Review Article

A narrative review of biomarkers in advanced triple negative breast cancer

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Abstract: Triple negative breast cancer (TNBC) is a heterogeneous disease; while clinically diagnosed as a single entity disease, at the molecular level, TNBC includes characteristic subtypes with potential for subtype specific targeted therapies which are still underway. Chemotherapy remains the backbone of treatment of TNBC. Although new targeted therapies have been introduced in the metastatic setting, including immunotherapy, PARP inhibitors and antibody drug conjugates (ADC), identifying patients who would selectively benefit from these treatments is awaiting a more refined selection process driven by better understanding of the biology of TNBC subtypes. More importantly, there is a need for validated tools of genomic precision and biomarker driven targeted therapy that can readily identify TNBC subtypes in the clinic and translate complex molecular analysis into individualized treatment plans for patients. This review presents biomarkers in advanced TNBC with potential for targeted therapies and discusses ongoing strategies to managing the heterogeneity of TNBCs. We discuss biomarkers including *TP53*, androgen receptor, breast cancer susceptibility genes (*BRCA*), homologous recombination deficiency (HRD), PI3K/AKT/mTOR, immune biomarkers, and ADC. The review concludes with a summary of the landscape of biomarker driven targeted therapies in advanced TNBC that has been improving outcomes of this aggressive disease.

Keywords: Triple negative breast cancer (TNBC); molecular markers; targeted therapy

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Introduction

Triple negative breast cancer (TNBC) is clinically defined by the lack of expression of the estrogen receptor (ER), progesterone receptor (PR) and low expression of human epidermal growth factor receptor (HER2). As these cancers are defined by what they are not rather than what they are, they naturally represent a heterogenous group of cancers that are still largely managed as a single entity disease.

TNBCs represent 15–20% of breast cancers, are more common in younger women and those of African American descent (1,2), as well as, in *BRCA* mutation carriers (3). Women with TNBC tend to present with large tumors that are usually higher grade and involve the lymph nodes (4). TNBCs have been characterized by an aggressive natural history with higher rates of relapse within the first 5 years, in addition to higher rates of distant recurrences, worse disease-free survival (DFS) and overall survival (OS) compared to other breast cancer subtypes (4). Despite molecular advances in characterizing TNBCs and the availability of few targeted therapies in the advanced setting,

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the overall survival of women with metastatic TNBC remains low (4).

TNBCs have been characterized at the genetic and epigenetic levels (5-8), yet therapeutic targets have been lagging. Chemotherapy has been the backbone line of treatment for TNBCs. Recent advances in treatment include immune checkpoint inhibitors (ICIs), such as Atezolizumab with nab-paclitaxel or Pembrolizumab in combination with chemotherapy for PD-L1 positive TNBCs in the metastatic setting (9,10), and PARP inhibitors for previously treated *BRCA* mutation carriers with metastatic TNBCs (11-13). Antibody drug conjugate (ADC), sacituzumab govitecan, has recently been FDA approved in patients with metastatic TNBC who received at least two prior therapies (14,15). Current challenges include translating the heterogeneity within TNBC to individualized treatment plans for the patient, identifying and utilizing biomarkers that predict survival and/or treatment response and identifying optimal tools to help guide precision medicine. This is in addition to a need to better understand mechanisms of chemoresistance in TNBC. The landscape of biomarker driven targeted therapy in TNBC is rapidly changing, and there are several ongoing clinical trials with potential to personalize the standard care of treatment for this heterogenous disease. Here, we present a review of the recent literature and our current knowledge of the molecular characteristics of this unique subset of breast cancer. Furthermore, we highlight clinically relevant biomarkers that have been described for TNBC, and we focus on emerging potential therapeutic targets. We present the following article in accordance with the Narrative Review Reporting Checklist (available at: http://dx.doi.org/10.21037/pcm-20-76).

Methods

A literature search was conducted on PubMed using the terms 'advanced triple negative breast cancer' and 'biomarkers' from 2000 to December 2020. The same search terms were used for the ClinicalTrials.gov registry of clinical trials. Abstracts from the annual meetings for the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and San Antonio Breast Cancer Symposium (SABCS) were included. Only English studies were included.

On the origins of TNBCs: more than basal-like entity

The human breast is organized into a branching system of ducts and lobules. At the cellular level, the breast epithelium is organized into an inner layer of luminal epithelial and an outer layer of basal/myoepithelial cells embedded in a stromal matrix. Each of these cells is characterized by distinct set of genetic features in addition to expression of differentiation markers and show different repopulating capacity *in vitro* and *in vivo* (16-18). At the histological level, while luminal epithelial cells stain positive for cytokeratins 8/18, basal epithelial cells stain positive for cytokeratins 5/6, 17 (5,19). Dissection of mammary epithelium *in vitro* reveals four subpopulations based on cell surface markers, EpCAM and CD49f which are mature luminal cells, luminal progenitor cells, stromal and basal/mammary stem cells. There is data to suggest *BRCA1* associated TNBCs which tend to be of the basal-like subtype at the gene expression level arise from the aberrant luminal progenitor subpopulation (16), raising the interest in characterizing mammary stem/progenitor cells to identify potentially actionable targets.

Decrypting the heterogeneity of TNBCs

Immunohistochemical (IHC), DNA, epigenome, RNA, protein and recently immunome analysis have revealed the extensive heterogeneity of TNBCs. While TNBC is defined at the histological level by lack of expression of ER, PR and low expression of HER2, at the molecular level, it is more complex. Initial efforts to molecularly characterize TNBCs from 2 decades ago were through gene expression, revealing TNBCs encompass basal subtype (50–70%), in addition to claudin-low, luminal, HER2+ and normal breast-like subtypes, albeit at lower rates compared to basal subtype (5,6,19-23). Cancers of the basal subtype express basal epithelial markers and tend to occur in younger patients, have poor baseline prognosis, higher mutation rate, higher frequency of *TP53* nonsense and frameshift mutations, *RB1* and *BRCA1* mutations (4,7).

There have been several studies that further examined TNBC at the transcriptional level, subclassifying it into multiple subtypes (24-26). Lehmann *et al.* (24) initially subclassified TNBC into several subtypes: basal-like (BL1 and BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), luminal androgen receptor (LAR), and unstable (UNS). A subsequent refined analysis which made use of laser-capture microdissection to isolate and specifically characterize tumor cells outside of the tumor microenvironment classified these TNBCs into 4 main subtypes including basal-like (BL1 and BL2), mesenchymal

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subtype (M), and luminal androgen receptor subtype (LAR) (25). These subtypes have distinct genomic signatures, prognosis and response to chemotherapy (24,27-29).

The BL1 subtype is highly proliferative as determined by elevated expression of proliferation marker Ki67 and is enriched in cell cycle and DNA damage response pathways. The BL2 subtype is enriched in growth factor signalling, glycolysis and gluconeogenesis and expression of myoepithelial markers including TP63. The mesenchymal subtype is defined by its high expression of genes associated with motility and epithelial to mesenchymal transition (EMT). The LAR subtype represents the luminal phenotype and is composed of genes involved in steroid synthesis including androgen receptor, as well as mutations in *PIK3CA* (24,25).

These subtypes also have distinct clinical characteristics where LAR subtype tends to have more regional nodal involvement, preferentially metastasize to the bone and has a favorable prognosis whereas mesenchymal subtype tends to spread to the lungs and has worse prognosis (25,29). When examining the response to neoadjuvant chemotherapy in TNBCs, the basal subtype had a significantly higher pathological complete response (pCR) compared with mesenchymal subtype while LAR subtype had lowest pCR (30). Burstein *et al.* used gene expression profiling of 198 TNBCs and identified 4 subtypes: luminal androgen receptor (LAR), mesenchymal (MES), basal-like immunosuppressed (BLIS) and basal-like immune activated (BLIA) (31). BLIS had the worst prognosis whereas BLIA had the best prognosis (31). Similarly, in a transcriptomic analysis of 465 TNBCs by Jiang *et al.*, four subtypes were identified: LAR subtype with enrichment for *ERBB2* and *PI3K* pathway mutations, immunomodulatory subtype, BLIS subtype characterized by upregulation of cell cycle and activation of DNA repair, and a mesenchymal-like subtype enriched in mammary stem cell pathways (26). Overall, gene expression analysis studies showed that classification of TNBC into four subtypes remains unchanged (32). Understanding the biology of these molecular subtypes has helped inform potential subtype targeted therapies. While platinum-based chemotherapy and PARP inhibitors have been suggested to target BL1 subtype and *BRCA1* mutation carriers, AR antagonists, PI3K and CDK4/6 inhibitors are suggested to target LAR subtype, and FGFR and NOTCH inhibitors to target M subtype (24-27,29).

The Cancer Genome Atlas (TCGA) Network provided great insight into the heterogeneity of TNBCs through analysis of genomic DNA copy number arrays, DNA methylation, exome sequencing, messenger RNA arrays, microRNA sequence and protein arrays in 510 breast tumors (7). This study confirmed genes already implicated in breast cancer (*PIK3CA*, *PTEN*, *AKT1*, *TP53*, *GATA3*, *CDH1*, *RB1*, *MLL3*, *MAP3K1* and *CDKN1B*), as well as provided novel alterations, mutational frequency, genomic alterations commonly observed in luminal A, luminal B, HER2 positive and basal-like subtypes. In this study, 80% of basal-like subtype consisted of TNBCs characterized by mutated *TP53* (84%), *PIK3CA* mutations (7%), *PTEN* mutation/loss (35%), *RB1* mutation/loss (20%), high proliferation, hypomethylation and high expression of DNA repair proteins (7). This data along with the breadth of molecular alterations in breast cancer and TNBCs can be explored through platforms, such as cBioPortal (33).

At a single cell level, treatment naive TNBC exhibits a spectrum of heterogeneity related to mutational burden and clonal evolution; some tumors have high mutational burden whereas other tumors have few somatic mutations. As previously stated *TP53* is the most frequently mutated gene. In addition, mutations in *PIK3CA*, *RB1*, *PTEN*, *MYO3A* and *GH1*, *BRAF* V600E, *EGFR* amplifications and *ERBB2/ERBB3* mutations show evidence of single gene selection (8). Commonly activated pathways include *TP53* and DNA damage pathway, PIK3 signaling, *ERBB2* signaling, integrin signaling and focal adhesion, WNT/cadherin signaling, growth hormone and nuclear receptor co-activators. The *TP53* and *PIK3CA* pathways have higher clonal frequencies, suggesting early role in tumorigenesis (8). The heterogeneity of TNBCs whether at the subtype level or in terms of single cells presents a challenge to identifying potential targets for treatment.

Biomarker targeted therapy in TNBCs

We have reviewed the characteristic features of TNBC subtypes, and in this section, we outline subtype driven biomarkers as potential targets of personalized therapy.

TP53: time to target the guardian

While historically considered a challenge to target tumor suppressor genes, there might be a future for targeting *TP53* in TNBC. *TP53* is the most frequently mutated gene across various cancers, including breast cancer. TP53 controls functions essential to cell cycle progression, DNA damage repair and apoptosis (34). Among breast cancers subtypes, *TP53* is the most frequently mutated

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Table 1 Selected clinical trial targeting TP53 in TNBC

Agent	Pathway	Setting	Phase	Sample size	Duration	Identifier
APR-246 + Pembrolizumab	TP53 + anti-PD-1	Advanced solid tumors	phase I/II	118	Jun 2022	NCT04383938

TNBC, triple negative breast cancer; PD-1, programmed death receptor-1.

gene in TNBCs. TCGA identified 80% of basal subtype cancers were TNBCs with 84% having *TP53* mutations (Network, 2012). Clinical and experimental data suggest *TP53* mutations constitute an early event in TNBC but not necessarily the first step (7,8,35,36).

TP53 expression is a prognostic marker in TNBC. TP53 IHC expression occurs in 55–70% of TNBC cases and correlates with worse prognosis (37-41). TP53 expression coincided with proliferative TNBCs as determined by high Ki67 expression (41). Overall, TP53 positivity was associated with worse prognosis in TNBC (38,40-42); however, survival was significantly improved with chemotherapy (38). TP53 expression by IHC in TNBC, however, could not predict the response to neoadjuvant chemotherapy (39).

Until Recently, TP53 has proved to be a challenging actionable target; however, compounds that restore wildtype *TP53* function to induce cell cycle arrest or apoptosis have been developed. APR-246 is a compound that reactivates mutant *TP53* and converts it to a wild type form which has been shown to have anticancer activity in *TP53* mutant breast cancer cell lines (43). Another compound, COTI-2, reactivates p53, has shown antitumor activity in TNBC cell lines and is being evaluated in clinical trials (*Table 1*) (44).

Androgen receptor: target hormonally sensitive subset of TNBC

The androgen receptor is a member of the nuclear steroid hormone receptor family which includes ER and PR. Androgens, including testosterone and dihydrotestosterone, activate AR leading to its translocation to the nucleus and concomitant binding to target genes, resulting in downstream transcriptional activation. AR is expressed in >75% of ER positive breast cancer (45,46). AR expression is positive in around 28% of TNBCs (47). There has been mixed data on AR expression and prognostic relevance in TNBC (45-47). A recent systematic review of 27 studies including 4914 patients with TNBC found AR protein expression was not associated with prognosis (47).

AR antagonists have been explored in AR positive metastatic TNBC. In single arm phase 2 clinical trials, bicalutamide use resulted in a six-month clinical benefit rate of 19% and a median PFS of 12 weeks (48). Abiraterone/prednisone demonstrated a 6-month clinical benefit rate of 20% and a median PFS of 2.8 months (49), but it didn't meet the hypothesis cut-off of clinical benefit of 25%. AR positivity in these studies was determined by protein expression >10% by IHC. The Enzalutamide study included patients with AR positive status defined as AR expression >0% and revealed a 16-week clinical benefit rate of 25%, median PFS of 2.9 months and a median OS of 12.5 months (50). Interestingly, patients with AR expression >10% had a 16-week clinical benefit rate of 33%, median PFS of 3.3 months and a median OS of 16.5 months suggesting an AR expression level dependent response; however, based on the study, AR expression by IHC was suboptimal as a predictive biomarker. Overall, the data suggests targeting AR might be beneficial in a selective niche of patients with metastatic TNBC and positive AR expression and warrants further study. Alternatively, combined targeting of AR and activated downstream signaling pathways are proposed to be more effective in this subgroup. Given that the LAR subtype has frequent *PIK3CA* mutations, there is potential to combine PI3K inhibition and AR antagonism in AR positive TNBC. Ongoing Phase I/II clinical trials are investigating enzalutamide plus alpelisib or taselisib, PI3K inhibitors, in patients with AR positive TNBCs (*Table 2*). In vitro and *in vivo* studies using LAR TNBC cell lines showed high sensitivity to CDK4/6 inhibitor (51). Accordingly, there is an ongoing clinical trial looking at combining ribociclib with bicalutamide in metastatic AR positive TNBCs (*Table 2*).

BRCA: the beginning to a world of targeting synthetic lethality

BRCA1 is a tumor suppressor gene involved in DNA damage repair of double strand breaks through homologous recombination (52). Women who inherit germline mutations

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Table 2 Selected clinical trials targeting AR in TNBC

Agent	Targets of therapy	Setting	Phase	Sample size	Completion date	Identifier
Ribociclib + bicalutamide	CDK4/6 + NSAA	Metastatic	Phase I/II	11	Sept 2021	NCT03090165
Bicalutamide	NSAA	Metastatic	Phase III	262	Dec 2020	NCT03055312
Enzalutamide	NSAA	Metastatic	Phase II	118	Mar 2021	NCT01889238
Darolutamide verses capecitabine	NSAA versus chemotherapy	Metastatic	Phase II	90	Sept 2021	NCT03383679
Taselisib + enzalutamide	NSAA + PI3Ki	Metastatic	Phase I/II	30	Dec 2020	NCT02457910
Alpelisib + enzalutamide	NSAA + PI3Ki	Metastatic	Phase I	28	Dec 2020	NCT03207529
Pembrolizumab + enobosarm	Anti-PD-1 + SARM	Metastatic	Phase II	29	Nov 2020	NCT02971761
CR1447 (4-OH-testosterone)	Steroidal AI	Metastatic	Phase II	90	Jun 2027	NCT02067741
Orteronel	Nonsteroidal CYP17A1 inhibitor	Metastatic	phase II	71	Dec 2020	NCT01990209

TNBC, triple negative breast cancer; NSAA, nonsteroidal antiandrogen; AR, androgen receptor; SARM, selective androgen receptor modulator; PI3Ki, PI3K inhibitor; AI, aromatase inhibitor.

in *BRCA1/ BRCA2* have increased risk of developing breast (50–80%) and ovarian cancer (40% *vs.* 20%, respectively) (53-55), with *BRCA2* carries likely at a higher risk of breast cancer (53,56). *BRCA1* mutation carriers predominantly develop basal subtype while *BRCA2* mutations are mostly associated with luminal B subtype (57-59). Germline mutations in *BRCA* genes are present in 10% of TNBC (55).

As a biomarker, *BRCA1/2* mutation status may influence treatment selection. Loss of *BRCA* results in homologous recombination deficiency (HRD) rendering cells sensitive to platinum chemotherapy as well as to inhibitors of the DNA repair enzyme poly-ADP ribose polymerase (PARP). In the TNT Trial, a phase III study in advanced TNBC patients, *BRCA* mutation carriers treated with carboplatin had a 2-fold increase in overall response rate as compared to those treated with docetaxel. This benefit was limited to *BRCA1* mutation carriers and was not observed in tumors with HRD or *BRCA1* methylation (60). Interestingly, the location of *BRCA* mutation may impact the level of HRD and sensitivity to platinum as well as PARP inhibitors in TNBC (61-63).

PARP inhibitors use the concept of synthetic lethality resulting from the inability of *BRCA* deficient cells to repair double strand breaks (DSBs) (64). PARP use base excision repair (BER) to repair DNA damage at the site of single strand breaks (SSBs). Inhibiting PARP results in accumulation of SSBs which stall the replication fork causing DSBs. In the absence of functional *BRCA*, DSBs accumulate causing cell death (64-66). Three major clinical trials showed efficacy of PARP inhibitors in metastatic TNBC in germline *BRCA* mutation carriers including phase III OLYMPIAD, EMBRACA, BROCADE3 (11,12,67). In OlympiAD, patients with *BRCA1/2* germline alteration were randomly assigned to receive olaparib or standard therapy with single-agent chemotherapy of physician's choice. Median PFS was significantly longer in the olaparib group than in the standard-therapy group (7.0 *vs.* 4.2 months, respectively). The response rate was 59.9% in the olaparib group and 28.8% in the control group. In EMBRACA, patients with advanced breast cancer and a germline *BRCA1/2* mutation were assigned to receive talazoparib or standard single-agent therapy of physician's choice (11). Median PFS was significantly improved in the talazoparib group than in the standard-therapy group (8.6 *vs.* 5.6 months, respectively) (11). The objective response rate was higher in the talazoparib group than in the standard-therapy group (62.6% *vs.* 27.2%) (11). In the BROCADE3 trial, adding veliparib to platinum doublet, with continuation as monotherapy if the doublet were discontinued, resulted in significant improvement in PFS in *BRCA* patients with advanced TNBCs (14.5 *vs.* 12.6 months) (67). Up to this point, PARP inhibitors did not show a statistically significant overall survival (OS) benefit for patients with metastatic breast cancer and mutations in the BRCA1/2 genes. Interestingly, PARP inhibitors may modulate the tumor microenvironment which may improve response to immunotherapy. As such, there are ongoing

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Table 3 Selected clinical trials of PARPi in TNBC

Agent	Targets of therapy	Setting	Phase	Sample size	Completion Date	Identifier
Olaparib + carboplatin/ paclitaxel	PARPi + chemotherapy	Metastatic	I	189	Dec 2020	NCT00516724
MEDI4736 + olaparib and/or cediranib	Anti-PD-L1 + PARPi + anti-VEGFR	Advanced	I/II	384	Dec 2022	NCT02484404
Olaparib + durvalumab	PARPi + anti-PD-L1	Metastatic	Phase II	28	Dec 2020	NCT03801369
Veliparib + cisplatin	PARPi + chemotherapy	Metastatic	Phase II	333	Oct 2021	NCT02595905
Talazoparib	PARPi	Recurrent/metastatic (no requirement for *BRCA* mutation)	Phase II	49	Jan 2022	NCT03901469
Talazoparib	PARPi	Metastatic	Phase II	40	Dec 2022	NCT02401347
Olaparib + onalespib	PARPi + anti-HSP90	Recurrent/refractory/ metastatic	Phase I	40	Dec 2020	NCT02898207
BKM120/BYL719 + olaparib	PI3Ki + PARPi	Recurrent/metastatic	Phase I	118	Dec 2020	NCT01623349

PARPi, poly ADP ribose polymerase inhibitor; TNBC, triple negative breast cancer; PD-L1, programmed death ligand-1; VEGFR, vascular endothelial growth factor receptor; HSP90, heat shock protein 90.

clinical trials investigating combined PARP inhibition and immunotherapy (*Table 3*) (68).

Homologous recombination deficiency (HRD): targeting HRD beyond BRCA

Homologous recombination (HR) is essential for genomic integrity. While the previously described mutations in *BRCA1/BRCA2* highlighted the connections between homologous recombination deficiency (HRD) and cancer predisposition, the term HRD is a broader entity that encompasses various mechanisms contributing to a "BRCAness" phenotype (64). This includes genetic inactivation of other components of the HR pathway at the germline or somatic level including *PALB2*, *BARD1*, *BRIP1*, *RAD51B*, *RAD51C*, *RAD51D*, ATM, *CHEK2* or mutations in non-HR gene mutations, such as *MSH6* and *PTEN* or epigenetic hypermethylation of *BRCA1*. The BRCAness feature is predictive of response to platinum-based chemotherapy and PARP inhibitors. Identifying assays that can predict BRCAness phenotype and corresponding response to platinum/PARP inhibitors has been the focus of several research studies. Genomic signatures, RAD51 foci and HRD scores have been considered as potential assays (69-72).

Genomic signatures have been previously described in breast, ovarian and pancreatic patients with BRCA1/2 mutations (69). Signature 3, a signature characterized by tandem genomic duplications, has been shown to be associated with HRD, *BRCA1/2* and *PALB2* mutations as well as *RAD51C* promotor methylation but not *ATM* or *CHEK2* mutations (73). Another assay is the HRD score, the sum of three metrics of chromosomal level aberration including loss of heterozygosity (LOH), telomeric allelic imbalance (TIA), and large-scale state transitions (LST). HRD score >42 and/or tumor *BRCA1/2* mutation identified tumors that respond to neoadjuvant platinum-containing chemotherapy in patients with TNBC (74). In a study that incorporated HRD score to identify BRCAness, the addition of velaparib to cisplatin significantly improved PFS and showed a trend towards improved OS for *BRCA*-like advanced TNBC (74). In addition, olaparib was shown to have activity in metastatic breast cancer patients with somatic *BRCA1/2* alterations and germline *PALB2* but not in patients with *ATM* and *CHEK2* alterations (75). *BRCA1* promoter hypermethylation represents another form of BRCAness. In an analysis of 237 early TNBC cases, 24.1% of TNBC patients were *BRCA1* hypermethylated which is more frequent than *BRCA* mutations (70). A higher frequency of *BRCA1* hypermethylation was noted in young patients and was associated with basal phenotype. However, in the TNT trial, *BRCA1* hypermethylation was not

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Table 4 Selected clinical trials targeting HRD in TNBC

Agent	Targets of therapy	Setting	Phase	Sample size	Completion Date	Identifier
HX008 + niraparib	Anti-PD-1 + PARPi	Metastatic	Phase II	44	Apr 2022	NCT04508803
AMXI-5001	Dual PARPi and microtubule polymerization inhibitor	Metastatic/advanced	Phase 1/II	80	Jan 2023	NCT04503265
Prexasertib	CHK1 inhibitor	Advanced	Phase II	50	Apr 2022	NCT02873975
Talazoparib	PARPi	Advanced	Phase II	40	Dec 2022	NCT02401347
Olaparib	PARPi	Metastatic	Phase II	39	Nov 2021	NCT03367689
High dose chemotherapy (carboplatin, thiotepa, and cyclophosphamide)	Chemotherapy	Metastatic	Phase III	74	Oct 2023	NCT01646034
IDX-1197	PARPi	Metastatic	Phase I/II	310	Mar 2023	NCT04174716
Olaparib + pembrolizumab	PARPi + anti-PD-1	Metastatic/advanced	Phase II	300	Dec 2023	NCT04123366
Niraparib + carboplatin	PARPi + chemotherapy	Advanced	Phase I	146	July 2022	NCT03209401
Olaparib	PARPi	Metastatic	Phase II	390	Feb 2024	NCT03742895

HRD, homologous recombination deficiency; TNBC, triple negative breast cancer; PARPi, poly ADP ribose polymerase inhibitor; PD-L1, programmed death ligand-1.

associated with response to platinum-based therapy (60). Identifying an optimal test that captures the BRCAness phenotype is the focus of ongoing research, as well as exploring the use of PARP inhibitors in metastatic TNBCs with alterations in the HR pathway (*Table 4*).

PI3K/AKT/MTOR pathway: time to tackle kinase world

The PI3K/AKT/mTOR kinases regulate key pathways essential to cell survival, proliferation and differentiation and are activated through different mechanisms in TNBC (76). *PIK3CA* mutations are associated with luminal cancers and the LAR subtype of TNBCs (7,26). In basal-like cancers, PI3K/AKT pathway activation is mediated through a different mechanism, i.e., loss of negative regulators of the PI3K pathway such as *PTEN* and *INPP4B* phosphatase (7,77,78). PTEN protein expression loss by IHC is significantly associated with large tumor size, high grade, recurrence and TNBC, as well as poorer prognosis (79) while INPP4B loss is associated with higher tumor grade and basal-like breast cancers (77). In mouse models, INPP4B loss led to dose-dependent increase in tumor incidence in *INPP4B* homozygous and heterozygous knockout mice compared to wild-type mice, supporting a role for *INPP4B* as a tumor suppressor in TNBC (78). Another mechanism of pathway activation includes mutations in the catalytic subunit of PI3K (p110α) which occur in about 10% of TNBC cases (7). Contrary to hormone receptor positive breast cancer, *PIK3CA* mutations in TNBCs are associated with improved survival (80).

The LOTUS trial is a phase II clinical trial including patients with treatment native metastatic TNBC who were randomized to paclitaxel plus either ipatasertib, oral ATP-competitive small molecule AKT inhibitor, or placebo. median OS (mOS) was 25.8 months in the ipatasertib plus paclitaxel arm *vs.* 16.9 months in the placebo plus paclitaxel (81). Interestingly, PTEN-low and PIK3CA/AKT1/PTEN altered subgroups had better OS in ipatasertib plus paclitaxel group (81). This, however, did not translate to a meaningful benefit in phase III IPATunity130 that randomized patients with advanced TNBC and alterations in the PIK3CA/AKT1/PTEN pathway to ipatasertib plus paclitaxel verses placebo plus paclitaxel. There was similar overall response rate between the ipatasertib plus paclitaxel verses placebo plus paclitaxel arms (39% *vs.* 35%, respectively). At a median follow-up of 8.3 months, PFS was similar between the experimental and placebo arms (7.4 *vs.* 6.1 months, respectively) (82). This suggests there is likely redundant downstream signaling that bypasses AKT mediated inhibition. This is pending further analysis to explore potential biomarkers of benefit from ipatasertib in this trial. Interestingly, addition of ipatasertib to atezolizumab and

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chemotherapy (paclitaxel or nab-paclitaxel) in 26 patients with advanced TNBC had an objective response rate of 73% seen regardless of PD-L1 or PIK3CA/AKT/PTEN pathway alteration status (83), suggesting a promising trend toward combining targeted therapies in TNBC.

Another phase II trial, the PAKT trial, investigated capivasertib, an oral AKT inhibitor, with paclitaxel versus paclitaxel alone as first-line treatment of metastatic TNBC. With capivasertib, PFS improved (5.9 *vs.* 4.2 months, respectively) and in patients with *PIK3CA/AKT1/PTEN* alterations, this benefit was prominent (PFS, 9.3 *vs.* 3.7 months, respectively) (84). An improvement in median OS was seen in the entire population (19.1 *vs.* 12.6 months) (84). A better understanding of the redundancy in the pathway and the main downstream drivers is required to drive precision medicine. Clinical trials are currently ongoing to evaluate PI3K/AKT/mTOR inhibitors in treating TNBC (*Table 2*).

Immunotherapy and tumor microenvironment: a world of hot and cold and all in-between

The advent of immunotherapy to the realm of metastatic TNBC treatment has triggered interest in identifying biomarkers of response. Compared to other breast cancer subtypes, TNBC has an immune rich tumor microenvironment characterized by tumor infiltrating lymphocytes (TILs), expression of immune markers including programmed death-ligand 1 (PD-L1) and high tumor mutational burden (TMB) (85).

PD-L1 is a cell membrane protein expressed on tumor cells and immune cells (IC). PD-L1 binds to PD-1 on T cells to inhibit their antitumor function (86). Immune checkpoint inhibitors (ICIs), including anti-PD-L1/anti-PD-1 release the inhibition on T cells thereby activating the immune system to attack cancer cells. Currently, PD-L1 is approved as a biomarker for selection of patients who are most likely to benefit from immunotherapy in metastatic TNBC based on findings from the IMpassion130 trial for atezolizumab and nab-paclitaxel use, as well as Keynote-355 for pembrolizumab plus chemotherapy (9,10,87).

In examining the prognostic value of PD-L1 expression by IHC, there are mixed results depending on type of assay, differential expression of PD-L1 on tumor verses immune cells, in addition to differential expression of PD-L1 in early verses metastatic settings as well as differential expression by site of metastases (88). In a systematic review and meta-analysis of PD-L1 expression from five studies, four of which included early-stage breast cancer, encompassing a total of 2,546 breast cancers, Zhang *et al.* showed PD-L1 positivity is in the range 21–56%. PD-L1 expression was associated with positive lymph node metastasis, higher histological grade, estrogen receptor negativity, and TNBC (89). In another systematic review and meta-analysis of PD-L1 expression in breast cancer, PD-L1 positivity rate was 24% in tumor cells, 33% in immune cells and 25% in both with highest PDL-L1 expression in TNBC. PD-L1 expression in breast tumors was associated with shorter DFS and OS. However, in TNBC subtype, PD-L1 expression in immune cells was associated with improved DFS and OS. In a study examining PD-L1 expression by IHC using SP142 antibody in 223 TNBC cases and assessed in tumor cells (TC) as well as tumor-infiltrating lymphocytes (TILs), PD-L1 expression was detected in both tumor cells and TILs at a level of 8.5% and 25.1% respectively (90). PD-L1 expression on TILs but not tumor cells was associated with a poor outcome (90). Overall, the data suggests PD-L1 expression is higher in TNBC and in the immune cell compartment, and the data for prognosis is heterogeneous. The use of different antibodies has contributed to the complexity.

PDL-1 is predictive of response to immunotherapy based on the clinical trials (*Tables 5,6*). In IMpassion 130, patients with untreated metastatic TNBC cancer were randomized to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel (9,87). Forty percent of the tumors were PD-L1 positive. While there was no significant difference in OS between the two groups in the intent-to-treat (ITT) analysis (mOS of 21 months in the atezolizumab plus nab-paclitaxel versus 18.7 months in the placebo plus paclitaxel), in the PD-L1 positive population, median OS was longer with atezolizumab plus nab-paclitaxel versus placebo plus nab-paclitaxel at 25.4 and 17.9 months, (stratified HR 0.71, 0.54–0.94), respectively (9,87). In Keynote-355 trial, patients with untreated metastatic TNBC cancer were randomized to receive pembrolizumab plus chemotherapy versus placebo plus chemotherapy (10). Among 847 patients, 25% had PD-L1 CPS <1, 75% had PD-L1 CPS of ≥1 or more, and 38% had PD-L1 CPS of ≥10 (10). Among patients with CPS ≥10, mPFS was statistically significantly higher in the pembrolizumab plus chemotherapy group compared to placebo plus chemotherapy (9.7 *vs.* 5.6 months, respectively). mPFS was not significant among patients with CPS of ≥1 (7.6 *vs.* 5.6 months, respectively). The data indicated treatment response is PD-L1 expression dependant, and OS data is yet to be reported (10).

There is a technical component to assessing PD-L1 expression status in these trials. PD-L1 positivity was

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Table 5 Selected clinical trials of immunotherapy in TNBC

Agent	Targets of therapy	Setting	Phase	Sample size	Completion data	Identifier
Avelumab	Anti-PD-L1	Metastatic	Phase II	620	Feb 2024	NCT02554812
Atezolizumab + BDB001 + RT	Anti-PD-L1 + TLR agonist	Metastatic	Phase II	247	Jan 2025	NCT03915678
Atezolizumab	Anti-PD-L1	Metastatic	Phase II	200	Oct 2024	NCT04273061
Nivolumab + bicalutamide + ipilimumab	Anti-PD-1+ AR antagonist+ anti-CTLA4	Metastatic	Phase II	138	Apr 2025	NCT03650894
Nivolumab + eribulin	Anti-PD-L1 + chemotherapy	Metastatic	Phase I/II	90	Sep 2021	NCT04061863
PVX-410 vaccine+ pembrolizumab in HLA-A2 positive patients	Vaccine + anti-PD-1	Metastatic	Phase I	20	Dec 2024	NCT03362060
Pembrolizumab + olaparib	Anti-PD-1 + PARPi	Metastatic	Phase I	20	Nov 2025	NCT03025035
Durvalumab + tremelimumab + metronomic vinorelbine	Anti-PD-L1 + anti-CTLA4 + chemotherapy	Metastatic	Phase I/II	150	Dec 2024	NCT03518606
Avelumab + binimetinib, utomilumab, or anti-OX40 antibody	Anti-PD-L1 + MEK 1/2 inhibitor, CD 137 agonist or anti-OX40	Metastatic	Phase II	150	July 2021	NCT03971409
Cryoablation + atezolizumab + nab-paclitaxel	Anti-PD-L1 + chemotherapy	Advanced/ metastatic	Phase I	5	Dec 2020	NCT04249167
Atezolizumab in different combinations	Anti-PD-L1 in different combinations, including chemotherapy, ADC, anti-CD40, anti-IL6R, anti-VEGFA, anti-AKT inhibitor	Metastatic	Phase 1/II	280	Jan 2022	NCT03424005
Spartalizumab + LAG525 in combination with NIR178, capmatinib, MCS110, or canakinumab	Anti-PD-1 + anti-LAG-3 in combination with anti- adenosine A2A receptor, anti-Met receptor, anti-CSF-1 or anti-IL1β	Advanced/ metastatic	Phase I	220	Jan 2022	NCT03742349

PD-L1, programmed death ligand-1; PD-1, programmed death receptor-1; TLR, Toll-like receptor; CTLA4, cytotoxic T-lymphocyte-associated protein 4; MEK1/2, mitogen activated protein kinases; PARPi, poly ADP ribose polymerase inhibitor; ADC, antibody drug conjugate.

defined by PD-L1 expression in immune cells using the Ventana SP142 IHC assay in the IMpassion130 (9,87). Whereas PD-L1 positivity was determined by the combined positive score (CPS) defined as the ratio of PD-L1 expressing cells (tumor cells, lymphocytes and macrophages) to the number of all tumor cells, using the DAKO PD-L1 22C3 IHC assay in Keynote-355 (10). Of note, these assays identified different percentages of PD-L1 positive cases and antibodies are not interchangeable.

Furthermore, genomic analysis of 641 TNBCs identified PD-L1 amplification (3%), TMB of ≥10 mutations/ Megabase mut(mb) (9%), MSI - high (0.4%) in addition to positive PD - L1 staining of ICs (47%) as potential markers of benefit to ICIs whereas inactivating *STK11* mutations (2%) and *MDM2* amplification (3%) confer resistance to ICI (85). High levels of TILs appear to have a better prognosis in TNBC patients (97). High TIL expression correlates with PD-L1 in the tumor microenvironment (97). TILs, PD-L1 along with other biomarkers for ICIs, such as TMB, PD-L1 gene expression, neoantigen burden, T-regulatory cells, myeloid-derived suppressor cells, immune signatures, gut microbiome represent complex interactions of the immune system, host and the tumor. In fact, 36 different variables of response to immune checkpoint inhibitors have been identified across tumor types with CD8-T-cells abundance, TMB and high PD-1 gene expression being most predictive

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Table 6 Key clinical trials of immunotherapy in metastatic TNBC

PD-1/PD-L1 Inhibitors	Phase	Indication	Regimen	PD-L1 Assay	PD-L1 Cuttoff	Overall PD-L1 expression level	Results	References
Pembrolizumab, N=32	Phase 1	Heavily pretreated	Pembrolizumat 10 mg/kg IV q2 weeks	PD-L1 IHC 22C3pharmDx assay	PD-L1 in the stroma or ≥1% of tumor cells	111 patients were screened for the trial and 58.6% had positive PD-L1 status	ORR, 18.5% (6.3–38.1%); mPFS, 1.9 (1.7–5.5) months; mOS, 11.2 (5.3–NR) months	Keynote-012 (91)
Pembrolizumab, N=170	Phase II	Second line or later line	Pembrolizumab 200 mg IV q3 weeks	PD-L1 IHC 22C3pharmDx assay	CPS ≥1	61.8% had PD-L1 positive status	Data analysis on PD-L1 positive *vs.* overall population; ORR, 5.7% (2.4–12.2%) *vs.* 5.3% (2.7–9.9%); mPFS, 2.0 (1.9–2.1) *vs.* 2.0 (1.9–2.0) months; mOS, 8.8 (7.1–11.2) *vs.* 9.0 (7.6–11.2) months	Keynote-086, cohort A (92)
Pembrolizumab, N=84	Phase II	First line	Pembrolizumat 200 mg IV q3 weeks	PD-L1 IHC 22C3pharmDx assay	CPS ≥1	61.8% had PD-L1 positive status	ORR, 21.4% (13.9–31.4%); mPFS, 2.1 (2.0–2.2) months; mOS, 18.0 (12.9–23.0) months	Keynote-086, cohort B (93)
Pembrolizumab verses chemotherapy, N=622	Phase III	Second line or later line	Pembrolizumab 200 mg IV q3 weeks	PD-L1 IHC 22C3pharmDx assay	CPS ≥1	65% had PD-L1 CPS of ≥1, 31% had PD-L1 CPS ≥10, and 18% had PD-L1 CPS ≥20	Data analysis on PD-L1 CPS ≥10 cases *vs.* PD-L1 CPS ≥1 case *vs.* overall population *vs.* control arm: ORR, 17.7% (10.7–26.8%) *vs.* 12.3% (8.1–17.6%) *vs.* 9.6% (6.6–13.4%) *vs.* 10.6% (7.4–14.6%); mPFS, 2.1 (2.0–2.5) *vs.* 2.1 (2.0–2.1) *vs.* 2.1 (2.0–2.1) *vs.* 3.3 (2.7–4.0) months; mOS, 12.7 (9.9–16.3) *vs.* 10.7 (9.3–12.5) vs 9.9 (8.3–11.4) vs 10.8 (9.1–12.6) months	Keynote-119(94)
Atezolizumab + nab-paclitaxel, N=33	Phase 1	0 to 2 lines of prior chemotherapy	Atezolizumab IV 800 mg on days 1 and 15 of each cycle q2 weeks and nab-Paclitaxel, 125 mg/m^2, on days 1, 8, and 15 of each cycle (3 weeks on, 1 week off)	Roche Ventana SP142	Exploratory analysis on PD-L1 IC ≥1	PD-L1 expression was more frequent on immune cells (50%) compared with tumor cells (17%)	Data analysis on PD-L1 positive cases verses overall population: ORR, 41.7% (15.2–72.3%) *vs.* 39.4 (22.9–57.9%); mPFS, 6.9 (5.2–11.0) *vs.* 5.5 (5.1–7.7) months; mOS, 21.9 (13.1–NE) *vs.* 14.7 (10.1–NE) months	(95)
Atezolizumab +nab-paclitaxel verses chemotherapy, N=902	Phase III	First line	Atezolizumab IV 840 mg on days 1 and 15 of each cycle q2 weeks and nab-paclitaxel, 100 mg/m^2, on days 1, 8, and 15 of each cycle (3 weeks on, 1 week off)	Roche Ventana SP142	IC≥1%	40.9% had PD-L1 positive status	Data analysis on PD-L1 IC ≥1 case *vs.* overall population *vs.* control arm: ORR, 58.9% (51.5–66.1%) *vs.* 56% (51.3–60.6%) *vs.* 45.9% (41.2–50.6%); mPFS, 7.5 (6.7–9.2) *vs.* 7.2 (5.6–7.5) *vs.* 5.5 (5.3–5.6) months; mOS, 25 (19.5–30.7) *vs.* 21 (19–22.6) *vs.* 18.7 (16.9–20.3) months	IMpassion130 (9,87)

Table 6 (*continued*)

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Table 6 (*continued*)

PD-1/PD-L1 Inhibitors	Phase	Indication	Regimen	PD-L1 Assay	PD-L1 Cuttoff	Overall PD-L1 expression level	Results	References
Atezolizumab + paclitaxel verses placebo plus paclitaxel, N=651	Phase III	First line	Atezolizumab IV 840 mg on days 1 and 15 of each cycle q2 weeks and paclitaxel, 90 mg/m^2, on days 1, 8, and 15 of each cycle (3 weeks on, 1 week off)	Roche Ventana SP142	IC ≥1%	44.7% had PD-L1 positive status	Data analysis on PD-L1 IC ≥1 case *vs.* overall population *vs.* control arm: ORR, 63.5% *vs.* 53.6% *vs.* 47.5%; mPFS, 7.5 (6.7–9.2) *vs.* 7.2 (5.6–7.5) *vs.* 5.5 (5.3–5.6) months; mOS, 22.1 *vs.* 19.2 *vs.* 22.8 months	IMpassion131 (96)
Pembrolizumab with chemotherapy verses chemotherapy, N=847	Phase III	First line	Pembrolizumab 200 mg IV q3 weeks plus chemotherapy (nab-paclitaxel; paclitaxel; or gemcitabine plus carboplatin) or placebo plus chemotherapy	PD-L1 IHC 22C3 pharmDx	CPS ≥1	75% had PD-L1 CPS ≥1 and 38% had PD-L1 CPS ≥10	Data analysis on CPS ≥10 cases *vs.* CPS ≥1 case vs control arm; interim analysis: mPFS 9.7 *vs.* 7.6 *vs.* 5.6 months	Keynote-355 (10)

ORR, overall response rate; mPFS, median progression free survival; mOS, median overall survival; CPS, composite positive score; PD-L1, programmed death ligand-1; IHC, immunohistochemistry; IC, immune cells.

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Table 7 Selected clinical trials of ADCs in TNBC

Agent	Targets of therapy	Setting	Phase	Sample size	Completion date	Identifier
SGN-LIV1A (Ladiratuzumab Vedotin)	ADC	Metastatic	Phase I/II	418	Mar 2022	NCT01969643
Sacituzumab govitecan + talazoparib	ADC + PARPi	Metastatic	Phase I/II	65	Aug 2024	NCT04039230
DS-8201a (Trastuzumab Deruxtecan)	Anti-HER2 ADC	Metastatic	Phase II	162	Apr 2026	NCT04132960

ADC, antibody drug conjugate; PARPi, poly ADP ribose polymerase inhibitor; HER2, human epidermal growth factor receptor 2.

of response to anti-PD-1/PD-L1 therapy (98). Therefore, there's no one size fits all to predict response to immune checkpoint inhibition and likely a tailored approach to patient's immunome may be necessary.

ADC: time for loaded guns

ADCs are multiagent drugs aimed at tumor targeted delivery of therapeutic small molecules and have shown promising results in TNBC. ADCs include three agents: an antibody directed to a tumor antigen, a cytotoxic molecule, and a linker in between (14). Sacituzumab govitecan is an anti-trophoblast cell-surface antigen (Trop-2) antibody conjugated to a DNA damaging agent, SN-38, via a pH-sensitive cleavable linker. Elevated expression of Trop-2 in breast cancer is correlated with poor prognosis (14). In a single-arm phase I/II study, 108 patients with metastatic TNBC treated with at least two prior therapies received sacituzumab govitecan with objective response rate (ORR) of 33.3%, median PFS of 5.5 months and median OS of 13.0 months regardless of Trop-2 expression in tumors (14). In a phase III trial, the study compared sacituzumab govitecan with single-agent chemotherapy in 468 patients with relapsed/refractory TNBC. Median PFS was significantly longer with sacituzumab govitecan versus control group (5.6 *vs.* 1.7 months, respectively). Median OS was 12.1 months with sacituzumab govitecan compared to 6.7 months with chemotherapy and objective response rates were 35% and 5%, respectively (15). Side effect profile is similar to other chemotherapy drugs and include but are not limited to neutropenia, anemia, GI symptoms such as nausea, diarrhea as well alopecia and fatigue. Common grade 3 or 4 toxicities included neutropenia, diarrhea, anemia. This led to accelerated approval by FDA for adult patients with metastatic TNBC who had received at least two prior therapies. Another ADC, Ladiratuzumab vedotin, is a humanized antibody targeting the zinc transporter LIV-1 conjugated with a microtubule-disrupting agent, monomethyl auristatin E (MMAE) by a proteolytically cleavable linker. LIV-1 is a multi-span transmembrane protein with putative zinc transporter and metalloproteinase activity expressed in 68% of metastatic TNBC tumors (99). Interim results of the phase I study showed promising clinical activity of ladiratuzumab vedotin with key adverse events including GI symptoms, neutropenia and peripheral neuropathy (100). Trastuzumab deruxtecan, a humanized antibody against HER2 conjugated with a topoisomerase I inhibitor, extecan derivative (DXd) by a cleavable peptide linker, has shown activity in low HER2 (IHC 1+ or 2+/ISH negative) expressing metastatic breast cancer (101) and is currently under further investigation. Ongoing clinical trials with ADCs in metastatic TNBC are outlined in *Table* 7.

Conclusions

While the identification of multiple molecular subtypes of TNBC and the characterization of their unique tumor microenvironments have increased our knowledge and understanding of TNBC, the application of these findings has not yet been adapted in the clinical setting. The median overall survival of metastatic TNBC has improved from 12 months to around 24 months as seen in clinical trials due to the availability of more lines of treatment for this subtype. Although PARP inhibitors and immune checkpoint inhibitors have been recently integrated into the therapeutic arsenal, cytotoxic chemotherapy remains the backbone of therapy of TNBC.

Current research is focused on identifying biomarkers that may potentially serve as therapeutic targets, prognostic markers, or predictors of therapeutic response. Several promising markers have been described, but there still remains a need for further validation in prospective clinical studies. Identifying a gene signature panel that can

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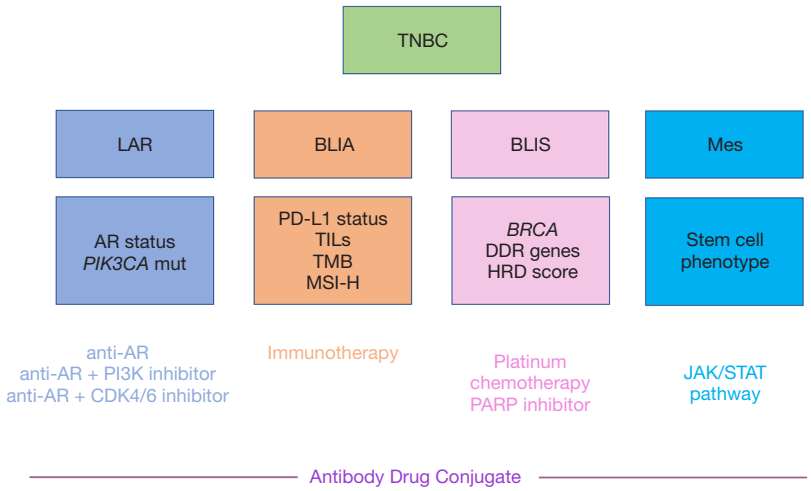

Figure 1 Biomarker-driven targeted therapies in metastatic triple negative breast cancer (TNBC). At the transcriptional level, TNBC is largely subclassified into four types with potential for targeted therapies. These subtypes include: luminal androgen receptor (LAR), basal-like immune suppressed (BLIS), basal-like immune activated (BLIA), and mesenchymal (MES). At this time, transcriptional analysis of tumours is not readily available in the clinic; however, identifying TNBC subtypes is available through various tests that would help guide management in the metastatic setting. AR testing through IHC and *PIK3CA* mutational status can classify LAR subtype. This in turn can identify a niche of patients who would benefit from AR antagonists or a combination of AR antagonists with either PI3K inhibitor in patients who harbor *PIK3CA* mutations or alternatively CDK4/6 inhibitor. For BLIA subtype, identifying PD-L1 status by IHC is available to select patients who would benefit from immunotherapy. There are a number of other tests that can determine response to immunotherapy. This includes identification of TILs by IHC, identification of tumour mutational burden (TMB) by next-generation sequencing (NGS) and/or identification of microsatellite instability (MSI-H) based on IHC of MMR protein expression (MLH1, MSH2, MHS6 and PMS2). For the BLIS subtype, identifying homologous recombination deficiency (HRD) or BRCAness phenotype which is the hallmark of response to platinum-based chemotherapy and PARP inhibitors can be done through different modalities. This includes testing for *BRCA* germline and somatic mutations as well as testing for mutations in genes involved in the DNA damage response pathway (DDR). Testing for *BRCA1* hypermethylation is also another option. The HRD score is NGS based and is unweighted sum of loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST) that can be done on DNA extracted from formalin-fixed paraffin-embedded (FFPE) or frozen tumors samples. HRD is defined as high HRD score (above the HRD threshold, ≥42). For the mesenchymal subtype, there are no current active targeted therapies; future studies would look into characterizing cancer stem cells (CSCs) and possible targeting of the JAK-STAT pathway which was previously identified to be enriched in this subtype. Antibody dug conjugates (ADCs) are new multidrug targeted agents that have shown promise in metastatic TNBC, including sacituzumab govitecan which has been FDA approved for patients who had received at least two prior therapies.

subclassify TNBCs into their respective subtypes would help personalize therapeutic targets. Meanwhile there is a potential to identify the four common TNBC subtypes classified based on gene expression through various established tests that would help guide management in the metastatic setting (*Figure 1*). AR testing through IHC and *PIK3CA* mutational status can classify LAR subtype. This, in turn, would identify a niche of patients who would benefit from AR antagonists alone or in combination with PI3K inhibitor in patients who harbor *PIK3CA* mutations to overcome the redundancy in the pathway or alternatively CDK4/6 inhibitor. In the immune activated subtype, using PD-L1 status by IHC selects patients who would benefit from immunotherapy with the caveat that PD-L1 antibody tests are not interchangeable and may not be depictive of the true population that would mostly benefit for ICI. Biomarkers of response to ICI under investigation include TILs, TMB and MSI-H. There is also interest in understanding the tumor microenvironment and turning immunologically cold tumors into hot ones that can respond to immunotherapy. For the basal immunosuppressed subtype, characterized by genomic instability, identifying

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BRCAness phenotype in addition to *BRCA1/2* mutations would help inform the response to platinum-based chemotherapy and PARP inhibitors, taking into account that certain mutations, such as *ATM* and *CHEK2* don't respond to these treatments. Expanding the tests to include somatic *BRCA1/2* mutations, *BRCA1* methylation status and HRD score have potential for a broader selection of tumors with BRCAness phenotype. For the mesenchymal subtype, there are no current actionable targeted therapies; future studies would look into characterizing cancer stem cells (CSCs) and possible targeting of driver pathways, such as the JAK-STAT pathway. The advent of ADCs has opened a world of multi-drug targeted therapies in heavily treated metastatic TNBC awaiting more combination drugs in clinical trials.

To sum it up, as we head toward more personalized treatments in TNBCs, there is a need to manage the heterogeneity of the disease with finesse; that would require a multi-modal arsenal of biomarker driven targets. More importantly, a uniform and accessible panel of biomarkers is warranted to allow for wider universal adoption.

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