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Exploiting Therapeutic Vulnerabilities in Triple-Negative Breast Cancer: Successes, Challenges, and Opportunities

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Abstract

Purpose of Review Triple-negative breast cancer (TNBC) is notoriously difficult to treat. Recent technological advances have led to the identification of novel targets and new approaches to treat this devastating disease. The aim of this review is to highlight therapeutic vulnerabilities of TNBC and discuss novel therapeutic strategies.

Recent Findings Interrogating the inherent heterogeneity and rich cellular and transcriptional diversity within TNBC has led to the discovery of vulnerabilities and actionable targets for therapeutic development. Characterization of the tumor immune environment, discovery of novel molecular targets, and identification of somatic alterations which confer sensitivity to DNA repair inhibitors are just a few examples.

Summary The key to developing effective strategies to treat TNBC is to exploit vulnerabilities using a multifaceted approach. The identification of actionable targets has led to numerous therapeutic advances for TNBC, resulting in substantial improvements in patient outcomes and quality of life.

Keywords Triple-negative breast cancer · Targeted therapy · Immunotherapy · DNA repair · Androgen receptor · Tumor microenvironment

Introduction

Triple-negative breast cancer (TNBC) refers to a heterogeneous group of breast tumors which lack expression of the estrogen receptor (ER), progesterone receptor (PR), and HER2/neu (HER2) receptors [1]. Historically, treatment has been limited to chemotherapy; however, advances in technology have facilitated the discovery of molecular targets as well as vulnerabilities within the tumor microenvironment, ushering in an era of novel therapies and improved patient outcomes [2] (Fig. 1). Notably, the application of omics-based analyses facilitated development of clinically relevant biomarkers and therapeutic targets [3, 4, 5••]; single-cell profiling provided further characterization and contextualization of intrinsic heterogeneity [3, 4, 6].

TNBC heterogeneity occurs within tumor cell populations, the tumor immune microenvironment, and the composition of the extracellular matrix. This heterogeneity contributes to numerous therapeutic obstacles, including the identification of targetable mutations and a variable response to treatment [7–9, 10•, 11].

Enhancing the Immune Response

The emergence of immune checkpoint inhibitors (ICI) has dramatically enhanced treatment outcomes for a variety of malignancies, including TNBC. Continued investigation to maximize the immune response in TNBC is an area of active research [12–14]. Compared to other breast cancer subtypes, TNBCs tend to have a higher tumor mutational burden (TMB), number of tumor-infiltrating lymphocytes (TILs), PD-L1 expression, and neo-antigen burden [9, 15].

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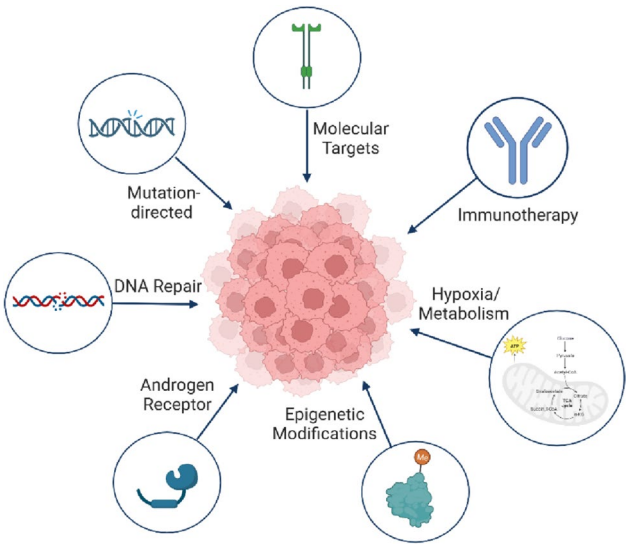

Fig. 1 Overview of current therapeutic strategies for triple-negative breast cancer. Current and emerging therapeutic targets in TNBC include molecular alterations, the immune microenvironment, hypoxia/metabolism, epigenetic modifications, androgen receptor signaling, and DNA repair. Created with BioRender.com

The efficacy of immunotherapy in TNBC has been demonstrated in multiple studies. While ICI monotherapy had limited efficacy in TNBC, a subset of patients maintained a durable response, demonstrating the relevance of immune pathways in some TNBCs [16–19]. In an effort to increase response rates, combination strategies with chemotherapy and other agents have been studied (Fig. 2).

Chemoimmunotherapy Combinations in Advanced TNBC

KEYNOTE-355 was a randomized phase III trial which investigated the addition of pembrolizumab to first-line chemotherapy of physician's choice (nab-paclitaxel, paclitaxel, or carboplatin/gemcitabine) in patients with advanced TNBC [20]. In this study, the addition of the anti-PD-1 therapy pembrolizumab to chemotherapy demonstrated a statistically significant improvement in both progression free survival (PFS; 9.7 vs 5.5 months, $p = 0.001$) and overall survival (OS; 23.0 vs 16.1 months, $p = 0.018$) as compared to chemotherapy alone in those with PD-L1 positive advanced TNBC defined as a combined positive score > 10 via the 22C3 assay. The results of this trial led to the full regulatory approval of pembrolizumab plus chemotherapy for PD-L1 positive advanced TNBC. The randomized phase III IMpassion130 trial demonstrated a modest but statistically significant improvement in PFS with the addition of atezolizumab to first-line nab-paclitaxel in those with PD-L1 positive advanced TNBC defined as PD-L1 > 1% via SP142 assay [21]; based on this result, the combination was granted accelerated approval by the US FDA. While IMpassion130 did demonstrate a numerical improvement in OS favoring the chemoimmunotherapy arm, this improvement was not assessable for significance due to the hierarchical statistical design [21]. The IMpassion131 phase III trial assessed the benefit of adding atezolizumab to paclitaxel in the same TNBC population and failed to demonstrate a PFS or OS advantage [22]. Based on the negative results of this trial

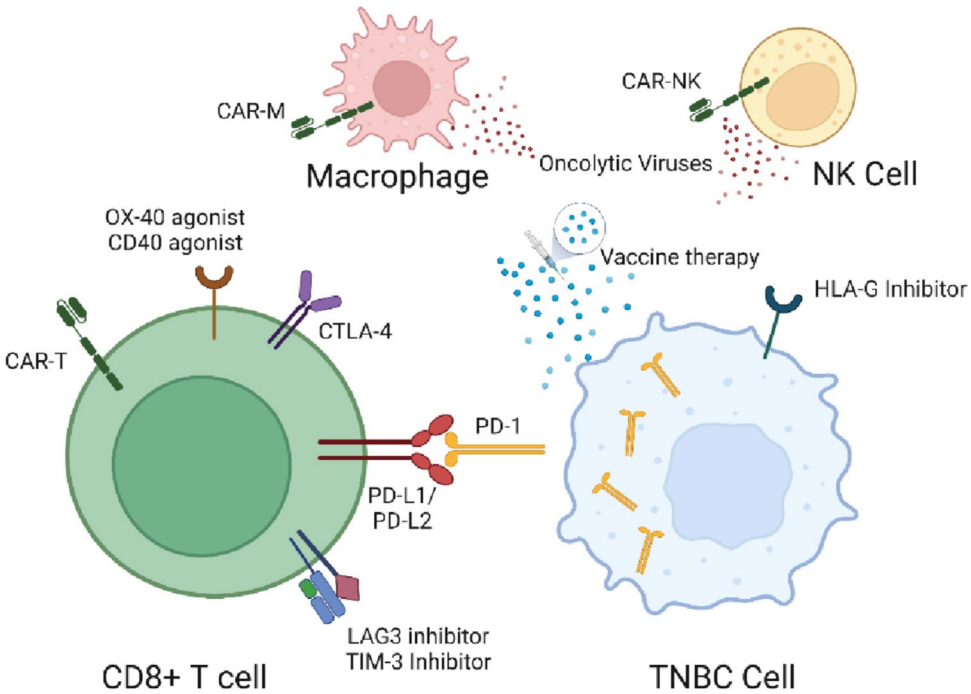

Fig. 2 Immunosurveillance targets in early-stage clinical trials for TNBC. Overview of the diverse immunosurveillance targets for TNBC in clinical investigation. Created with BioRender.com

and the failure of IMpassion130 to demonstrate an overall survival advantage, the approval of atezolizumab for TNBC was withdrawn in 2021.

Chemoimmunotherapy Combinations in Early-Stage TNBC

Given its success in advanced TNBC, a number of trails have explored ICI in the early-stage, neoadjuvant TNBC setting. The first trial to demonstrate an improvement in response and long-term outcomes in those with early-stage TNBC was the I-SPY2 adaptively randomized phase II trial. One of the arms of this trial investigated the addition of four cycles of pembrolizumab to paclitaxel followed by four cycles of doxorubicin plus cyclophosphamide (pembro-4) [23]. The primary endpoint from I-SPY2 is the likelihood that an investigational arm will have a significantly higher pathological complete response (pCR) rate as compared to the control arm in a randomized phase III trial. The pembro-4 arm of I-SPY2 "graduated" for efficacy.

Subsequently, the industry-sponsored, phase III KEYNOTE-522 trial randomized patients with stage II and III TNBC to chemotherapy (paclitaxel plus carboplatin followed by doxorubicin plus cyclophosphamide) and a year of pembrolizumab vs placebo [24, 25••]. This trial demonstrated that the addition of pembrolizumab significantly improved pCR and event-free survival (EFS) and led to the regulatory approval of pembrolizumab in the early-stage TNBC setting [25••]. Unlike in advanced disease, PD-L1 expression was not predictive of response to ICI [24]. Even in patients without a pCR, the addition of pembrolizumab down-staged residual cancer burden, improving event-free survival overall [24]. In the GeparNuevo trial, the addition of durvalumab to anthracycline and taxane–based neoadjuvant therapy modestly improved pCR rates, but significantly improved EFS, even in the absence of adjuvant durvalumab, raising the question of whether adjuvant ICI therapy is needed [26].

A number of randomized phase III trials are evaluating the optimization of ICI-based therapy in the early-stage TNBC setting. The Optimice-pCR (NCT04266249) trial will randomize TNBC patients who achieve a pCR after neoadjuvant therapy to adjuvant pembrolizumab vs observation, to evaluate if adjuvant ICI therapy is necessary. The SWOG S2212 SCARLET study will evaluate the non-inferiority of an anthracycline-free chemoimmunotherapy regimen to the KEYNOTE-522 regimen, to see if similar outcomes can be attained with less chemotherapy. And the ongoing I-SPY2.2 adaptively randomized platform trial is concurrently evaluating a number of investigational anthracycline-free regimens, with the option for patients to go to surgery early should imaging reveal a complete clinical response.

Immune Modulation Beyond Anti-PD-1/PD-L1

Many other immunotherapies have been studied in TNBC in an effort to enhance efficacy of approved agents or identify novel therapeutic regimens. T-lymphocytes are regulated by activation of co-stimulatory (CD28, OX40, CD40) and co-inhibitory receptors (CTLA-4, PD-1, TIM-3, LAG-3) [27]. The anti-CTLA-4 agent ipilimumab has demonstrated efficacy in a number of tumor types. The efficacy of dual ipilimumab and nivolumab in mTNBC patients with TMB > 14 mutations/Mb was evaluated. This combination demonstrated an ORR of 60%, compared to ORR 4% with TMB between 9 and 14 suggesting a role for dual checkpoint blockade in high TMB TNBC tumors [28]. The DART trial investigated dual CTLA4 and PD-L1 blockade in metaplastic breast cancer and noted durable responses in 18% of patients in this refractory population [29]. LAG-3, a co-inhibitory receptor, activation leads to cytotoxic T-cell exhaustion and decreases anti-tumor activity and is also found on regulatory T-cells where it inhibits the cytotoxic T-cell response [30]. The ISPY-2 trial revealed dual immune modulation with a LAG-3 inhibitor and anti-PD-1 therapy revealed high pCR rates in TNBC, however at the cost of an increase in immune-related adverse events (irAEs), including high rates of adrenal insufficiency and diabetes mellitus, precluding further development for early breast cancer at this time [31].

CD47, an inhibitory signal of phagocytosis by macrophages, is a novel immunotherapy target [32]. A trial investigating the combination of the anti-CD47 agent magrolimab with paclitaxel or nab-paclitaxel (NCT04958785) is currently ongoing. Another anti-CD47 agent, ALX148, is being evaluated in the I-SPY Phase I platform trial in combination with trastuzumab deruxtecan (T-DXd) (NCT04602117) for HER2-low advanced breast cancer.

Combining Immunotherapy with DNA Repair Inhibition

PARP inhibition (PARPi) can synergize with ICI by sensitizing the tumor microenvironment to immunomodulatory therapy [33, 34]. PARPi enhances immune activation by upregulating type I interferon activation through the STING pathway, cell-death mediated inflammation, and increased neoantigen load [15, 35, 36]. These observations led to trials testing the combination of PARPi and ICI. In the TOPACIO trial, the combination of niraparib and pembrolizumab achieved an objective response rate (ORR) of 21% and disease control rate (DCR) of 49% in mTNBC [37], including responses observed in those without germline BRCA1/2 (gBRCA) mutations. In the MEDIOLA trial, the DCR with Olaparib plus durvalumab at 12 weeks was 80% in participants with gBRCA1/2 and advanced HER2 negative breast cancer [38]. These non-randomized trials demonstrated the

safety of this combinatorial approach, although it remains to be seen if there is synergy between ICIs and PARPi in either those who harbor deleterious gBRCA1/2 mutations or the overall TNBC population.

Vaccines

While neoantigen vaccine therapy is a promising approach to induce an immune response and enhance cytotoxic T-cell activity, several large randomized phase II or III clinical trials using vaccines as a monotherapy did not meet the efficacy endpoints of demonstrating improvements in PFS or OS [39•]. However, a number of vaccines are currently under investigation in combination with ICI, chemotherapy, and/or radiation [38]. Vaccines, including PVX-410 and mRNA-2752 are under clinical investigation as monotherapy and in combination with ICI in both early and advanced TNBCs [40–42]. PVX-410 is a tetra-peptide vaccine with 3 antigens overexpressed in TNBC including 2 splice variants of XBP1 and CD138 (NCT04634747). mRNA-2752 consists of three mRNAS that encode for OX-40 ligand, IL-23, IL-36γ (NCT03739931).

Cellular Therapy

Employing chimeric antigen receptor T-cell (CART) therapy in TNBC also takes advantage of robust TNBC neoantigens [43, 44]. CART therapies are in early phase trials for TNBC. Preliminary safety data testing CAR-T therapy targeting cMET in TNBC patients with advanced TNBC and melanoma patients who had received prior lines of therapy revealed that five out of seven patients experienced grade 1 or 2 toxicities, an no grade > 3 toxicities or cytokine release syndrome were observed [45]. Other CAR-T directed therapies are also in early stages of clinical trials in both TNBC and other aggressive solid tumors (ROR1-targeted CART: NCT05274451; mesothelin-targeted: NCT02792114; TnMUC1 targeted: NCT04025216). Furthermore, the T-cell receptor gene therapy targeting KK-LL-C1 is also in safety clinical trials (NCT05035407). Newer T-cell directed therapies target two different antigens (often with one including the CD3 + antigen), called bispecific antibody (bsAb) or bispecific T-cell engager (BiTe) [46] and are in phase I or II clinical trials alone (NCT03219268, NCT04424641, NCT05585034, NCT03517488) or in combination with ICI pembrolizumab (NCT03849469) or ipilimumab (NCT03752398) in TNBC and other advanced solid tumors. With the success of CAR-T therapy in hematologic malignancies, CAR-NK and CAR-M (macrophage) therapy are novel concepts to harness immune system vulnerabilities. While only preclinical studies exist now that test CAR-NK and CAR-M efficacy with various targets in TNBC [47–50], clinical trials are planned to test the utility of this strategy for TNBC.

The Tumor Immune Microenvironment

Hijacking the innate immune response triggered by oncolytic viral (OV) infections is another novel technique to enhance chemotherapy efficacy in TNBC by inciting an immune response [39•, 51]. Talimogene laherparepvec (T-VEC) is a modified herpes simplex virus that can generate a local and systemic anti-tumor immune response. A small study enrolling patients with non-operable local recurrence receiving T-VEC did not demonstrate any partial or complete responses [52]. However, a study in the early-stage demonstrated encouraging results. Patients received T-VEC in addition to standard of care taxane and anthracycline-based chemotherapy and 45.9% of patients had a pCR at time of surgery, supporting further investigation in the neoadjuvant setting [53]. Furthermore, because OV therapies enhance immune reactivity, they have been proposed to have more robust effects in combination with ICI [54, 55]. Directly injecting immune modulating agents into the TME is also being tested, using a plasmid for IL-12 tavokinogene telseplasmid (NCT03567720).

Targeting Tumor-Associated Antigens

Targeting cell surface glycoproteins expressed on epithelial cancer cells provides the basis of novel antibody-drug conjugate therapies (ADCs) [56, 57]. The discovery of a novel target in epithelial malignancies including TNBC, trophoblast cell-surface antigen (Trop-2), led to the development of the antibody drug conjugate Sacituzumab govitecan (SG). Trop-2 and topoisomerase-1 (TOPO1) expression is present in 56–80% of primary and metastatic TNBC tumors [58, 59]. An antibody targeting Trop-2 is conjugated to an active metabolite of irinotecan, SN-38, and inhibits topoisomerase activity and affects DNA repair. The ASCENT randomized phase III trial compared SG to single-agent chemotherapy of physician's choice (TPC; eribulin, vinorelbine, capecitabine, or gemcitabine) in mTNBC. PFS and OS were significantly improved with SG compared to TPC (5.6 vs 1.7 months, $p < 0.001$, and 12.1 vs 6.7 months, $p < 001$, respectively), with chemotherapy and median OS 12.1 compared to 6.7 [60, 61••]. Active areas of research interrogate resistance mechanisms from Trop2-targeted therapies and have identified acquired SG resistance that involves direct antibody and drug payload targets including defective plasma membrane localization and reduced cells-surface binding within metastatic subclones of individual TNBC patients [62]. Furthermore, not all Trop-2 positive tumors are TOPO1 positive, suggesting a separation in the expressed enzyme and cell

surface marker, which may have treatment implications with acquisition of ADC-therapy resistance [58]. The investigational ADC, datopotamab deruxtecan (Dato-DXd) targets a similar vulnerability in TNBC and contains a humanized anti-TROP2 IgG1 monoclonal antibody conjugated to a topoisomerase I inhibitor payload. Dato-DXd has a longer half-life than SG and is currently in clinical development for both advanced and early stage TNBC. Results of the TROPION-01 study showed that amongst the 43 patients with mTNBC who received > 2 prior lines of therapy (including immunotherapy or SG), ORR was 39% and DCR 84%, overall revealing promising anti-tumor activity with adequate safety profile [63]. Dato-DXd is currently being investigated in the I-SPY2.2 neoadjuvant trial with and without durvalumab in HER2-negative stage II/III breast cancer.

Trastuzumab deruxtecan is another ADC approved in HER2-low advanced breast cancer based on the DESTINY-Breast04 trial with significantly improved PFS and OS compared to standard chemotherapy, demonstrating a unique role for HER2-targeted therapies in HER2-low breast cancer. As approximately one-third of hormone receptor-negative tumors have HER2-low expression, subsets of patients with TNBC can derive substantial benefit from this therapy [56]. Within the BEGONIA trial, amongst HER2-low expressing mTNBC patients who received anti-PD1 (durvalumab) with T-DXd, 56.9% of patients had a response to therapy, including one complete response and 32 partial responses, with no concerning safety signals [64–66]. Preliminary results from the Dato-DXd plus durvalumab arm also exhibited anticancer activity in advanced TNBC, with an ORR of 73.6% and an adequate safety profile [64].

Numerous ADCs targeting novel antigens in TNBC are in various phases of clinical development. Ladiratuzumab vedotin (LV) targets LIV-1A, a transmembrane protein with zinc transporter and metalloproteinase activity [56, 67, 68]. The payload of LV is monomethyl-auristatin-E (MMAE), an inhibitor of tubulin polymerization [67]. LV has demonstrated efficacy in advanced TNBC, with an ORR of 25% in heavily pretreated patients; combination studies with pembrolizumab in the frontline advanced TNBC setting are ongoing (NCT03310957). Enfortumab vedotin targets nectin-4 with MMAE as payload and is in clinical trials for TNBC as well as a number of other malignancies (NCT04225117). Another novel ADC target is the folate receptor alpha (FR-α). Mirvetuximab soravtansine (IMGN853) is an ADC which targets FR-α for tumor-directed delivery of maytansinoid DM4, a compound which induces mitotic arrest by inhibiting microtubules [56, 69]. While a trial of IMGN853 was aborted early due to the low percentage of FR-α positivity in TNBC samples, identifying a unique subset of patients who could potentially respond to this therapy is worthy of additional study. A similar ADC, AMT-151, also uses FR-α as the target, and is in early phase trials [56]. ROR-1 is an attractive novel target that is highly expressed on TNBC and is minimally present or absent on healthy tissues. A new ADC targeting ROR1, NBE-002, uses the anthracycline-derivative PNU-159682 modified to a humanized recombinant IgG1 monoclonal anti-human ROR1 antibody, XBR1-402. In preclinical trials with PDX models, NBE-002 had dramatic anti-tumor effect in TNBC and is now in early stage clinical trials (NCT04441099) [70]. XB002, an ADC targeting tissue factor is currently being investigated in phase I trial alone and in combination with nivolumab or bevacizumab for TNBC, in addition to other aggressive cancers (NCT04925284) [56].

Exploiting Molecular Aberrations

Classification of TNBC was developed based on intrinsic molecular characteristics identified through gene expression analyses and biological signatures [71, 72]. TNBC subsets include basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal-like (M), and luminal androgen receptor (LAR). The classification precipitated discovery of novel anticancer agents in TNBC [5••, 73, 74•]. The subtypes have distinct susceptibilities to various targeted inhibitors; however, these patterns of sensitivity are not restricted to one subset. TNBC has the highest mutation rate compared to other BC subtypes, with EGFR, FGFR2 and MYC amplifications as well as PTEN loss more frequent, although other mutations including TP53 exist [3]. While the concept of employing multi-receptor tyrosine kinase inhibitors in TNBC is attractive, the cross-talk and side effects of these therapies have prevented clinical success of receptor tyrosine kinase (RTK) inhibitors in TNBC [75]. One approach to targeting molecular diversity and preventing cross-talk is to generate multi-drug regimens that target various molecular tumor drivers in TNBC [9, 76] although clinical studies are required to determine the utility of these approaches.

DNA Repair

DNA repair is crucial for maintaining cell survival. Poly (ADP-ribose) polymerase (PARP) is an integral enzyme in DNA repair and other cellular processes; PARP plays an important role in base-excision repair and nucleotide excision repair. Tumors arising in patients with gBRCA1/2 mutations have limitations in DNA repair, and treatment with PARPi induces synthetic lethality [77]. Numerous PARP inhibitors have been evaluated in TNBC. Olaparib and talazoparib are both approved for advanced TNBC in individuals with gBRCA1/2 mutations after randomized phase III trials, OlympiAD and EMBRACA, respectively, demonstrated that these PARPi were associated with significant improvements in PFS as compared to TPC [78••, 79]. Olaparib has also demonstrated efficacy in patients with

gPALB2 and somatic BRCA1/2 mutations, and larger studies are ongoing in patients with these other alterations in DNA repair pathway [80, 81].

The PARPi veliparib was evaluated in gBRCA1/2 patients in combination with platinum-based doublet chemotherapy in the BROCADE-3 randomized phase II trial and demonstrated a significant but modest improvement in PFS compared to chemotherapy alone [82]; however, this study failed to demonstrate an overall survival advantage. As PARPi monotherapy was associated with a significantly better quality of life (QoL) as compared to TPC in the OlympiAD and EMBRACA trials, it is unclear if these is a role for this combination of PARPi and chemotherapy, given the failure of this approach to yield a survival advantage.

Veliparib plus carboplatin and paclitaxel (T) followed by dose dense doxorubicin and cyclophosphamide (AC) was also investigated in the neoadjuvant ISPY-2 platform trial; this investigational arm demonstrated a significant improvement in pCR in patients with early-stage TNBC and graduated for efficacy. The subsequent randomized phase III BrighTNess trial compared this combination to taxane and anthracycline-based neoadjuvant chemotherapy (T-AC) with and without carboplatin. BrighTNess found that the addition of carboplatin to T-AC significantly improved pCR rates and long-term outcome but adding veliparib only served to increase toxicity without any additional therapeutic benefit [83].

PI3K/AKT/PTEN/mTOR

A quarter of TNBC patients will have activating mutations in the PI3K/AKT/PTEN/mTOR pathway which drives tumor progression and promotes survival [84]. The basal-like molecular subtype has high rates of PI3K/AKT/mTOR pathway mutations [84, 85]. Oral PI3K and AKT inhibitors have been studied in TNBC. Patients with advanced TNBC were treated with paclitaxel with or without capivasertib, and in a randomized phase II trial, the combination significantly improved both PFS and OS, most notably in patients with *PI3KCA/AKT1/PTEN* mutations [86]. In the phase II LOTUS trial, ipataserib and paclitaxel also demonstrated improved PFS compared to paclitaxel alone [87]. However, the follow-up randomized phase III Ipatunity130 trial failed to demonstrate a significant improvement in PFS and OS [88], and in the FAIRLANE neoadjuvant trial, ipataserib plus paclitaxel did not improve the rate of pCR in comparison to paclitaxel alone [89]. The pan-PI3K inhibitor buparlisib did not improve PFS nor OS in advanced, PI3K-activated, HER2-negative tumors [90]. Downstream targeting of mTOR has also had limited success in advanced stage TNBC, and the role of therapies targeting PI3K/AKT/PTEN/mTOR pathway alterations in TNBC remains unclear.

Cell Cycle

Dysregulation of cyclin-dependent kinases (CDK) that regulate cell cycle transitions are highly relevant in BC. While CDK-targeted agents are first-line therapy in hormone receptor positive cancers, TNBCs initially exhibited resistance. The CDK4/6 inhibitor trilaciclib in combination with chemotherapy-enhanced OS in a randomized phase II trial in patients with TNBC (19.8 vs 12.6 months, $p < 0.001$) [91]; a follow-up randomized phase III trial is ongoing [92]. Synergistic activity of PI3K and CDK4/6 inhibitors in PIK3CA mutant TNBC has been documented and are partially due to enhanced tumor immune cell infiltration [93]. These findings have led to ongoing randomized trials of CDK4/6 inhibitors in combination with ICIs, androgen receptors (NCT02605486) and other targeted therapies (NCT02978716; NCT03805399; NCT02978716; NCT03756090).

Androgen Receptor

Recognition that the androgen receptor (AR) is expressed in a subset of TNBC tumors has opened the door to a new avenue of clinical research, and a number of studies have explored repurposing the anti-androgens used for the treatment of prostate cancer for this form of breast cancer. Enzalutamide and bicalutamide exhibited 33% and 19% of clinical benefit rates (CBR) in AR-positive TNBC at 16 weeks [94, 95]. Abiraterone and steroid combination resulted in a 16-week CBR of 20% [96]. In a recently completed randomized phase II trial, darolutamide was compared to capecitabine in patients with AR-positive TNBC; while capecitabine was found to have a higher 16-week CBR than darolutamide (59.4 vs 29.3%) [97], there is clearly a subset of patients with advanced AR-positive TNBC who benefit from anti-AR therapy, and the development of a better predictive biomarker is crucial.

Epidermal Growth Factor Receptor (EGFR)

Growth factors drive diverse signaling pathways in cancer development and many TNBC have EGFR over-expression [74•]. Cetuximab, a monoclonal antibody targeting EGFR, used in combination with cisplatin did modestly improve ORR compared to cisplatin alone (20% vs 10%) and median PFS (3.7 vs 1.5 months) [98]. However, in TBCRC 011, cetuximab alone or in combination with carboplatin had very low clinical activity, and correlative studies demonstrated that while most TNBCs in the study had EGFR pathway activation, cetuximab only blocked activation in a minority of tumors [99]. Overall, EGFR inhibitors have not had significant success in clinical trials compared to chemotherapy, and while the EGFR pathway appears to be activated in a

number of TNBCs, currently available EGFR inhibitors do not appear to adequately modulate this activity to elicit a clinical benefit.

Other Signaling Pathways

While targeting the RAS/MAPK signaling pathway with MEK inhibitors as monotherapy has not been successful in TNBC [100], the COLET study explored the combination of cobimetinib with immunotherapy and chemotherapy in untreated mTNBC. Cobimetinib with paclitaxel did not increase PFS or ORR, and cobimetinib added to atezolizumab and taxane did not increase ORR [101].

The Wnt signaling pathways drive cell survival, proliferation, differentiation, cell migration and polarity [102]. Several inhibitors that target the Wnt pathway are in early phase clinical trials [103]. Gedatolisib (dual PI3K/mTOR inhibitor) plus cofetuzumab (an ADC against PTK7) in phase I clinical trial revealed promising results [104], and planning of later phase studies is underway.

TGF-β has crucial functions in many central signaling pathways of TNBC [105]. Using anti-TGF-β agents to enhance activity of other investigative drugs is of current interest. Targeting TGF-β with fresolimumab improved effects of radiotherapy with respect to median overall survival and enhanced systemic immune response [106]. Current trials are evaluating effects of the neutralizing antibody NIS793 with the PD-1 inhibitor spartalizumab, as well as the combination of anti-TGF-β plus eribulin in mTNBC [107].

Cancer Cell Metabolism

TNBC takes advantage of metabolic reprogramming to fuel tumor progression. Identifying therapeutic vulnerabilities within cell metabolism that are unique to cancer cells facilitates new targetable opportunities.

TNBC tumors are characterized by states of high glycolytic flux and low mitochondrial-driven oxidative phosphorylation activity, and enhanced glycolysis is noted in hypoxic environments [108–110]. Genome-wide screens have identified glycolytic and oxidative phosphorylation genes that are crucial to survival of TNBC cells [111]. In TNBC there is added metabolic heterogeneity, suggesting unique therapeutic regimens catering to these distinct profiles will be required to harness such vulnerabilities [112]. In a subset of TNBC tumors with enhanced glycolysis and carbohydrate nucleotide metabolism, it has been proposed that inhibition of lactate dehydrogenase could enhance tumor response to anti-PD-1 by inhibiting tumor immunosurveillance by T- and NK cells [112]. FASN produces long-chain saturated fatty acids de novo in growing cells, and a FASN inhibitor, TVB-2640 is in early-stage clinical trials for advanced breast cancer [112, 113]. Additional promising metabolic targets for TNBC in preclinical development include the glucose transporter 1 (GLUT1), glutaminase GLS2 (induced by p53), and pyruvate kinase isozymes M2 (PKM2) [114, 115].

Vulnerabilities in Epigenetics Regulation

While genetics play a large role in breast cancer development and risk, epigenetic processes including DNA methylation, histone modification, and microRNAs (miRNAs) also dramatically alter the tumor microenviroment, affecting tumor progression and therapeutic response. Epigenetic events result in aberrant overactivation of downstream signaling pathways and epigenetic targets have emerged in TNBC [116]. While epigenetic biomarkers have been implicated in breast cancer as prognostic and diagnostic markers [117], the role of epigenetics in identifying therapeutic vulnerabilities in TNBC is still under investigation. Unfortunately, previous clinical trials in TNBC involving HDAC inhibitors or other inhibitors of epigenetic processes have not had success with toxic adverse effects and nonspecific pharmacodynamics as the major challenges [118]. Future investigations are warranted to determine the therapeutic potential of combination strategies.

DNA Methylation

Methylation of DNA is a mechanism by which gene expression is regulated. Generally, hypomethylation causes activation of genes that can regulate metastasis and chemoresistance, while hypermethylation supports uncontrolled proliferation [118]. Compared to other subtypes, TNBC is characterized by genome-wide hypomethylation, thereby activating genes regulating metastasis and chemoresistance [117]. Targeting epigenetic pathways can alter gene expression and the tumor microenvironment. Low expression of superoxide dismutatase 3 (SOD3) is common in TNBC; epigenetic silencing of SOD3 via methylation represents a novel therapeutic target in TNBC [119]. DNA methylation has also been linked to cancer stemness, and dysregulated methylation binding sites of canonical genes promote a stem cell phenotype [117, 120, 121]. DNMT inhibitors can activate expression of endogenous retroviral double stranded RNAs which in turn stimulate an interferon-1 response, suggesting that DNMT inhibition may enhance immunotherapy efficacy in breast cancer [122].

Histone Modification

Histone modification encompasses acetylation, deacetylation and methylation events. Histone methyltransferases (HMT) and histone demethylases (HDM) mediate this delicate balance [123]. Balances between H3K9ac accumulation and

H3K17me3 dysregulation have been observed to affect tumorigenesis, oncogenic signaling pathways, metastasis [116].

Histone deacetylase (HDAC) inhibitors have had limited success in TNBC. With the emergence and success of immunotherapy in TNBC, the HDAC inhibitor romidepsin has re-emerged in active trials for locally recurrent or metastatic TNBC with systemic chemotherapy (cisplatin) and immunotherapy (nivolumab) (NCT02393794). More recently, HDAC inhibitors have been tested in combination with immunotherapy (NCT02708680), and CDK4/6 inhibitors (NCT04315233). Furthermore, HDAC inhibitors have had promising results in attenuation of drug resistance in BC cells by targeting efflux transporters multidrug resistance protein, MDR-1, and breast cancer resistance protein, BCRP [124]. In addition to DNA methylation aberration, histone modification events also drive stemness and metastasis in breast cancer [123, 125–129].

Non-coding RNAs

Epigenetic dysregulation of non-coding RNAs (ncRNAs) has also been associated with enhanced metastasis and stemness features [117, 130–132]. Select long-noncoding RNAs (lncRNAs) are under pre-clinical investigation as potential therapeutic targets that drive tumorigenesis and tumor invasiveness, namely FLVCR1-AS1 and HOTAIR [133, 134]. The lncRNA DANCR has been associated with cancer stemness in late-stage TNBC by downregulating SOCS3 [135] and another lncRNA associated gene, cancer susceptibility candidate 9 (CASC-9) promotes doxorubicin resistance [136].

Targeting Hypoxia and the Stress Response

Approximately 25–40% of invasive breast cancers contain focal areas of hypoxia, often associated with abnormal angiogenesis [137]. Under hypoxia, cancer cells hijack stress pathways to overcome hostile microenvironments and survive [138]. In solid tumors, hypoxia drives cancer cell programming, stem cell signaling pathways, angiogenesis, extracellular matrix regulation, and development of metastasis [137, 138]. Because hypoxia has an expansive signaling network and is influenced by stress-induced environments, the key to targeting hypoxia and assessing prognostic implications of a hypoxic environment is to identify hypoxia-inducible molecular markers and specific targets [115]. Targeting hypoxia-inducible factors (HIFs) has proven to be difficult due to the diverse function of HIFs, and in fact two major clinical trials with HIF inhibitors tirapazamine and evofosfamide failed [115, 137, 139]. Carbonic anhydrase IX, a hypoxia inducible factor, is a novel prognostic marker for hypoxia in breast cancer [140].

Adenosine triphosphate (ATP) conversion to ADP and AMP is exacerbated in hypoxia, and AMP is metabolized to adenosine by CD73 on tumor cells. Adenosine interacts with ADA-2 adenosine receptor (A2AR) which has pivotal effects in the immune response. In addition to limiting natural killer cell maturation [141], A2AR enhances cytotoxic T-cell activity suggesting its role as a promising anti-cancer target. Early-stage clinical trials in TNBC, as well as multiple other malignancies, aim to evaluate the dual effect of targeting hypoxia and the immune response in TNBC.

Tumors take advantage of physiologic stress responses and hijack regulatory pathways and stress signaling, to promote cancer cell survival. Hypoxia contributes to tumor escape from immune surveillance and immunotherapy, and resistance to immunotherapy [142–145]. Hypoxia has been shown to induce T and NK effector cell dysfunction through a HIF1α-mediated mechanism [142], suggesting that targeting HIF1α pathway is a possible method to enhance effector cell function and response to anti-PD1 immunotherapy.

Conclusions

TNBC is characterized by marked heterogeneity, and no "one size fits all" therapeutic strategy will work for this collection of diverse tumors. A better understanding of the underlying mechanisms driving aggressive clinical behavior through technological advances has led to various innovative and novel strategies to treat TNBC. Advances in drug development, recognition that a subset of TNBCs are immunogenically active, and identification of novel targets have led to improved outcomes for patients with early and advanced TNBC alike (Fig. 1).

Further technological advances to aid in the identification of therapeutic vulnerabilities coupled with novel treatments will enable the continued realization of precision medicine for TNBC.

Declarations

Conflict of Interest Margarite Matossian declares that she has no conflict of interest. Nan Chen has received personal fees from AstraZeneca and Gilead Sciences. Rita Nanda serves on the advisory boards for AstraZeneca, BeyondSpring, Fujifilm, GE, Gilead, Infinity, iTeos, Merck, OBI, Oncosec, Sanofi, Seagen. Rita Nanda has received research funding from Arvinas, AstraZeneca, Celgene, Corcept Therapeutics, Genentech/Roche, Gilead/Immunomedics, Merck, OBI Pharma, OncoSec, Pfizer, Relay, Seattle Genetics, Sun Pharma, Taiho.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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••Of major importance

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