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The evolving management of metastatic triple negative breast cancer

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ABSTRACT

Advanced triple negative breast cancer (TNBC) is an incurable disease classified by its lack of expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2. Due to its lack of therapeutic targets, it has historically been treated with single agent chemotherapy, with combination cytotoxic therapy typically reserved for patients with high disease burdens, symptomatic disease, and/or impending visceral crisis. Recent molecular analyses have revealed that this clinical group of TNBCs is in fact quite biologically heterogeneous, with multiple TNBC subtypes defined by distinct biology and clinical behavior. Building on this biology, 2 targeted strategies are now approved for selected patients with advanced TNBC: the poly (ADP-ribose) polymerase inhibitors for advanced TNBC with a germline mutation in BRCA1/2, and the combination of the programmed death ligand 1-specific antibody atezolizumab with *nab*-paclitaxel for advanced TNBC that expresses programmed death ligand 1 on immune cells within the tumor. These targeted agents tend to be associated with a more favorable side effect profile and longer disease control than standard chemotherapy. A number of other targeted therapies have shown promise in early clinical trials, and several are now in definitive phase 3 testing for advanced TNBC. These include the antiapoptotic kinase inhibitors ipatisertib and capivasertib, and the antibody-drug conjugate sacituzumab govitecan-hziy. Approved biomarker-driven treatment options for this disease are thus likely to expand in the near-term. Here we review current treatment options and emerging targeted therapies for advanced TNBC. For patients who do not meet criteria for approved targeted therapies, participation in clinical trials evaluating precision medicines with candidate predictive biomarkers in advanced TNBC should be encouraged.

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Triple negative breast cancer (TNBC) represents about 15% of breast cancers, and fails to express the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor-2 (HER-2) [1,2]. Treatment options have thus historically been limited to chemotherapy due to the lack of standard therapeutic targets in TNBC. Although early stage TNBC has a high response rate to chemotherapy, relapse is common and tends to occur quickly [3]. Once metastasis occurs, TNBC is incurable with a median overall survival (OS) that averages only 10–13 months [4].

TNBC represents a highly heterogeneous group of breast tumors

Beyond the ASCO/CAP classification, transcriptomic analyses have more precisely classified breast cancers into intrinsic subtypes, including normal breast-like, luminal A and luminal B (ER+ and/or PR+), HER-2-enriched, claudin-low, and basal-like [5]. Importantly, the majority (50–75%) of ASCO/CAP-defined TNBCs are basal-like, whereas breast cancers with low levels of ER and PR expression (1–10%) are more likely to be luminal (46%) or HER-2-enriched (29%) by gene expression [6]. Most claudin-low breast tumors fail to express ER, PR, and HER-2 by IHC, and have metaplastic/medullary differentiation, elevated expression of immune-related genes, stem cell and mesenchymal features, and active transforming growth factor-beta signaling. Thus, TNBC (defined by IHC criteria) and the basal-like and claudin-low breast cancer subtypes (defined by gene expression criteria) are not synonymous.

Further gene expression analyses of over 500 breast tumors identified 2 basal-like (BL1 and BL2) subtypes, and 5 other clusters: immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), luminal androgen receptor (LAR) and unstable (UNS) (Table 1) [7]. Laser capture microdissection was subsequently used to remove immune and stromal cells, simplifying these clusters into BL1, BL2, M, and LAR based on tumor cell intrinsic gene expression patterns [8]. The BL1 subtype has high expression of DNA damage response and cell cycle genes (including 92% with p53 mu-

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Table 1
Genomic subtypes of TNBC.

TNBC genomic subtype	Biologic alterations	Candidate therapies
Basal-like 1	DNA repair Cell proliferation Cell cycle	PARP inhibitors Platinum-based chemotherapy
Basal-like 2	Cell cycle	Taxane-based chemotherapy
Immunomodulatory	Immune cells Cytokines signaling Chemokine signaling Antigen presentation	Immune checkpoint inhibitors and other immune-based therapies
Mesenchymal-like*	Epithelial-to-mesenchymal transition Growth factor signaling	mTOR inhibitors PI3K inhibitors SRC inhibitors
Mesenchymal stem cell-like*	Angiogenesis Claudin-low Epithelial-to-mesenchymal transition Growth factor signaling	Antiangiogenic therapy mTOR inhibitors PI3K inhibitors SRC inhibitors
Luminal androgen receptor	Androgen receptor gene	Antiandrogen therapy

TNBC = triple negative breast cancer; DNA = deoxyribonucleic acid; PARP = poly (ADP-ribose) polymerase; mTOR = mammalian target of rapamycin; SRC = proto-oncogene tyrosine-protein kinase Src; PI3K = phosphoinositide 3-kinase.

* Mesenchymal stem-like is similar to mesenchymal-like but with greater angiogenesis and lower levels of claudin.

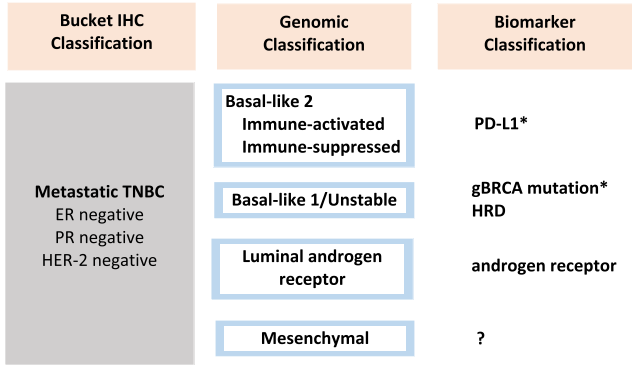

Fig. 1. Subtypes of triple negative breast cancer (TNBC). Triple negative breast cancer has historically been classified by immunohistochemistry by the biomarkers that it lacks: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2). More recent genomic studies revealed significant biologic heterogeneity within TNBC. Although the genomic subtype classifications are not used to guide patient management, they can be broadly grouped into several subtypes from which potentially actionable biomarkers are emerging: basal-like immune activated, basal-like immune suppressed, basal-like 1/unstable, luminal androgen receptor, and mesenchymal. Of these, programmed death ligand-1 (PD-L1) and germline BRCA mutations are predictive biomarkers that are already in routine clinical use to guide treatment selection; homologous recombination deficiency (HRD) and androgen receptor are biomarkers that remain under investigation.

tations and high gain/amplification of c-*MYC*), and is thought to respond to platinum-based agents. The BL2 subtype has high levels of metabolic and cell cycle signaling, and may respond best to mitotic inhibitors such as taxanes. The M and MSL subtypes have high expression of genes associated with cell motility, differentiation, and epithelial-to-mesenchymal transition, with MSL also enriched for angiogenesis and stem-cell-related genes and low claudin expression. The M and MSL subtypes may respond to phosphoinositide 3-kinase (PI3 kinase)/mammalian target of rapamycin and SRC pathway inhibition. The LAR subtype is associated with a luminal gene expression profile with high levels of androgen receptor (AR) expression; the AR antagonist bicalutamide has shown evidence of clinical activity in metastatic AR+ TNBC [9]. Finally, the IM subtype is associated with expression of immune signaling pathways, including antigen processing and presentation, immune cell (IC) signaling, and cytokine activity, suggesting potential responsiveness to immune-based therapy. Yet another study classified TNBC into 4 molecular subtypes including basal-like immune activated, basal-like immune suppressed, LAR, and mesenchymal (MES) [10]. Here, basal-like immune activated has the best prognosis and basal-like immune suppressed has the worst [10–12].

The oncogenic drivers for most of these distinct TNBC subtypes remain unvalidated, and gene expression profiling to delineate the various TNBC subtypes is not the standard of care. However, consideration of the unique biology of the distinct subsets of TNBC is critical for effective clinical research to improve outcomes in this disease (Fig. 1). Recent progress has identified 2 groups of patients with metastatic TNBC for which biomarker-driven targeted therapy has been approved by the US FDA. These 2 groups are metastatic TNBC patients with germline BRCA mutations, for whom the poly (ADP-ribose) polymerase (PARP) inhibitors olaparib and talazoparib are approved for use after progression on chemotherapy in the metastatic setting [13,14], and metastatic TNBC patients with tumors that express programmed death ligand 1 (PD-L1) in ICs occupying 1% or more of the tumor area, for which immunotherapy with the PD-L1 inhibitor atezolizumab in combination with *nab*-paclitaxel is approved for use [15].

Table 2
Chemotherapy options for metastatic TNBC.

Single agent chemotherapy	Combination chemotherapy
Taxanes* (paclitaxel, nab-paclitaxel, docetaxel)	Doxorubicin + cyclophosphamide (AC)
Platinum agents* (cisplatin, carboplatin)	Doxorubicin + docetaxel (AT)
Anthracyclines* (doxorubicin, epirubicin)	Gemcitabine + paclitaxel or docetaxel (GT)
Capecitabine*	Gemcitabine + carboplatin or cisplatin (GC)
Eribulin	Capecitabine + docetaxel
Ixabepilone	Capecitabine + ixabepilone
Gemcitabine	
Vinorelbine	

* Denotes agents often used in the (neo)adjuvant setting. Choice of first/second line chemotherapy will depend on the disease-free interval from prior exposure to the agent, and different agents in the same drug class may be used without cross-resistance. In general, sequential single agent chemotherapy is preferred to maximize treatment options, minimize toxicity, and maximize quality of life. Combination chemotherapy has higher response rates but also greater toxicity, and is typically reserved for use in metastatic disease when rapid responses are needed.

Chemotherapy for metastatic TNBC

Single agent chemotherapy remains the treatment of choice for the majority of patients with metastatic TNBC [4,16,17]. Single agent chemotherapy agents used for TNBC result in response rates that average 20–30%, and include anthracyclines, taxanes, platinum drugs, eribulin, capecitabine, gemcitabine, vinorelbine, ixabepilone, and cyclophosphamide (Table 2). Anthracyclines, taxanes, and platinum drugs are the most active cytotoxic agents in the frontline setting in metastatic TNBC, although all 3 are also often used in the (neo)adjuvant setting.

A single arm phase 2 trial enrolled 86 patients with metastatic TNBC to receive first-line (n = 69) or second-line (n = 17) chemotherapy with single agent cisplatin (75 mg/m^2) or carboplatin (area under the curve 6) by physician's choice every 3 weeks [18]; co-primary endpoints included objective response rate (ORR) and response prediction by p63/p73 gene expression. The ORR was 25.6% (95% CI 16.8–36%), numerically higher with cisplatin than with carboplatin (32.6% *v* 18.7%). In patients with germline BRCA mutations (n = 11), the ORR was 54.5%. A BRCA-like genomic instability signature was associated with response, whereas p63/p73 expression status, p53 and PIK3CA mutation status, and gene

expression subtype were not. The phase 3 TNT trial randomized 376 patients with unselected TNBC to receive carboplatin area under the curve 6 every 3 weeks or docetaxel 100 mg/m^2 every 3 weeks as first-line treatment [19]. The primary endpoint of ORR was similar in both arms for the overall population at 31.4% versus 34.0%, $P = 0.66$. Notably, for the 43 women with a known germline BRCA1/2 mutation, carboplatin resulted in a higher response rate (68% *v* 33%, biomarker treatment interaction $P = 0.01$)) and longer progression-free survival (PFS) compared to docetaxel (6.8 *v* 4.4 months; 95% confidence interval (CI) 0.11–5.12 months). Importantly, this clinical benefit was not observed for patients whose tumors had BRCA1 methylation, low levels of BRCA1 mRNA, or a high Myriad homologous recombination deficiency score—only for patients with a germline BRCA1/2 mutation. A significant interaction between treatment and the basal-like subtype was driven by high ORRs to docetaxel in the nonbasal subtype group. Thus, gene expression subtype may help guide the choice of single agent chemotherapy. No difference in OS was observed.

Two nontaxane microtubule inhibitors are available for treating metastatic TNBC. Eribulin, an analog of halichondrin B derived from the sea sponge, is approved for the treatment of metastatic TNBC after disease progression on or intolerance to at least 2 chemotherapeutic regimens for metastatic disease in patients who have received prior therapy with an anthracycline and a taxane in the adjuvant or metastatic setting. A phase 3 trial randomized 721 patients with unselected metastatic breast cancer at a 2:1 ratio to receive eribulin or physician's choice chemotherapy [20]. Eribulin was associated with longer median OS than other chemotherapy at 13.1 months (95% CI 11.8–14.3) versus 10.6 months (95% CI 9.3–10.5, hazard ratio (HR) = 0.81, 95% CI 0.66–0.99, $P = 0.041$). Ixabepilone, a novel microtubule-stabilizing epothilone B analog, was tested in a phase 2 trial that enrolled 126 metastatic breast cancer patients previously treated with a taxane, an anthracycline, and capecitabine to receive ixabepilone 40 mg/m^2 every 3 weeks; the primary endpoint was ORR [21]. In this trial the ORR was 11.5% (95% CI 6.3–18.5), the median duration of response (DOR) was 5.7 months and the median OS was 8.6 months. A phase 3 trial enrolled 799 patients with chemotherapy-naïve advanced breast cancer to receive the antiangiogenic antibody bevacizumab with paclitaxel (90 mg/m^2), weekly nab-paclitaxel (150 mg/m^2) or ixabepilone (16 mg/m^2) weekly for 3 weeks every 28 days; 25% of the patients (n = 201) had TNBC [22]. The clinical activity of paclitaxel and *nab*-paclitaxel were similar, ixabepilone was inferior to paclitaxel, and toxicity was higher with *nab*-paclitaxel and ixabepilone.

Combination chemotherapy regimens can increase ORRs, but they are also associated with more toxicity without increasing OS [4,16,17]. Single agent chemotherapy is typically preferred unless high disease burdens or impending visceral crisis necessitate a combination chemotherapy strategy to achieve a more rapid response. Anthracycline-based regimens used for metastatic TNBC include doxorubicin plus cyclophosphamide (AC), doxorubicin with docetaxel (AT), and doxorubicin with docetaxel plus cyclophosphamide (TAC), with ORRs of 47%, 59%, and 77%, respectively [23-25]. Gemcitabine can be administered with paclitaxel or docetaxel, with ORRs of 41% and 43%, respectively [26,27]. Capecitabine and docetaxel can be given every 21 days, with an ORR of 42% [28]. Alternatively, ixabepilone in combination with capecitabine has an ORR of 35% [29]. Although these chemotherapy combinations tend to have higher ORRs, there is limited OS benefit. These findings together with the toxicities associated with chemotherapy highlight the urgent need for new therapies for metastatic TNBC.

Poly (ADP-ribose) polymerase inhibitors for metastatic TNBC

Mutations in the BReast CAncer-associated genes BRCA1 and BRCA2 are found in up to 20% of TNBC patients [30]. BRCA genes encode proteins that help repair double-strand DNA breaks [31]. Therefore, cells harboring deleterious BRCA mutations have impaired DNA repair machinery, and are dependent on the enzyme PARP to repair single-strand DNA breaks. Since PARP inhibitors block single-strand DNA break repair and platinum agents induce multiple single-strand DNA breaks [32], the treatment of BRCA1/2 mutated cancers with PARP inhibitors or platinum agents produces an accumulation of DNA damage that cannot be repaired. This ultimately results in cell death, a condition known as synthetic lethality [33,34]. PARP inhibitors block DNA repair in 2 major ways: (1) by inhibiting the enzymatic activity of PARP; and (2) by trapping PARP at sites of DNA damage. Preclinical studies suggest that PARP trapping on DNA may induce cancer cell death more efficiently than catalytic inhibition of PARP.

Iniparib was the first candidate PARP inhibitor to demonstrate clinical activity in metastatic breast cancer. A phase 2 study randomized 123 patients with metastatic TNBC who had received ≤2 prior chemotherapy regimens for metastatic disease to receive weekly gemcitabine with carboplatin alone or with iniparib, with primary endpoints of safety and clinical benefit rate (CBR) [35]. The addition of iniparib to gemcitabine and carboplatin increased the CBR from 34% to 56% ($P = 0.01$), and the ORR from 32% to 52%. It also prolonged the median PFS from 3.6 months to 5.9 months (HR 0.59; $P = 0.01$) and the median overall OS from 7.7 months to 12.3 months (HR 0.57; $P = 0.01$). Based on these results, a phase 3 trial was conducted in a similar population of 519 patients with metastatic TNBC, but it failed to meet the co-primary end points of PFS and OS in the intent-to-treat population [36]. Iniparib was subsequently found not to inhibit PARP, which likely accounts for the failure of this trial [37].

The phase 3 OLYMPIAD trial enrolled 302 patients with metastatic HER2-negative breast cancer and a germline BRCA mutation who had received ≤2 prior chemotherapies for metastatic disease, randomizing them 2:1 to receive olaparib 100 mg bid or chemotherapy of investigator's choice (capecitabine, vinorelbine, or eribulin) every 3 weeks; the primary endpoint was PFS [38,39]. Patients treated with olaparib had a longer median PFS than patients treated with chemotherapy, at 7 months versus 4.2 months (HR 0.58; 95% CI 0.43–0.80; $P < 0.001$). The ORR was 59.9% for olaparib and 28.8% for standard chemotherapy. Median OS was 19.3 months with olaparib and 17.1 months with standard chemotherapy (HR 0.90, 95% CI 0.66–1.23, $P = 0.513$). In prespecified subgroups of patients (those treated first-line, TNBC *v* ER+/PR+, and those previously exposed to platinum agents), there was evidence of OS benefit only in the group of patients treated first-line (n = 87), with a median OS of 22.6 months versus 14.7 months for olaparib versus chemotherapy respectively (HR 0.51, 95% CI 0.29–0.90). Olaparib was generally well-tolerated, with the most common side effects of nausea, vomiting, anemia, neutropenia, and thrombocytopenia, no evidence of cumulative toxicity, and low rates of treatment discontinuation.

A second PARP inhibitor, talazoparib, demonstrated the greatest potency in preclinical studies. It has strong catalytic inhibition, and also traps PARP at levels 100-fold higher than the other PARP inhibitors [35]. EMBRACA is a randomized open-label phase 3 study that enrolled 431 patients with advanced HER-2-negative breast cancer and a centrally confirmed germline BRCA mutation 2:1 to receive talazoparib or physician's choice of single agent chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) [40]. Patients could have received ≤3 prior chemotherapy regimens for advanced disease, and the primary endpoint was PFS. The median PFS for talazoparib and chemotherapy was 8.6 months and 5.6 months, respectively (HR 0.54; 95% CI 0.41–0.71; $P < 0.001$). The ORR was higher in the talazoparib group than in the chemotherapy group (62.6% *v* 27.2%, odds ratio 5.0, 95% CI 2.9–9.9, $P < 0.001$). The most common side effects were nausea, anemia, and fatigue, with

neutropenia and thrombocytopenia also observed. Patient-reported outcomes were superior with talazoparib. Based on these trials, both olaparib and talazoparib have been approved by the FDA for use in patients with metastatic breast cancer and a germline BRCA mutation. Several other PARP inhibitors including rucaparib, niraparib, and veliparib, have been tested in advanced TNBC as single agents [41–43].

PARP inhibition in combination with chemotherapy has also been evaluated. A phase 1 trial enrolled patients with metastatic TNBC who had received ≤1 chemotherapy regimen for advanced disease to receive the combination of olaparib 200 mg bid with weekly paclitaxel 90 mg/m^2 [44]. Dose modifications due to neutropenia were required in the initial group of 9 patients. Therefore, a second cohort of 10 patients was enrolled who received growth factor support prophylactically for cycle 2 and beyond if they experienced neutropenia ≥Grade 2 in cycle 1. Seven patients had a confirmed partial response, but the rate of neutropenia remained higher than expected even with growth factor support.

The myelosuppression observed with the combination of PARP inhibition and chemotherapy may result from PARP trapping [45]. As veliparib potently inhibits PARP with minimal PARP trapping, it may be more suitable for use in combination with chemotherapy. Accordingly, a randomized phase 2 trial enrolled 290 metastatic TNBC patients with germline BRCA1/2 mutations, randomizing them 1:1:1 to receive veliparib with paclitaxel and carboplatin (VPC), veliparib with temozolomide, or placebo with paclitaxel and carboplatin (PCP); the primary endpoint was PFS, with secondary endpoints of OS and ORR [46]. For VPC versus PCP, the median PFS was 14.1 versus 12.3 months (HR 0.789, 95% CI 0.536–1.162). The ORR for VPC compared to PCP was 77.8% *v* 61.3% $P < 0.027$), and adverse event rates were similar in the 2 arms; veliparib with temozolomide was inferior to PCP. Building on these findings, BROCADE 3 is a randomized phase 3 trial that enrolled 513 patients with HER-2 negative metastatic breast cancer and a germline BRCA mutation who had received ≤2 prior lines of chemotherapy for metastatic disease, randomizing them 2:1 to receive VPC or PCP; the primary endpoint was PFS, and crossover to veliparib at disease progression was allowed for patients on PCP [47]. The median PFS for VPC and PCP was 14.5 months (95% CI 12.5–17.7) and 12.6 months (95% CI 10.6–14.4) (HR = 0.71 95% CI 0.57–0.88; $P = 0.002$), respectively; no significant difference in median OS was observed (median OS 33.5 months, 95% CI 27.6–37.9 for VPC versus 28.2 months, 95% CI 24.7–35.2 months for PCP (HR = 0.95, 95% CI 0.73–1.2; $P = 0.67$). The regimen was well-tolerated with <10% of patients discontinuing veliparib due to toxicity. PARP inhibitors in combination with chemotherapy are not currently approved for the treatment of patients with metastatic TNBC.

In summary, for patients with advanced TNBC and germline BRCA mutations, both platinum-based chemotherapy and monotherapy with PARP inhibitors are currently appropriate treatment options. PARP inhibitors are associated with high rates of grade ≥3 hematological toxicities and this must be taken into consideration when making treatment decisions. About 28% of patients in the OlymiAD study and about 20% of patients in the EMBRACA study received platinum agents prior to trial participation, and about one third of patients in both studies received platinum agents after trial participation. There are limited data to appropriately guide the sequencing of platinum-based chemotherapy and PARP inhibitors, and no data to support the use of sequential PARP inhibition. In addition, randomized clinical trials that directly compare the clinical activity of PARP inhibitors to platinum-based chemotherapy are still needed. Finally, developing combination strategies that add PARP inhibitors to other targeted agents, radiation therapy, and immunotherapy are an area of active clinical investigation.

Table 3
Phase 1 and 2 trials of single agent PD-1/PD-L1 blockade for metastatic TNBC.

Antibody	Disease target	Patients	ORR
Avelumab	Unselected breast cancer	n = 168	4.8%
	PD-L1+ breast cancer	n = 12	33.3%
	Unselected TNBC	n = 58	8.6%
	PD-L1+ TNBC	n = 9	44.4%
	PD-L1- TNBC	n = 39	2.6%
Pembrolizumab	PD-L1+ TNBC	n = 27	18.5%
	Unselected TNBC	n = 170	5.3%
	PD-L1+ TNBC	n = 105	5.7%
	PD-L1- TNBC	n = 64	4.7%
	PD-L1+ TNBC 1st line	n = 84	21.4%
Atezolizumab	Unselected TNBC	n = 115	10.0%
	PD-L1+ TNBC	n = 91	11.0%
	PD-L1- TNBC	n = 21	0.0%
	Unselected TNBC 1st line	n = 21	24.0%

PD-1 = programmed death-1; PD-L1 = programmed death ligand-1; ORR = objective response rate; TNBC = triple negative breast cancer.

Immune checkpoint blockade for advanced TNBC

Of the breast cancer subtypes, TNBC is most likely to express PD-L1 in the tumor microenvironment and harbor stromal tumor-infiltrating lymphocytes (sTILs) [48,49]. High sTILs at diagnosis are prognostic of better outcome, and also predict clinical benefit from systemic therapy for early stage disease. Based on this evidence of immune activation in TNBC, several phase 1 and 2 clinical studies evaluated monotherapy with the anti-PD-1 antibody pembrolizumab and the anti-PD-L1 antibodies avelumab or atezolizumab in patients with metastatic TNBC (Table 3) [50–54]. Some of these trials enrolled patients with unselected metastatic breast cancer, and others required PD-L1 expression in the tumor microenvironment for eligibility. The data from these early studies are overall remarkably consistent, with an ORR of ~5% across the trials; these responses tended to be durable. These trials also revealed 2 major insights that informed the clinical development path forward in advanced TNBC: (1) Patients with tumors that are PD-L1+ had a higher likelihood of clinical benefit, and (2) Patients treated in the first-line setting had higher ORRs than patients treated second-line or later, with responses of 20–25% compared to responses of 5–8%, respectively. A phase 1b trial tested atezolizumab with *nab*-paclitaxel in 33 unselected patients with metastatic TNBC, where *nab*-paclitaxel was chosen as a steroid-free regimen with potential for inducing immunogenic cell death [55]. The ORR was 39.4%, with a disease control rate of 51.5% and a median DOR of 9.1 months. The median PFS and OS were 5.5 months (95% CI 5.1–7.7 months) and 14.7 months (95% CI 10.1 to not estimable), respectively. Together, these trials provided data supporting the phase 3 clinical trials that have been reported to date evaluating pembrolizumab monotherapy and the combination of atezolizumab and *nab*-paclitaxel in patients with advanced TNBC.

KEYNOTE 119 is a phase 3 clinical trial that evaluated pembrolizumab monotherapy versus single agent chemotherapy of physician's choice (capecitabine, gemcitabine, eribulin, and vinorelbine) in metastatic TNBC [56]. The study enrolled 622 patients with recurrent TNBC who had previously received an anthracycline and a taxane and 1–2 prior systemic therapies for metastatic disease, randomizing them 1:1 to receive pembrolizumab monotherapy (200 mg/m^2 every 3 weeks) or standard chemotherapy; patients were required to provide a tumor sample for analysis of PD-L1 expression. The 3 co-primary endpoints of the study were OS in PD-L1+ patients with CPS ≥ 10, OS in PD-L1+ patients with CPS ≥ 1, and OS in the ITT population; PD-L1 was assessed by the 22C3 assay. Key secondary endpoints included safety and tolerability, PFS and ORR in the ITT group, and disease control rate and DOR in PD-L1+ patients (CPS ≥ 10 or ≥1). The prevalence of PD-L1-positivity

in the study was ~65% for CPS ≥ 1, ~31% for CPS ≥ 10, and ~17% for CPS ≥ 20. The study failed to demonstrate a difference in PFS and OS at a CPS of ≥10 or ≥1, but an exploratory analysis revealed improved PFS and OS with pembrolizumab at a CPS ≥ 20, with HRs of 0.76 (95% CI 0.49–1.18) and 0.58 (95% CI 0.38–0.88), respectively. The ORRs at a CPS ≥ 20 were 26.3% and 11.5% for pembrolizumab and chemotherapy, respectively, with DORs at CPS ≥ 20 of not reached and 7.1 months for pembrolizumab and chemotherapy, respectively. These data show a trend toward greater efficacy with pembrolizumab relative to chemotherapy with PD-L1 enrichment. Overall, the side effect profile was as expected for the individual drugs tested. Thyroid dysfunction was the most common immune-related adverse event associated with pembrolizmab, with rates of hypothyroidism and hyperthyroidism (mostly grade 1–2) of 7.8% and 3.6%, respectively.

IMpassion 130 is a global, randomized, double-blind, placebo-controlled phase 3 clinical trial that enrolled 902 treatment-naïve patients with advanced TNBC, randomizing them equally to receive atezolizumab or placebo with *nab*-paclitaxel [57,58]. Eligible patients could have received chemotherapy in the early stage setting provided the treatment-free interval was ≥12 months, and had to provide a tumor sample for the analysis of PD-L1 expression. The study had 4 prespecified co-primary endpoints that included PFS and OS in the ITT patient group, and PFS and OS in the PD-L1+ patient group. Disease was classified as PD-L1+ if tumor-infiltrating ICs expressing PD-L1 occupied at least 1% of the tumor area by the SP142 assay; secondary endpoints included ORR and DOR. Overall, the arms were well-balanced with a PD-L1 IC+ prevalence of 41%. The study showed a significantly longer PFS with atezolizumab and chemotherapy in both the ITT and PD-L1 IC+ patient groups, with a 1.7-month improvement in the ITT group (HR 0.80, 95% CI 0.69–0.92, $P = 0.0021$) and a 2.2-month improvement in the PD-L1 IC+ group (HR 0.63, 95% CI 0.50–0.80, $P < 0.0001$). For OS, with atezolizumab and *nab*-paclitaxel there was a numerical improvement in OS of 2.3 months that was not statistically significant in the ITT population (HR 0.86, 95% CI 0.72–1.02, $P = 0.078$), and a clinically meaningful improvement of 7 months in the PD-L1 IC+ population (HR 0.71, 95% CI 0.54–0.94) that could not be formally tested for statistical significance due to the hierarchical statistical plan for assessment of OS. Additional analyses showed that the clinical benefit is driven by the PD-L1 IC+ patient population, with no treatment effect for atezolizumab and nab-paclitaxel in the PD-L1 IC- patient group. In the PD-L1 IC+ subgroup, the DOR was 8.5 months versus 5.5 months, with an ORR of 59% versus 43% and a CR rate of 10% versus 1% for atezoliuzmab combined with *nab*-paclitaxel compared to placebo with *nab*-paclitaxel. Overall, the adverse events were consistent with the side effect profiles of the individual drugs, with a higher rate of neuropathy observed in patients receiving atezolizumab with *nab*-paclitaxel compared to placebo with *nab*-paclitaxel (6% *v* 3%, respectively). The most common immune-related adverse event was hypothyroidism (typically grade 1–2), which occurred at a rate of 18% with atezolizumab and *nab*-paclitaxel and 5% with placebo with *nab*-paclitaxel; pneumonitis rates were low (4% *v* <1%, respectively), with only 2 grade 3–4 events in the atezolizumab and *nab*-paclitaxel arm. Based on this trial, the FDA granted accelerated approval for the use of atezolizumab with nab-paclitaxel in patients with PD-L1 IC+ advanced TNBC in March 2019, where PD-L1 status is determined using an FDA-approved assay (currently limited to only SP142 for metastatic TNBC)—thus defining a new standard of care for this patient group. More detailed biomarker analyses revealed that clinical benefit was observed provided PD-L1+ IC occupied at least 1% of the tumor area, with a denser PD-L1+ IC infiltrate not conferring additional benefit [59]. Also, the presence of CD8+ T cells, sTILs, or mutations in BRCA1/2 did not add additional predictive value to the PD-L1 IC status. Moreover, patients derived clinical benefit regardless of whether the PD-L1 status was determined using a primary tumor specimen, or a metastatic tumor sample [60]. The prevalence of PD-L1 IC+ in primary tumors was 44%, and in metastatic tissues was 36%. The PD-L1 IC prevalence was 30%-50% across most of the different metastatic sites tested; the exception of the liver where it was only 13%. These data suggest that sampling a liver metastasis should be avoided when selecting patients for therapy with the combination of atezolizumab and *nab*-paclitaxel. Moreover, the concordance between 3 PD-L1 assays in clinical use across a range of tumors—SP142, 22C3, and SP263—was explored [60]. The assays were found to be nonequivalent, and SP142 most effectively identified patients likely to derive clinical benefit from atezolizumab and *nab*-paclitaxel. These biomarker studies provide guidance for the effective implementation of this combination in the clinic.

Several other phase 3 clinical trials in advanced TNBC are eagerly awaited. These include KEYNOTE 355, evaluating pembrolizumab with *nab*-paclitaxel, paclitaxel, or gemcitabine and carboplatin, IMpassion 131, evaluating atezolizumab with paclitaxel, and IMpassion132, evaluating atezolizumab with either carboplatin and gemcitabine or capecitabine for patients with early relapsing advanced TNBC (<12 months since completing therapy for early stage disease). Combination immunotherapy approaches that may include the strategic use of cancer immunotherapy with chemotherapy is the future of cancer immunotherapy in TNBC. The TONIC trial is an innovative clinical trial that evaluated various chemotherapies or radiation sequenced with the PD-1 antagonist nivolumab to capitalize on their immune-modulating properties of enhance the responses of patients with metastatic TNBC to PD-1 blockade [61]. The trial tested nivolumab alone, or given in sequence with low dose radiation, cyclophosphamide, cisplatin, or doxorubicin. The ORR across the trial was 20%, with most responses observed in patients primed with cisplatin (23%) or doxorubicin (35%). Responses were associated with the upregulation of immune-related and T cell cytotoxicity genes with both cisplatin and doxorubicin, with the additional upregulation of genes related to inflammation, JAK/STAT signaling, and tumor necrosis factor-alpha signaling with doxorubicin. This study highlights the potential immunomodulating activity of standard cancer modalities, and underscores that this activity depends not only on the drug itself, but also the drug dose and sequence [62].

The evolving landscape of targeted therapies for advanced TNBC

The approval of PARP inhibitors and atezolizumab plus *nab*-paclitaxel are the first 2 targeted therapies available for advanced TNBC, which is notable progress in expanding treatment options for this disease. As discussed earlier, in-depth molecular analyses revealed substantial biologic heterogeneity with the subgroup of breast cancers that fail to express ER, PR, or HER-2, and have identified multiple promising targets for precision medicine strategies in TNBC. Some of these have entered clinical evaluation.

Targeting key signaling pathways in advanced breast cancer

Epidermal growth factor receptor signaling

Epidermal growth factor receptor (EGFR) is highly expressed by the basal cluster of TNBC [63]. A randomized phase 2 clinical trial evaluated the therapeutic potential of cetuximab, a monoclonal antibody specific for EGFR, randomizing patients with advanced TNBC to receive cetuximab with carboplatin or cetuximab monotherapy followed by the addition of carboplatin at disease progression [64]. Fewer than 20% of patients had objective responses, and both time to progression (2.1 months [95% CI 1.8–5.5 months]) and median

OS (10.4 months (95% CI 7.7–13.1 months)) were short. The analysis of serial biopsies revealed the presence of EGFR pathway activation in most TNBCs; however, cetuximab blocked signaling in only a minority, suggesting alternative mechanisms of EGF pathway activation. Another phase 2 trial randomized metastatic TNBC patients to receive cisplatin alone or with cetuximab, demonstrating ORRs of 10% (95% CI 4–21) and 20% (95% CI 13–29), respectively [65]. Median PFS was 1.5 months and 3.7 months (HR 0.67; 95% CI 0.47–0.97, $P = 0.032$), respectively.

Mitogen-activated protein kinase signaling

Preclinical models suggest that upregulation of mitogen-activated protein kinase (MAPK) activity is one mechanism of resistance to taxane-based chemotherapy. Additionally, about 40% of basal-like TNBCs have *c-myc* amplification, and MYC interacts with the RAS-MAPK pathway to drive tumor progression. Moreover, increased MAPK signaling is associated with a relative lack of immune activation. The randomized phase 2 COLET trial enrolled about 90 patients to receive either the MEK inhibitor cobimetinib given with paclitaxel or paclitaxel alone for the first-line therapy of metastatic TNBC [66]. This study showed ORRs of 38% and 21%, respectively, with median PFS of 5.5 months versus 3.1 months, respectively (HR 0.73, 95% CI 0.43–1.24, $P = 0.2$). This trial also randomized 125 patients to receive atezolizumab and cobimetinib with either paclitaxel (n = 63) or *nab*-paclitaxel (n = 62) [67]. The ORRs were similar at 34% and 29%, respectively.

The phosphoinositide 3-kinase/antiapoptotic kinase signaling

PI3K/antiapoptotic kinase (AKT) signaling is frequently upregulated in TNBC through activating mutations in *PIK3CA* or *AKT1*, and through alterations in *PTEN* or overt *PTEN* loss. Ipatisertib is a highly selective oral ATP-competitive small-molecule AKT inhibitor. The LOTUS trial is a randomized, double blind, placebo-controlled phase 2 trial that enrolled 124 patients with untreated metastatic TNBC, randomizing them 1:1 to paclitaxel (80 mg/m^2 weekly × 3) with either ipatasertib (400 mg) or placebo daily every 28 days [68]. Co-primary endpoints were PFS in the ITT group, and PFS in the subgroup of patients that are *PTEN*-low by IHC (48% of assessable tumors). Median PFS in the ITT population was 6.2 months (95% CI 3.8–9.0) with ipatasertib versus 4.9 months (95% CI 3.6–5.4) with placebo (HR 0.60, 95% CI 0.37–0.98, $P = 0{\cdot}037$). There was a numerical increase in OS with ipatisertib in the ITT population. In 48 patients with *PTEN*-low tumors, median PFS was 6.2 months (95% CI 3.6–9.1) with ipatasertib versus 3.7 months (95% CI 1.9–7.3) with placebo (HR 0.59 95% CI 0.26–1.32, $P = 0.18$). Prespecified analyses of the 42 patients with PIK3CA/AKT1/PTEN-altered tumors by genomic profiling (41% of assessable tumors) also revealed clinical benefit in this group. The most frequent adverse events were diarrhea, low neutrophil count, neuropathy, and pneumonia. IPATunity130 (NCT03337724), a pivotal randomized phase 3 clinical trial evaluating ipatisertib and paclitaxel as first-line therapy for patients with *PIK3CA/AKT1/PTEN*-altered advanced HER-2-negative breast cancer, is actively accruing with an enrollment target of 450 subjects.

The PAKT trial is a randomized double-blind, placebo-controlled phase 2 clinical trial that tested the AKT inhibitor capivasertib combined with paclitaxel as first-line therapy for 140 patients with advanced TNBC [69]. The trial randomized patients 1:1 to receive paclitaxel 90 mg/m^2 weekly x 3 with either capivasertib (400 mg bid) or placebo days 2–5, 9–12, 16–19 every 28 days. The primary endpoint was PFS in the ITT group, and secondary endpoints included OS in the ITT group, and PFS and OS in the subgroup with alterations in *PI3KCA/AKT1/PTEN*. In the ITT population, the addition of capivasertib to paclitaxel increased median PFS from 4.2 to 5.9 months (HR 0.74, 95% CI 0.50–1.08, $P = 0.06$), and median OS from 12.6 to 19.1 months (HR 0.61, 95% CI 0.37–0.99, $P = 0.04$). For patients with *PIK3CA*/*AKT1*/*PTEN*-altered tumors (n = 28), median PFS increased from 3.7 to 9.3 months (HR 0.30, 95% CI 0.11–0.79, $P = 0.01$). The most common adverse events were diarrhea, neutropenia, rash, infection and fatigue. The CapiTello290 study (NCT 039997123) is a phase 3 double-blind, randomized, placebo-controlled study evaluating capivasertib with paclitaxel as first-line therapy for patients with advanced TNBC. It is actively accruing with an enrollment target of 800 subjects.

Androgen-receptor signaling

About 10% of TNBCs have enriched expression of AR and are classified as the luminal AR subtype [70]. A phase 2 trial tested bicalutamide, a nonsteroidal antiandrogen, in 28 patients with advanced AR+ (>10%) TNBC [71]. Bicalutamide 150 mg daily was associated with a 6-month CBR of 19% (95% CI 7–39) and a median PFS of 12 weeks (95% CI 11–22). Another study evaluated abiraterone acetate 1,000 mg daily with prednisone 5 mg bid in 34 evaluable patients with metastatic AR+ (≥10%) TNBC [72]. The 6-month CBR was 20.0% (95% CI 7.7–38.6), with 5 patients still on treatment at the time of analysis (6.4+, 9.2+, 14.5+, 17.6+, and 23.4+ months). The median PFS was 2.8 months (95% CI 1.7–5.4). Another single arm, open label, 2-stage phase 2 trial evaluated the AR inhibitor enzalutamide 160 mg daily in 118 patients with AR+ (>0%) metastatic TNBC; 78 patients were evaluable [73]. The CBR at 16 weeks was 25% (95% CI 17–33) in the ITT population and 33% (95% CI 25–43) in the evaluable subgroup. The median PFS was 2.9 months (95% CI 1.9–3.7) in the ITT population and 3.3 months (95% CI 1.9–4.1) in the evaluable population. For patients with AR expression of ≥10% or <10%, the median PFS was 14.7 and 8.1 weeks, respectively. Modulating the AR pathway thus has promise for the subset of patients with advanced AR+ TNBC.

Antibody-drug conjugates that target TNBC cell surface molecules

A number of antibody-drug conjugates (ADCs) have been explored in advanced TNBC. The 3 for which the most mature data are available are summarized below.

LIV-1

LIV-1 is a cell-surface zinc-transporter protein expressed by about 70% of advanced breast cancers. Ladiratuzumab vedotin is an ADC that targets the cell-surface protein LIV-1, and delivers MMAE. In the metastatic TNBC cohort of a phase 1 clinical trial, 44 patients were evaluable for efficacy. The ORR was 32%, and the median PFS was 11.3 weeks (95% CI 6.1–12.1) [74]. This agent is still in early phase clinical evaluation.

Glycoprotein NMB (pgNMB)

Glembatumumab vedotin is an ADC that targets gpNMB, a cell surface protein expressed by about 40% of TNBCs, and delivers the cytotoxic agent MMAE. The randomized phase 2 study EMERGE randomized 125 patients with advanced, treatment-refractory breast cancer selected for gpNMG expression at 2:1 to receive glembatumumab vedotin (n = 83) or investigator's choice of chemotherapy (n = 41) [75]. The study did not meet its primary endpoint of ORR, which was 12% in each arm. Exploratory analyses revealed an ORR of 18% versus 0% in TNBC patients, and 40% versus 0% in gpNMB-overexpressing TNBC. The pivotal phase 2b METRIC trial enrolled 327 patients with gpNMB-overexpressing (≥25%

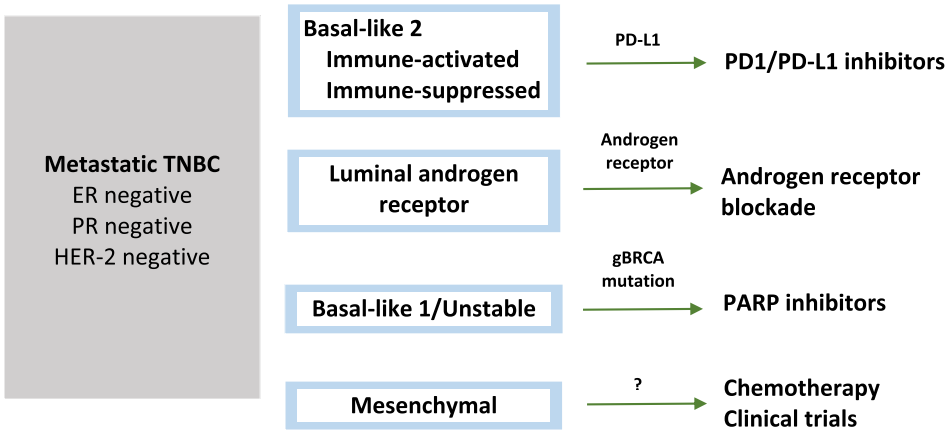

Fig. 2. Biomarker-driven therapy for metastatic triple negative breast cancer is a new and expanding standard of care. For metastatic breast cancers that fail to express the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor-2 (HER-2), it is now standard to test for expression of the programmed death ligand-1 (PD-L1), and for the presence of germline BRCA mutations, which predict the potential to respond to atezolizumab with *nab*-paclitaxel or platinum-based chemotherapy and PARP inhibitors, respectively. Emerging biomarkers of interest include the androgen receptor and alterations in PIK3CA/AKT1/PTEN, but these biomarkers and the agents that target them remain investigational for TNBC. Next generation sequencing is increasingly used to identify genomic alterations associated with clinically relevant biomarkers that may guide more personalized disease management.

tumor cells) metastatic TNBC, randomizing them 2:1 to receive either glembatumumab vedotin or capecitabine. This study failed to meet its primary endpoint of PFS, where the median PFS was 2.9 versus 2.8 months, respectively (HR 0.95, $P = 0.76$), with no differences in the secondary endpoints of ORR, DOR, and OS observed. Clinical development of this agent has ceased.

Trophoblast cell-surface antigen 2 (Trop-2)

Sacituzumab govitecan-hziy is an ADC specific for Trop-2, a cell surface calcium signal transducer, that delivers the cytotoxin SN-38, an analog of irinotecan. A phase 1/2 clinical trial evaluated sactizumab govitecan-hziy at a dose of 10 mg/kg in 108 patients with metastatic TNBC who had received ≥2 prior therapies for advanced disease; 88% expressed at least moderate levels of Trop-2 [76]. The ORR was 33.3% (95% CI 24.6–43.1), and the median DOR was 7.7 months (95% CI 4.9–10.8). The median PFS and OS were 5.5 months (95% CI 4.1–6.3) and 13.0 months (95% CI 11.2–13.7), respectively. The most common toxicities were anemia and neutropenia, with a 9.3% rate of febrile neutropenia. Only 3 patients (2.8%) discontinued therapy due to adverse events. The pivotal randomized phase III ASCENT trial has completed the accrual of 529 patients with metastatic TNBC who have progressed after ≥2prior chemotherapies (including a taxane) for metastatic disease (NCT02574455). Patients were randomized 1:1 to receive either sacituzumab govitecan-hziy or chemotherapy of physician's choice (eribulin, capecitabine, gemcitabine, or vinorelbine), with primary and secondary endpoints of PFS and OS, respectively. The results are eagerly awaited.

Conclusions

In summary, advanced TNBC has historically been treated with single agent chemotherapy. Recent progress has expanded standard treatment options for some patients to targeted options, with PARP inhibitors approved for patients with germline mutations in BRCA1/2, and the combination of atezolizumab and *nab*-paclitaxel approved for PD-L1 IC+ tumors (Fig. 2). One current clinical challenge is the appropriate sequencing of PARP inhibitors and immunotherapy for advanced TNBC that is both BRCA-mutated and PD-L1 IC+. Given the higher activity of PD-1/PD-L1 blockade in the first-line setting and the potential for OS benefit, we would argue for the use of immunotherapy first, reserving PARP inhibition for a later line unless the patient has a strong preference for a chemotherapy-free treatment regimen or a contraindication to immunotherapy. Several other targeted therapies are in advanced clinical testing, including the AKT inhibitors ipatisertib and capivasertib, and the ADC sacituzumab govitecan-hziy. As these become available in the clinic, questions related both to the optimal sequencing of distinct drug classes as well as the feasibility of sequencing drugs belonging to the same class will become more pressing. It is clear that the era of targeted therapy for TNBC has arrived, which is terrific news for patients and providers alike.

Note added in proof

On April 22, 2020, the FDA granted accelerated approval of sacituzumab govitecan-hziy for the treatment of metastatic TNBC who have recieved at least two prior therapies for advanced disease.

Conflicts of interest

Dr. Emens has participated on advisory boards for Vaccinex, Celgene, Bristol Meyers Squibb, AstraZeneca, Amgen, Syndax, Molecuvax, eTHeRNA, Peregrine, Bayer, Gritstone, Medimmune, Abbvie, Replimune, Bristol-Myers Squibb, Roche, Genentech, Macrogenics, Lilly, Silverback, and Chugai. She has received grant/research support from Genentech/Roche, EMD Serono, Maxcyte, Merck, AstraZeneca, Aduro Biotech, Corvus, and Tempest. In addition, under a licensing agreement between Aduro Biotech, and the Johns Hopkins University, the University and Dr. Emens are entitled to milestone payments and royalty on sales of a GM-CSF-secreting breast cancer vaccine. The terms of these arrangements are managed by the Johns Hopkins University in accordance with its conflict of interest policies. Dr. Malhotra has no conflicts to declare.

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