional adjuvant treatment can be avoided.

In July 2021, pembrolizumab was approved by the US Food and Drug Administration (FDA) for combined use with chemotherapy in high-risk TNBC in the neoadjuvant and adjuvant setting based on the KEYNOTE-522 trial. In this phase III trial, patients with previously untreated stage II or III TNBC were randomly assigned to receive NACT with or without pembrolizumab every three weeks during the NACT and continued for another nine cycles after surgery, regardless of the pathologic response to the neoadjuvant treatment. The trial used a regimen of four cycles of paclitaxel and carboplatin plus pembrolizumab followed by AC plus pembrolizumab as neoadjuvant treatment and then adjuvant pembrolizumab for a total of nine cycles. The trial showed that the pCR rates were higher among those who received pembrolizumab plus chemotherapy than chemotherapy alone (64.8% vs.51.2%). This improvement in pCR rates was seen in both programmed cell death (PD-L1) positive and negative stage II or III TNBC. The percentage of patients alive at 18 months without disease progression/local or distant recurrence in the pembrolizumab + chemotherapy group was 91.3% and, in the chemotherapy alone group, was 85.3% (HR for disease progression 0.63, 95% CI 0.43 to 0.93) [2]. Follow-up data presented at the ESMO conference showed that the addition of pembrolizumab showed improvement in the 36-month event-free survival (EFS), 84% in the pembrolizumab group vs. 77% in the placebo group, with 37% reduction in events (HR 0.63, 95% confidence interval 0.48 to 0.82). EFS improvement was also independent of the PD-L1 status [21]. It was also found that the addition of pembrolizumab was more beneficial in patients who had residual disease when compared to those who attained pCR. In those who did not attain pCR, the 3-year EFS was 67.4% in the pembrolizumab + chemo group and 56.8% in the chemotherapy alone group. Meanwhile, in the patients who attained pCR, the 3-year EFS was 94.4% in the pembrolizumab + chemotherapy group and 92.5% in the chemotherapy alone group [21][22]. Thus, the current standard of care for tumor stage T1c, nodal stage N1-2, or tumor stage T2-4, nodal stage N0-2 is neoadjuvant pembrolizumab with chemotherapy.

Similar findings were observed in the IMPassion031 clinical trial. IMPassion031 is a phase III randomized clinical trial for patients with TNBC with tumor size > 2 cm (N = 333). Patients were randomized to receive nab-paclitaxel followed by doxorubicin and cyclophosphamide, with or without atezolizumab, followed by surgery. After surgery, 11 doses of atezolizumab were administered every 3 weeks in the immunotherapy group. pCR was significantly improved in 57.6% of

patients in the atezolizumab plus chemotherapy group, and in approximately 41% of the patients in the placebo plus chemotherapy group. In the PD-L1-positive population, pCR was observed in 68.8% of the patients in the atezolizumab group vs. 49.3% in the placebo group [23].

The GeparNUEVO trial also investigated the effects of an anti-PD-L1 checkpoint inhibitor in the neoadjuvant setting. This trial investigated the effect of the addition of neoadjuvant durvalumab to anthracycline/taxane-based chemotherapy. In this trial, they randomized cT1b-cT4a-d TNBC patients to receive either durvalumab or placebo along with neoadjuvant nab-paclitaxel followed by epirubicin plus cyclophosphamide. The pCR rates were higher in the durvalumab group compared to the placebo group, but the difference was not statistically significant. However, durvalumab added to neoadjuvant chemotherapy has shown a statistically significant improvement in long-term outcomes. The 3-year distant disease-free survival (DDFS) and OS were 91.4% and 95.1% in the durvalumab group, compared to 79.5% and 83.1% in the placebo group, respectively, which was statistically significant [24].

As discussed, with the approval of checkpoint inhibitors along with chemotherapy in the neoadjuvant setting, the treatment for early-stage TNBC has become very aggressive, associated with several irAEs. They key question now is whether all patients need this aggressive treatment, or can the treatment be de-escalated for patients selected based on tissue biomarkers or tumor/genetic mutations.

3. Biomarkers and Imaging to Guide Systemic Therapy De-Escalation

3.1. Prognostic and Predictive Biomarkers

3.1.1. Tumor Microenvironment Biomarkers Predicting pCR

Several studies have shown that stromal tumor infiltrating lymphocytes (sTILs) play an important role in prognosis and response to chemotherapy in patients with TNBC [25]. In 2010, Denkert et al. reported that high sTILs in breast cancer are a predictor of pCR to NACT with pCR rates of 40–42% in the cohort with high sTILs vs. 3–7% in the cohort with low TILs [26]. TILs were then examined in an analysis of two randomized phase III adjuvant French studies in TNBC patients, which showed that high sTILs correlated with better ten-year OS (89% vs. 68%). However, they were not found to be predictive for response to anthracycline-based chemotherapy [27]. In a retrospective study from the Netherlands in 481 young (<40 years old) early-stage TNBC patients who only underwent surgery, De Jong et al. found that TIL expression levels correlate with overall survival (OS) and distant recurrence-free survival (DRFS). They found that the OS at 15 years for TIL <30%, 30–75%, and >75% was 59%, 76%, and 93%, respectively, and DRFS at 15 years was 67%, 83%, and 98%, respectively [28]. In a pooled analysis from four TNBC cohorts of early-stage mostly node-negative (83%) TNBC patients, Park et al. demonstrated excellent survival outcomes without systemic therapy in patients with sTIL >30%. The 3-year invasive disease-free survival (iDFS) was 93%, DDF 97%, and OS 99% [29]. These survival outcomes are similar to a pooled analysis from nine studies by Loi et al. in which a similar group of node negative early TNBC patients who received anthracycline-based chemotherapy with sTILs >30% had a 3-year iDFS 92%, DDFS 97%, and OS 92% [30]. These studies show that sTILs may be able to identify a subgroup of patients with Stage 1 TNBC with an excellent prognosis, in which systemic therapy may be able to be de-escalated or omitted altogether. A recent large meta-analysis shows TILs to be both prognostic for favorable long-term clinical outcomes as well as predictive for pCR among TNBC [31]. However, this evidence is mostly from retrospective studies and needs confirmation in prospective cohorts. Recent studies suggest that sTILs could possibly be added in the 8th edition of the American Joint Committee on Cancer (AJCC) staging system to up- or downstage early TNBC [32].

Similarly, single cell spatial analysis from the NeoTRIPaPDL1 trial (NCT02620280) found that GATA3 and CD20 in the tumor microenvironment, HLA-DR on the epithelial cells, and Ki67 both on the tumor microenvironment and the epithelial cells, were significant for their predictive ability for atezolizumab benefit. Expression of these biomarkers above the median was linked to a pCR rate increase of 10% or more ($p < 0.05$). It was also noted that higher expression of two cell phenotypes, PD-L1 positive, IDO-positive antigen presenting cells (APCs) and CD56-positive neuroendocrine (NE) epithelial cell, was associated with a higher pCR when treated with atezolizumab. In patients with PD-L1 positive, IDO-positive APCs who received atezolizumab, pCR was 64.6% vs. 24.6% for those with high and low expression, respectively ($p < 0.001$) [33].

3.1.2. PD-L1 as a Predictor of pCR

Immune checkpoint inhibitors targeting PD-1 or PD-L1 have become the standard of care in many solid tumor types. In TNBC, PD-L1 expression has been estimated to be 40–65% on the immune cells [34]. Nineteen percent of tumor cells were PD-L1 positive, defined by >5% membranous staining by IHC [35]. PD-L1 expression was investigated as a

biomarker of response to these therapies; however, even patients who are PD-L1 negative respond to these agents. Therefore, there is a lack of a quantitative association between PD-L1 expression and response.

3.1.3. Immune Gene Signature as a Predictor of pCR

Multi-gene signature has been studied as a comprehensive tool that can capture the immunogenicity of TNBC. The GeparSixto trial was analyzed for mRNA markers and showed that an immune signature composed of seven immune-activating genes (CXCL9, CCL5, CD8A, CD80, CXCL13, IGKC, CD21) and five immunosuppressive genes (IDO1, PD-1, PD-L1, CTLA4, FOXP3) was validated as a marker for immune reaction. The increased mRNA expression level of these genes, including immunosuppressive genes, was associated with pCR [36].

3.1.4. Circulating Tumor DNA (ctDNA) as a Predictor of pCR

Circulating tumor DNA (ctDNA) is the fragmented DNA released into the bloodstream from the necrosis of the tumor tissue. The detection of ctDNA has been progressively used in studies to demonstrate its predictive role in identifying minimal residual disease after neoadjuvant chemotherapy in early TNBC and thereby identifying the high-risk patients for recurrence. Riva et al., in a prospective study, demonstrated that ctDNA levels are associated with tumor proliferation rate and can be used to monitor tumor progression during NACT. They also found that those who had a slow decrease of ctDNA level during NACT had shorter survival [37]. In the BRE12-158 clinical trial that enrolled early-stage TNBC patients who had residual disease after the NACT, ctDNA was positive in 63% of patients (90 out of 142). The secondary analysis of the trial showed that detection of ctDNA and circulating tumor cells (CTCs) after NACT in patients with early-stage TNBC is significantly associated with inferior DDFS, DFS, and OS [38]. Similar results were seen in another study, which showed that next generation ctDNA sequencing of patients with early TNBC who did not attain pCR after NACT could predict recurrence with high specificity, and they had inferior DFS (median DFS: 4.6 months vs. not reached; HR = 12.6, 95% CI: 3.06–52.2, $p < 0.0001$). However, the sensitivity of detection of ctDNA was low in the study as they could identify the ctDNA in the plasma sample of only 4 out of 33 patients who had somatic mutations [39]. In a study by Magbanua et al., the authors found that high-risk early breast cancer patients who did not clear ctDNA during the NACT were more likely to have residual disease than those who cleared the ctDNA. The ctDNA was detected in 73% of patients (61 out of 84) pretreatment. The ctDNA positivity decreased during the NACT, and only 8.6% (N = 5) of patients remained ctDNA positive after completion of the NACT. In this study, all patients who attained pCR were ctDNA negative. An important finding was that patients who did not achieve pCR but were ctDNA negative had improved survival, comparable to those who attained pCR (HR 1.4, 95% CI 0.15–13.5) [40]. With more advancements in studies, ctDNA can be used as a reliable biomarker to identify a subgroup of patients who have a comparatively lower chance of disease recurrence after NACT in whom the adjuvant treatments could be effectively avoided.

3.2. Targeted Strategies to Improve pCR

3.2.1. Tumor-Associated Macrophages in the Tumor Microenvironment

Therapies targeting the tumor microenvironment (TME) are also currently under investigation. Tumor-associated macrophages (TAMs) are known to promote the progression and metastasis of TNBC by releasing inhibitory cytokines, reducing the functions of TILs, promoting regulatory T-cells (Tregs), and modulating the expression of PD-1/PD-L1 on the TME [41]. Cabiralizumab is a monoclonal antibody that blocks colony stimulating factor-1 receptor (CSF1R) and has demonstrated the ability to block activation of monocytes and macrophages. The combination of this antibody with immunotherapy (nivolumab) and an anthracycline-free chemotherapy regimen (carboplatin + paclitaxel) is being studied in the neoadjuvant setting, with the central hypothesis that it would decrease tumor-associated macrophages (TAMs) and increase TILs, thereby improving outcomes. The primary outcome measure of this entry includes the percentage change in TILs and TAMs, with pCR and RFS being looked at as secondary outcome measures (NCT04331067). Such novel agents, if found to be efficacious, may provide an alternative to current standard of care systemic therapy, thereby helping to minimize treatment related toxicity while maintaining excellent efficacy.

3.2.2. PARP Inhibitors for Germline BRCA Mutation

Among the patients with TNBC, approximately 10–30% have germline BRCA (gBRCA) mutations. Approximately 80% of breast cancers that occur in patients with gBRCA1 mutations are triple-negative with a basal-like profile. BRCA 1 and BRCA 2 are tumor suppressor genes that belong to the homologous recombination (HR) repair pathway that repairs double-strand DNA breaks. Platinum-based regimens are a focus of interest in several trials in patients with BRCA mutations. Cisplatin every three weeks for 4 cycles was evaluated in a randomized phase II INFORM clinical trial of neoadjuvant cisplatin vs. AC in gBRCA carriers (70% TNBC patients). The pCR rate was 18% with cisplatin and 26% with AC [42]. Poly ADP-ribose polymerase inhibitors (PARPi) showed efficacy in patients with BRCA mutations. Poly ADP-

ribose polymerase (PARP) 1 is a protein that facilitates the DNA repair process. PARPi traps PARP1 and induces cell death by preventing single-stranded break repair, followed by double-stranded breaks without functional homologous recombination in patients with BRCA mutations [6]. Talazoparib has been approved for patients with locally advanced or metastatic, HER2-negative breast cancer with deleterious gBRCA mutations [43].

There are several ongoing studies to evaluate the role of PARPi as a neoadjuvant treatment in early-stage BRCA mutated breast cancer. MD Anderson reported a study of neoadjuvant talazoparib in patients with gBRCA mutations (NCT02282345). TNBC patients consisted of 15 out of the 20 patients enrolled, and 53% achieved pCR after six months of single agent talazoparib. In this trial, patients subsequently received adjuvant standard chemotherapy based on physician's discretion [44]. These results supported the larger neoadjuvant phase II nonrandomized NEOTALA study, which investigated single agent talazoparib in gBRCA 1/2 mutated early HER2 negative breast cancer (NCT03499353). This study included patients with early TNBC, and they received 24 weeks of neoadjuvant talazoparib and then underwent surgery. Neoadjuvant talazoparib monotherapy resulted in pCR in 45.8% of evaluable patients (48 patients) and 49.2% in the intent to treat population (61 patients). This was comparable to standard combination anthracycline and taxane regimen, and the treatment was tolerated well [45]. This regimen could be especially useful for select patients where chemotherapy is contraindicated; for example, those exposed to prior chemotherapy for other cancers or those with a poor performance status where the treating clinician may not want to consider giving intensive chemotherapy/pembrolizumab in the neoadjuvant setting.

3.2.3. PI3K/AKT/mTOR Targeted Therapies

Mutations in PIK3CA, AKT, PTEN, or mTOR can activate the Phosphatidylinositol-3-kinase (PI3K) pathway, leading to cell growth. Deregulation of any PI3K pathway component has been seen in up to 50% of patients and are seen amongst all molecular subtypes. Ipatasertib, a highly selective pan-AKT small molecule inhibitor, was studied initially in the phase II LOTUS trial in the metastatic setting and showed a significant PFS improvement in patients with alteration in the PIK3CA/AKT/PTEN pathway [46]. Subsequently, it was studied in neoadjuvant early TNBC in the phase II FAIRLANE study. Weekly paclitaxel × 12 weeks plus ipatasertib or placebo (days 1–21 every 28 days) was given to a patient population that contained both low-PTEN and PTEN-altered tumors. There was an increase in pCR from 13% to 17% in the ipatasertib arm in the ITT population (N = 151, 95% CI −9.0 to 16.5), which was not statistically significant. In patients with low PTEN, pCR was 16% vs. 13% in placebo, and in patients with altered PTEN, pCR was 18% vs. 12% in placebo, which was not statistically significant. The addition of ipatasertib did not significantly increase pCR rates. The overall pCR rates in this entry are much less than typically expected in early TNBC, likely due to the short duration of treatment of 12 weeks and utilization of only paclitaxel as chemotherapy. In addition, there was no significant difference in pCR in PTEN mutated patients who received ipatasertib compared with those who did not have the mutation. This is likely due to the significant heterogeneity among TNBC. Though this was a negative trial, these results support further evaluation of this pathway in combination with chemotherapy [47].

3.2.4. Epidermal Growth Factor Receptor (EGFR) Targeted Therapies

EGFR overexpression can be used as a target in TNBC as 60% of triple negative tumors have EGFR expression. EGFR expression has been recognized as a poor prognostic factor in TNBC [48]. EGFR inhibitors, including Tyrosine kinase inhibitors (TKI) and monoclonal antibodies (mABs), have been used in multiple early phase clinical trials in the past, but the results have been mostly disappointing [8][49]. A neoadjuvant study using EGFR inhibitor cetuximab in combination with ixabepilone (NCT01097642) has recently completed accrual, and the final analysis is awaited. Inhibition of EGFR may be another targetable pathway that could be used to de-escalate treatment if EGFR inhibitors show benefit in ongoing clinical trials.

3.2.5. Antiangiogenic Agents

Vascular Endothelial Growth Factor (VEGF) inhibitors impair the neovasculature of the tumor, thus impairing tumor growth. Bevacizumab, an anti-angiogenic monoclonal antibody against VEGFR, has been evaluated in multiple studies in TNBC, especially in the metastatic setting. Most of the studies tend to escalate the treatment by the addition of bevacizumab to standard NACT regimens [6]. The addition of bevacizumab to anthracycline and taxane-based adjuvant chemotherapy in the BEATRICE study did not show a statistically significant improvement in the DFS or OS [50]. The use of bevacizumab in the neoadjuvant setting in stage II/III TNBC with or without carboplatin concurrent with AC-T was studied in the CALGB 40603/Alliance trial. The addition of either carboplatin or bevacizumab to the standard neoadjuvant chemotherapy increased the pCR rates but did not show improvement in long term outcomes [51][52]. VEGF inhibition continues to remain a potential pathway that can be used for developing targeted treatments in the (neo) adjuvant setting in early TNBC.

3.2.6. Androgen Receptor Targeting

Almost 10–40% of TNBC expresses androgen receptors (AR); this makes AR a potential target for treatment. Androgen Receptor inhibitors abiraterone and enzalutamide have shown clinical benefit in AR positive (>/=10% by Immunohistochemistry) metastatic TNBC [53][54]. This has led researchers to study the benefits of AR-targeted therapy in the neoadjuvant setting in early TNBC. A phase II trial studying the efficacy of enzalutamide and paclitaxel in the neoadjuvant setting in patients with Stage I–III AR-positive TNBC is actively accruing (NCT02689427). If the study shows promising results, enzalutamide with minimal chemotherapy can be used to de-escalate the current complex neoadjuvant regimen in early TNBC.

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