Novel Agents for Metastatic Triple-Negative Breast Cancer: Finding the Positive in the Negative

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ABSTRACT

Metastatic triple-negative breast cancer (TNBC) is associated with a poor prognosis, and the development of better therapeutics represents a major unmet clinical need. Although the mainstay of treatment of metastatic TNBC is chemotherapy, advances in genomics and molecular profiling have helped better define subtypes of TNBC with distinct biologic drivers to guide the therapeutic development of targeted therapies, including AKT inhibitors for PI3K/AKT-altered TNBC, checkpoint inhibitors for PD-L1–positive TNBC, and PARP inhibitors for *BRCA1/2* mutant TNBC. This progress may ultimately convert TNBC from a disease traditionally defined by the absence of therapeutically actionable receptors to one that is defined by the presence of discrete molecular targets with therapeutic implications. Furthermore, antibody drug conjugates have emerged as an important therapeutic strategy to target genomically complex tumors that lack actionable oncogenes but have overexpressed actionable surface receptors such as trop-2. In this article, we discuss promising novel agents for advanced TNBC, some of which have been incorporated into current clinical practice, and others that will likely change the therapeutic landscape and redefine the TNBC terminology in the near future.

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Triple-negative breast cancer (TNBC), conventionally defined as breast cancer that does not express the estrogen receptor, progesterone receptor, and HER2, accounts for approximately twenty percent of breast cancer.[1] TNBC often presents in an aggressive manner, with advanced stage at diagnosis in many cases, and a propensity for the development of distant metastases.[2] Median overall survival (OS) for metastatic TNBC (mTNBC) is 15 months.[3]

Although the mainstay of treatment of mTNBC is chemotherapy,[4–8] novel agents are being developed, and some of these agents have been incorporated into clinical practice. This review addresses the molecular heterogeneity of TNBC and discusses novel agents for mTNBC (Table 1).

Molecular Heterogeneity of TNBC

Genomic analyses have demonstrated that TNBC is a heterogeneous disease. Molecular profiling has classified TNBC into biologically relevant subtypes with molecular targets.

Lehmann et al[9] described 6 discrete subtypes of TNBC based on gene expression profiling: basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR). Each of these subtypes displays different but overlapping clinicopathologic characteristics, heterogenous mutational profiles, and genomic instability. More recently, Burstein et al[10] simplified the TNBC classification into 4 distinct subtypes, based on RNA- and DNA-based analyses, given that the previously defined IM and MSL subtypes were attributed in large part to lymphocytes and stromal cells in the bulk sequencing. In the revised classification, subtypes included (1) LAR, characterized by the presence of the androgen receptor and mutations in *PI3KCA* and *AKT1*, and biologically similar to the luminal estrogen receptor subtype; (2) mesenchymal, demonstrating expression of mesenchymal genes such as *IGF-1*, *c-kit*, and *prostaglandin F*; (3) basal-like immunosuppressed (BLIS), defined by the presence of SOX transcription factors and *VTCN1*; and (4) basal-like immune-activated (BLIA), demonstrating cytokine expression. Although the subtype classification can have prognostic implications, with the worst prognosis seen in BLIS tumors, and LAR subtype

Table 1. Summary of Novel Therapeutic Agents in Development for Advanced TNBC

Therapeutic Agent	Target	Key Efficacy Results	Main Toxicity	Phase III Clinical Trial[a]
Targeting oncogenes				
Olaparib	PARP inhibition	OlympiAD trial[15]: PFS, 7.0 mo (olaparib) vs 4.2 mo (chemotherapy)	Anemia thrombocytopenia gastrointestinal toxicity	OlympiAD trial completed with FDA approval of olaparib
Talazoparib	PARP inhibition	EMBRACA trial[16]: PFS, 8.6 mo (talazoparib) vs 5.6 mo (chemotherapy)	Anemia Thrombocytopenia gastrointestinal toxicity	EMBRACA trial completed with FDA approval of talazoparib
Veliparib in combination with carboplatin and paclitaxel	PARP inhibition	BROCADE 3 trial[18]: median PFS, 14.5 mo with veliparib compared with 12.6 mo with chemotherapy alone; 3-year PFS rate of 26% with veliparib vs 11% with chemotherapy alone	Myelosuppression	BROCADE 3 trial completed
Targeting key intracellular signaling pathways				
Ipatasertib	AKT inhibition	LOTUS trial[25]: PFS, 6.2 mo (ipatasertib) vs 4.9 mo (paclitaxel); PTEN low tumors: PFS, 6.2 mo (ipatasertib) vs 3.7 mo (paclitaxel)	Diarrhea Neutropenia	Ongoing phase III study (IPATunity130)[26]
Capivasertib	AKT inhibition	PAKT trial[27]: PFS, 5.9 mo (capivasertib) vs 4.2 mo (paclitaxel); PIK3CA/AKT1/PTEN mutant: PFS, 9.3 mo (capivasertib) vs 3.7 mo (paclitaxel)	Diarrhea Infection Rash Fatigue	Ongoing phase III study (Capltello290; ClinicalTrials.gov identifier: NCT03997123)
Bicalutamide	Androgen receptor inhibitor	Phase II trial[30]: CBR, 19%, median PFS, 12 wk	Fatigue Hot flashes Edema Elevated transaminases	
Enzalutamide	Androgen receptor inhibitor	Phase II trial[31]: CBR, 25%, median PFS, 2.9 mo	Fatigue Nausea Decreased appetite Gastrointestinal toxicity	
Targeting cell-surface markers for selective delivery of potent agents				
Sacituzumab govitecan	ADC targeting trop-2	Phase I/II study[33]: PFS, 5.5 mo; OS, 13 mo	Myelosuppression Gastrointestinal toxicity Fatigue Electrolyte abnormalities Skin changes Infection	FDA approval of sacituzumab govitecan Ongoing phase III study (ASCENT)[35]
Ladiratuzumab	ADC targeting LIV-1	Phase I study (ClinicalTrials.gov identifier: NCT03310957): ORR 32%	Fatigue Nausea Neuropathy Alopecia Decreased appetite Gastrointestinal toxicity Myelosuppression	
Targeting immune microenvironment				
Pembrolizumab	PD-1 inhibition	Phase I study[42]: response rate 18.5% in PD-L1–positive TNBC; phase III KEYNOTE-119 study[44] of pembrolizumab vs chemotherapy with no significant improvement in OS in overall population, but trend toward improved efficacy with greater PD-L1 enrichment; phase III KEYNOTE-355 study (ClinicalTrials.gov identifier: NCT04177108) of pembrolizumab and chemotherapy vs chemotherapy alone with improved PFS in pembrolizumab and chemotherapy arm	Fatigue Gastrointestinal toxicity Myelosuppression Alopecia Hypothyroidism Hyperthyroidism Pneumonitis Skin reactions Adrenal insufficiency	Phase III KEYNOTE 119 study completed; phase III KEYNOTE-355 study with initial results

(continued on next page)

Table 1. Summary of Novel Therapeutic Agents in Development for Advanced TNBC (cont.)

Therapeutic Agent	Target	Key Efficacy Results	Main Toxicity	Phase III Clinical Trial[a]
Targeting immune microenvironment (cont.)				
Atezolizumab	PD-L1 inhibition	Phase I study[43]: ORR 24%; phase III IMpassion130 OS with atezolizumab/nab-paclitaxel[48] of 25.0 mo vs nab-paclitaxel alone 18.0 mo (PD-L1–positive TNBC cohort)	Alopecia Nausea Cough Peripheral neuropathy Neutropenia Pyrexia Hypothyroidism	Phase III IMpassion130 study completed with FDA approval of atezolizumab/nab-paclitaxel for PD-L1–positive TNBC
Durvalumab maintenance therapy	PD-L1 inhibition	Phase II study[50] of durvalumab vs chemotherapy after 6–8 cycles of chemotherapy: OS with durvalumab 21 mo vs 14 mo with chemotherapy in TNBC	Higher rates of serious adverse events with durvalumab than chemotherapy (8.5% vs 1.6%)	
Other				
Oral paclitaxel with encequidar	Oral taxane	Phase III study[52]: response rate 40% with oral paclitaxel/encequidar vs 25.6% with paclitaxel	Neutropenia Infection Gastrointestinal toxicity	Phase III trial completed
Liporaxel	Oral taxane	Phase II study (OPTIMAL; ClinicalTrials.gov identifier: NCT03952325): ORR 44% in TNBC; ongoing phase II trial[53] comparing liporaxel with intravenous paclitaxel in US patients	Myelosuppression Neuropathy	
Tesetaxel	Oral taxane	Phase II studies with single agent[54] and immunotherapy[55]	Myelosuppression Neuropathy	
Trilaciclib	CDK 4/6 inhibitor	Phase II study of trilaciclib and chemotherapy vs chemotherapy alone[56]: improved OS with trilaciclib	Myelosuppression Nausea	

Abbreviations: ADC, antibody–drug conjugate; CBR, clinical benefit rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TNBC, triple-negative breast cancer.
[a]If results available or ongoing.

associated with more indolent features, it does not have predictive implications or clinical utility, and therefore is not used in clinical decision-making. Based on single-cell RNA sequencing, multiple subpopulations within primary TNBC tumors were identified, suggesting that molecular signatures identified through bulk sequencing may not accurately capture the biology of TNBC tumors.[11]

Although the classifications of TNBC may differ based on the methodology and classification used, clinically the identification of molecular targets in TNBC is most relevant, because this transforms TNBC into potentially actionable disease subsets. Broadly speaking, the actionable targets in mTNBC can be divided into (1) targeting genomic mutations and key intracellular signaling pathways, (2) targeting cell-surface markers for selective delivery of potent agents, and (3) targeting the immune microenvironment, as depicted in Figure 1.

Targeting Genomic Mutations and Key Intracellular Signaling Pathways

PARP Inhibition Targeting *BRCA1/2* Mutant Cancer

Germline mutations in *BRCA1/2* are present in 5% to 10% of breast cancer,[12] and often in association with TNBC.[13] The current recommendation for mTNBC is to evaluate for a germline *BRCA1/2* mutation based on the recent approval of 2 PARP inhibitors for the treatment of patients with advanced breast cancer with deleterious (pathogenic) germline *BRCA1/2* mutations. PARP1 and 2 are involved in the cellular response to single-strand DNA breaks.[14] DNA lesions caused by PARP inhibition may be repaired through homologous recombination, a pathway mediated by *BRCA1/2*. In vitro, cells deficient in *BRCA1/2* are sensitive to PARP inhibition, via synthetic lethality by which they cannot repair DNA damage via PARP,[14] providing support for investigating PARP inhibitors in advanced breast cancer.

In the phase III OlympiAD trial, a significant improvement in progression-free survival (PFS) was seen in patients with HER2-negative advanced breast cancer with germline *BRCA1/2* mutations treated with olaparib, a PARP inhibitor, versus chemotherapy (PFS, 7.0 vs 4.2 months; hazard ratio [HR], 0.58; $P<.001$),[15] leading to FDA approval of olaparib. In the EMBRACA study, in which patients with advanced breast cancer and germline *BRCA1/2* mutations received talazoparib, another PARP inhibitor with higher potency than olaparib, or

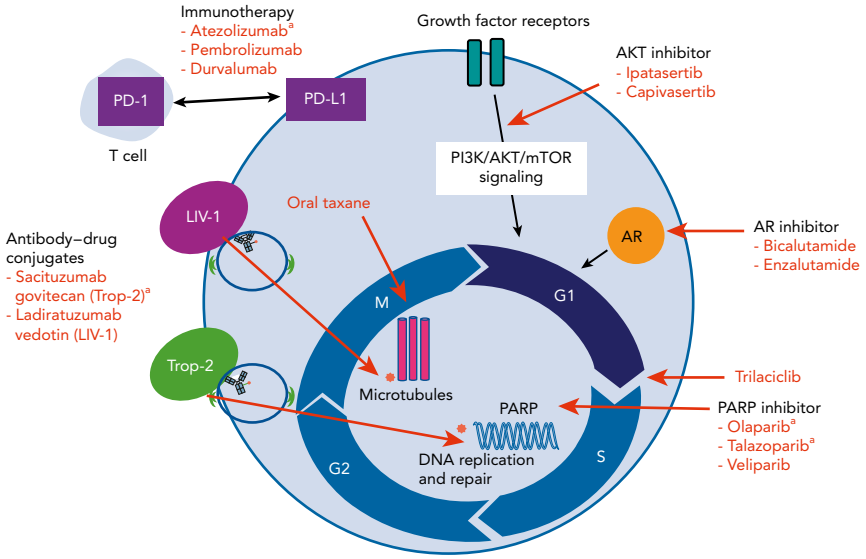

Figure 1. Novel targets in triple-negative breast cancer for therapeutic intervention.
Abbreviation: AR, androgen receptor.
[a]FDA-approved therapy.

chemotherapy,[16] median PFS was higher in those treated with talazoparib (8.6 vs 5.6 months; HR, 0.54; $P<.001$), and the objective response rate (ORR) was also improved (62.6% vs 27.2%; odds ratio, 5.0; $P<.001$). Talazoparib is FDA approved for HER2-negative advanced breast cancer with germline *BRCA1/2* mutations.[17] Both olaparib and talazoparib are well tolerated, but toxicity includes myelosuppression, fatigue, and gastrointestinal problems.

The BROCADE 3 phase III study compared veliparib with carboplatin and paclitaxel followed by maintenance veliparib versus chemotherapy in germline *BRCA1/2*-mutant HER2-negative advanced breast cancer.[18] Median PFS improved from 12.6 to 14.5 months with the addition of veliparib, and durable responses were seen with veliparib (3-year PFS rate, 26% with veliparib vs 11% with chemotherapy alone). The FDA's review of the BROCADE 3 data is awaited, and it is possible that this may become a new standard-of-care option for mTNBC. Notably, this study suggests that perhaps maintenance use of a PARP inhibitor may improve outcomes in germline *BRCA1/2* mutant mTNBC.

Additional efforts to broaden the applicability of PARP inhibitors to a larger population are underway, including targeting somatic *BRCA1/2* mutations with PARP inhibitors, similar to somatic *BRCA1/2*-mutant ovarian cancer in which PARP inhibitors are equally as effective as for germline *BRCA1/2* mutations,[19] and other DNA damage repair genes (ClinicalTrials.gov identifiers: NCT03990896 and NCT03344965). Combination therapy with a PI3K inhibitor and PARP inhibitor is being explored (NCT01623349) based on preclinical data demonstrating that PI3K inhibition can sensitize TNBC to PARP inhibition.[20,21] Combining a PARP inhibitor and immunotherapy has demonstrated preliminary efficacy, including in *BRCA1/2* wild-type cancer.[22]

AKT Inhibitors Targeting the PI3K/AKT Pathway

TNBC may overexpress PI3K/AKT.[23,24] A subset of TNBC harbors loss of *PTEN*, a tumor suppressor gene, which may increase AKT pathway activation. Altogether, approximately 45% of breast tumors may harbor mutations in the AKT pathway, including *PIK3CA*, *AKT1*, and *PTEN*. These observations have spurred interest in AKT inhibitors for TNBC.

A randomized phase II trial (LOTUS) in patients with advanced TNBC (aTNBC) evaluated ipatasertib, an AKT inhibitor, with paclitaxel versus paclitaxel alone in the first-line setting (n=124) and demonstrated an improvement in PFS with ipatasertib compared with paclitaxel alone (PFS, 6.2 vs 4.9 months; HR, 0.60; $P=.037$), particularly in the PTEN-low tumors (median PFS, 6.2 vs 3.7 months; HR, 0.59; $P=.18$).[25] Grade 3 or 4 toxicity with ipatasertib included diarrhea and neutropenia.[25] Further investigation with ipatasertib is ongoing in a phase III trial.[26]

The PAKT trial[27] investigated capivasertib, another AKT inhibitor, with paclitaxel versus paclitaxel alone as first-line treatment of mTNBC. With capivasertib, PFS improved (5.9 vs 4.2 months; HR, 0.74; $P=.06$), and in patients with *PIK3CA/AKT1/PTEN* alterations, this benefit was prominent (PFS, 9.3 vs 3.7 months; HR, 0.30; $P=.01$). An improvement in median OS was seen in the

entire population (19.1 vs 12.6 months; HR, 0.61; P=.04). Diarrhea, infection, rash, and fatigue occurred with capivasertib. A phase III study of capivasertib and paclitaxel is ongoing for aTNBC (ClinicalTrials.gov identifier: NCT03997123).

Combination therapy with an AKT inhibitor (ipatasertib), taxane, and immunotherapy (atezolizumab) is also being explored for mTNBC (NCT04177108).

Androgen Receptor Inhibitors Targeting the Androgen Receptor Pathway

A subset of TNBC expresses androgen receptor (AR).[9,10,28] A phase II study evaluated bicalutamide, an antiandrogen, in patients with AR-positive disease (immunohistochemical positivity >10%).[29] The 6-month clinical benefit rate (CBR) was 19% and median PFS was 12 weeks. No significant toxicity was seen.

A second phase II study evaluated the efficacy of enzalutamide, an AR inhibitor, in advanced AR-positive TNBC.[30] Patients with AR-positive disease defined by immunohistochemical staining >0% were treated with enzalutamide. Of 118 enrolled patients, the CBR at 16 weeks was 25% in the intent-to-treat population (ITT) and 33% in the evaluable subset. Median PFS was 2.9 months. Enzalutamide was well tolerated, with fatigue being the main grade 3 toxicity. Although these results are modest, they are intriguing for a targeted therapy that is well tolerated. Combination therapy with androgen inhibition is being evaluated. A study evaluated a PI3K inhibitor with an AR antagonist,[31] and observed better responses in LAR subtype TNBC, and provided translational insight into tumor subtypes likely to respond to AR antagonists.

An issue that has arisen with targeting AR is the best modality for AR testing. Although both immunohistochemical and genomic assays are available, currently there is a lack of consensus on the best way to define AR positivity given significant variability within these assays and within studies that have been conducted using them.

Targeting Cell Surface Receptors for Selective Delivery of Potent Agents

Antibody–Drug Conjugate Targeting Trop-2

Antibody–drug conjugates (ADCs) selectively deliver a cytotoxic agent to cancer cells through coupling with a monoclonal antibody. Sacituzumab govitecan-hziy is one ADC that combines an irinotecan metabolite (SN-38) to an antitrop-2 monoclonal antibody with a cleavable linker.[32] Trop-2 is widely expressed in breast cancer, including TNBC,[33] and participates in tumor growth.[34]

In a phase I/II study, patients with advanced cancer, including 108 with mTNBC (who had received ≥2 prior therapies), received sacituzumab govitecan-hziy.[32] Median PFS was 5.5 months and OS was 13.0 months; 3 patients had a complete response and 33 had a partial response, with an overall response rate of 33.3%. Median duration of response was 7.7 months, which is much higher than what has previously been seen with most chemotherapy agents. Common toxicities included myelosuppression, gastrointestinal toxicity, fatigue, electrolyte abnormalities, skin changes, and infection. Accelerated approval of sacituzumab govitecan-hziy for patients with mTNBC who have received at least 2 prior lines of therapy was granted in April 2020. The phase III randomized ASCENT study comparing sacituzumab govitecan-hziy versus chemotherapy for mTNBC will provide additional data (ClinicalTrials.gov identifier: NCT02574455).

ADC Targeting LIV-1

Ladiratuzumab vedotin is an antibody to LIV-1, a breast cancer–associated protein and zinc transporter, which is linked to auristatin.[35] LIV-1 is expressed in TNBC.[36] In a phase I study, ladiratuzumab vedotin agent was shown to have a preliminary ORR of 32% in TNBC.[37] Combination therapy with ladiratuzumab and pembrolizumab for aTNBC is being explored (NCT03310957). Preliminary results showed an ORR of 54% among 26 treated patients, with manageable toxicity.[38]

Targeting the Immune Microenvironment

Immune Checkpoint Inhibition Monotherapy

Immune checkpoint inhibitors that block interaction of the PD-1 receptor and PD-L1 are being explored in many advanced malignancies. Breast cancer has been viewed as being less immunogenic than other malignancies, such as melanoma and lung cancer, but among breast cancer subtypes, TNBC is considered more immunogenic. The interaction of PD-1 on T cells with PD-L1 and PD-L2 on host tissues was physiologically designed for host tissue protection against immune rejection. Cancer cells may usurp this pathway and evade tumor immune rejection by increasing expression of PD-1 on tumor-infiltrating lymphocytes and/or increasing expression of PD-L1 in cancer cells.[39] Prior studies demonstrated the presence of immune infiltration in TNBC.[40] By blocking this pathway, immunotherapy agents such as pembrolizumab (anti–PD-1 antibody), atezolizumab (anti–PD-L1 antibody), and durvalumab (anti–PD-L1 antibody) attempt to increase antitumor immunity.

Initial exploration of pembrolizumab as a single-agent therapy occurred in a phase I study of heavily pretreated patients with PD-L1–positive aTNBC.[41] Among 27 evaluable patients, the overall response rate to pembrolizumab was 18.5% and median time to response was approximately 18 weeks. Some patients had durable responses. A phase I study of atezolizumab in TNBC was also undertaken.[42]

An ORR of 24% was seen in the first-line setting, and an ORR of 6% was seen in the second-line or beyond setting, with a median duration of response of 21 months. ORR was higher in patients with tumor immune cell expression of PD-L1 >1%.

These studies demonstrated some preliminary efficacy with immunotherapy for aTNBC. The phase III KEYNOTE-119 study[43] compared pembrolizumab versus chemotherapy in patients with mTNBC who had received 1 to 2 prior therapies. The study included a stratification by tumor PD-L1 status defined using a combined positive score (CPS) based on the number of PD-L1–staining cells per total viable tumor cells, with analyses evaluating a CPS score of ≥1, ≥10, and ≥20. Although OS was not significantly improved in the entire population treated with pembrolizumab, there was a trend toward improved efficacy (OS, PFS, and ORR) in patients whose tumors had greater PD-L1 enrichment.

Combination Therapy With Immune Checkpoint Inhibition and Chemotherapy

Other studies are combining immunotherapy agents with chemotherapy, given the potential synergistic activity of combination treatment. In early-stage disease, the combination of pembrolizumab with chemotherapy was shown to result in improved pathologic complete response rates.[42,44]

In the phase III IMpassion130 study,[3] combination atezolizumab + nab-paclitaxel was compared with nab-paclitaxel alone in patients with aTNBC. In the first interim analysis,[3] median PFS with atezolizumab + nab-paclitaxel was 7.2 versus 5.5 months in the control arm (HR, 0.80; P=.002) in the ITT population. In the PD-L1–positive population (≥1% PD-L1 immune cell positivity), PFS was 7.5 months with atezolizumab versus 5.0 months in the control arm (HR, 0.62; P<.001). OS was 21.3 versus 17.6 months (HR, 0.84; P=.08) in the atezolizumab and control arms, respectively, in the ITT analysis, but 25.0 versus 15.5 months (HR, 0.62), respectively, in the PD-L1–positive subset. Based on the OS benefit in PD-L1–positive patients, atezolizumab + nab-paclitaxel was FDA-approved for PD-L1–positive aTNBC. In the second interim analysis,[45] with a median follow-up of 18.5 months for the atezolizumab arm and 17.5 months for the control arm, median OS in the ITT population was 21 versus 18.7 months (HR, 0.86; P=.078), respectively. In the PD-L1–positive population, OS was improved to 25.0 months with the addition of atezolizumab versus 18.0 months in the control arm (HR, 0.71). The FDA did not specify the treatment line in which atezolizumab + nab-paclitaxel may be prescribed, although data with immunotherapy in breast cancer generally suggest an increased response in the front-line setting for mTNBC. Of note, this study used the Ventana SP142 PD-L1 immunohistochemical assay, which is the companion diagnostic test for the FDA approval. A comparison of this assay with other assays, including the Ventana SP263 and Dako 22C3 PD-L1 assays, did not demonstrate concordance; therefore, ideally the Ventana SP142 assay should currently be used to identify PD-L1–positive patients for treatment with atezolizumab and abraxane.[46]

The phase III KEYNOTE-355 study similarly evaluated pembrolizumab in combination with chemotherapy for mTNBC as first-line treatment. An improvement in PFS (9.7 vs 5.6 months; HR, 0.65; 95% CI, 0.49–0.86; P=.0012) was noted in patients with PD-L1–positive tumors (defined as a combined positive score ≥10) treated with immunotherapy and chemotherapy versus chemotherapy alone.[47]

Maintenance immunotherapy is also being explored. In a recent study, patients with mTNBC or hormone receptor–positive breast cancer who received 1 to 2 prior lines of chemotherapy and did not have any actionable mutations were randomized to treatment with durvalumab versus chemotherapy after 6 to 8 cycles of chemotherapy.[48] An improvement in OS was seen in patients who received durvalumab compared with chemotherapy (21.7 vs 17.9 months), and this benefit was pronounced in the TNBC (21 vs 14 months; HR, 0.54) and PD-L1–positive populations (26 vs 12 months; HR, 0.42).

Although immunotherapy may have durable responses, a unique toxicity profile is seen. Immune-related adverse events related to hyperactivation of the immune system, such as thyroid disorders, hypophysitis, colitis, myocarditis and pericarditis, and pneumonitis, can sometimes present months after treatment. A multidisciplinary team should manage these types of toxicities, which sometimes may improve or resolve after holding the drug and/or initiation of corticosteroids.

There are many ongoing studies of immunotherapy for mTNBC. Currently, it appears that immunotherapy activity is largely seen in tumors that are PD-L1–positive.

A question that often arises clinically is how to optimally sequence immunotherapy and PARP inhibitors in patients who are germline *BRCA1/2* carriers with PD-L1–positive mTNBC. One approach would be to consider using immunotherapy upfront, given that the current literature suggests that immunotherapy often has better responses when sequenced earlier in the disease course, and immunotherapy is associated with an improvement in OS. Patients enrolled in the OlympiAD[15] and EMBRACA[16] studies also were allowed to have received prior lines of therapy, and PARP inhibitors could be used in the second-line (and beyond) setting, although the sequencing question has not been explicitly evaluated in a clinical trial and further research is needed.

Combination Therapy With Immune Checkpoint Inhibition and AKT Inhibition

The triplet combination of atezolizumab, ipatasertib, and a taxane was investigated as first-line treatment of aTNBC based on data suggesting that the loss of PTEN may contribute to immunotherapy resistance. In 26 patients treated, an ORR of 73% was seen, with common toxicity including diarrhea and rash.[49] A phase III trial is further evaluating this combination (NCT04177108).

Other Agents

Oral Taxanes

Although the recent focus in aTNBC has been on the development of therapies targeted to tumor biology, given that chemotherapy is the mainstay of treatment there is also interest in developing oral chemotherapy agents with less toxicity and less burden to patients than intravenous chemotherapy.

One study evaluating oral paclitaxel + encequidar versus intravenous paclitaxel demonstrated an improved response rate of 40% with the oral paclitaxel versus 25.6% for intravenous (P=.005).[50] Additionally, a phase II study is ongoing to compare liporaxel, an oral paclitaxel, with intravenous paclitaxel.[51] Liporaxel is approved in Korea for the treatment of gastric cancer, with similar efficacy as intravenous paclitaxel, and less neuropathy and no hypersensitivity reactions.[52] In the OPTIMAL phase II study of liporaxel, an ORR of 44.4% was seen in mTNBC.[53] A third oral taxane, tesetaxel, is being evaluated as a single agent for metastatic HER2-negative breast cancer (ClinicalTrials.gov identifier: NCT01221870) and in combination with immunotherapy in TNBC (NCT03952325).

A significant advantage of the oral formulation is the potential for less neuropathy and absence of infusion reactions compared with intravenous taxanes. The final results of the ongoing studies are eagerly anticipated.

Cell Cycle Inhibition With Chemotherapy

Trilaciclib, a cyclin-dependent kinase 4/6 inhibitor, was studied with gemcitabine and carboplatin, and compared with chemotherapy alone in patients with aTNBC.[54] A promising improvement in OS was seen with trilaciclib. An interesting feature of trilaciclib compared with other CDK4/6 inhibitors is that it transiently causes immune and bone marrow cells to be in G1 arrest of the cell cycle, protecting them from the myelosuppressive effects of chemotherapy and thereby enabling the antitumor effect of chemotherapy to be maximized.

Conclusions and Future Directions

Many novel agents are being developed for aTNBC that will transform the therapeutic landscape. A challenge in devising novel agents is the development of resistance, given the high mutation rate of TNBC, leading to the acquisition of new mutations under therapeutic pressure.[55,56] Precision medicine initiatives utilizing tumor tissue and blood genotyping to understand tumor biology and evolution in combination with correlative biomarker studies may identify novel targets, elucidate patterns of resistance, and improve therapies for aTNBC. Immunotherapy is a promising direction, but likely requires identification of additional predictive biomarkers to guide therapy. An understanding of heterogeneity in antigen expression, stability of linker, cross-resistance of toxic payload with prior therapy, and bystander effect will help optimize the therapeutic success of ADCs. Additional biomarker-driven clinical trials will lead to validation of novel targets and redefine the therapeutic landscape and molecular classification of TNBC.

At the present time, based on the current body of evidence, we recommend upfront PD-L1 testing on tumor tissue as well as germline *BRCA1/2* testing in patients with mTNBC who are eligible for therapy. If the tumor is PD-L1–positive, we recommend consideration of chemotherapy with immunotherapy, such as nab-paclitaxel + atezolizumab (chemotherapy + pembrolizumab is a potential option in the future, if FDA-approved), and if the patient is a germline *BRCA1/2* carrier, we recommend consideration of a PARP inhibitor. For PD-L1–negative tumors, standard chemotherapy agents can be considered, such as carboplatin, capecitabine (if the patient is interested in oral therapy), a taxane (if not received within 6 months of metastatic diagnosis), or an anthracycline (if not received within 6 months of metastatic diagnosis). For therapy in the third line and beyond, additional chemotherapy or sacituzumab govitecan can be considered. Clinical trials should always be considered whenever possible in the metastatic setting. Tumor genotyping may help identify actionable mutations and guide enrollment in appropriate clinical trials.

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