REVIEW

Searching for Better Outcomes among Patients with Metastatic Triple-Negative Breast Cancer – Do We Have Novel Options on the Treatment Landscape?

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Abstract: Triple-negative breast cancer (TNBC), which accounts for approximately 15% of breast cancers (BCs) is characterized by a lack of expression of the hormone receptors (HRs) (estrogen receptor (ER) and progesterone receptor (PR)), and human epidermal growth factor receptor 2 (HER2). TNBC reveals very aggressive behavior and often leads to poor prognosis. Unfortunately, standard chemotherapy (CHT) is related to low response rates and short progression-free survival (PFS) in patients with metastatic TNBC, creating an unmet need.

However, recent recognition of different molecular subtypes and mutations within TNBC has allowed exploring some innovative targeted therapies, bringing new hope for women suffering from TNBC. Currently, some promising systemic treatment options in this area have been developed, including targeted therapies, such as poly(ADP-ribose) polymerase (PARP) inhibitors, immune checkpoint inhibitors, antibody-drug conjugates, and AKT inhibitors.

The aim of this mini-review is to address these novel treatment modalities and highlight the main directions for further research and clinical practice in the advanced or metastatic forms of TNBC. This article presents poly(ADP-ribose) polymerase (PARP) inhibitors (e.g., olaparib, talazoparib, and valaparib for treatment of BRCA-mutated, HER2-negative metastatic BC), immune checkpoint inhibitors (atezolizumab and pembrolizumab), an antibody-drug conjugate (ADC) (sacituzumab govitecan), and AKT inhibitors (ipatasertib and capivasertib). A brief outline of the main clinical trials leading to the approval of these new medications has been provided. Moreover, this overview discusses the efficacy and safety of these innovative treatment options, focusing on women with metastatic TNBC. In addition, this paper comments on some recent considerations, regarding avenues of delivering care and conduct clinical trials in patients with BC, during the COVID-19 pandemic.

Keywords: Triple-Negative Breast Cancer (TNBC), targeted therapies; poly(ADP-ribose) polymerase (PARP) inhibitors; immune checkpoint inhibitors; antibody-drug conjugates (ADCs); AKT Inhibitors

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1. Introduction

Triple-negative breast cancer (TNBC), which is characterized by a lack of tumor-cell expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) accounts for about 15% -20% of all breast cancers (BC) [1]. TNBC that is more prevalent in younger women reveals aggressive behavior and is related to poor outcomes, especially in advanced or metastatic stages [2]. Unfortunately, most of the afflicted women experience TNBC progression after receiving the first-line chemotherapy (CHT) and the overall
survival (OS) in such patients usually remains below 18 months [3]. Recently, gene expression profiling has shown a large degree of heterogeneity in the TNBC and allowed to detect many molecular subtypes, characterized by specific genomic changes and mutational categories [4].

Importantly, BRCA1 and BRCA2 represent tumor suppressor genes that play a key role in repairing DNA damages in the cells [5]. TNBC is the main subtype of BC among women, who harbor germline BRCA1/2 mutations [6]. Elucidating such details with regard to TNBC has led to the development of some new therapeutic targets, which will hopefully permit a more accurate tailoring of certain therapies to the patients with different subtypes of TNBC.

This article addresses some innovative targeted treatments, such as poly(ADP-ribose) polymerase (PARP) inhibitors (e.g., olaparib, talazoparib, and veliparib for treatment of BRCA-mutated, HER2-negative metastatic BC), immune checkpoint inhibitors (atezolizumab and pembrolizumab), an antibody-drug conjugate (ADC) (sacituzumab govitacan), and AKT inhibitors (ipatasertib and capivasertib). Moreover, this overview highlights the main directions for further research and clinical practice in the advanced or metastatic TNBC. In addition, this paper briefly comments on some considerations about recent avenues of delivering care and conducting clinical trials in patients with BC, in the face of uncertainty and fear, aggravated by the COVID-19 pandemic.

2. Germline BRCA mutations and metastatic BC – How to take advantage of “Vulnerable” Tumors?

Recent advances in tumor DNA sequencing techniques have led to the detection of pathways linked to carcinogenesis and metastatic progression of BC, as well as to targeted approaches to TNBC [6]. It has been established that BRCA1 and BRCA2 genes play a critical role in the repair of double-strand DNA injuries [5,6]. It should be underscored that BRCA1 mutations are mostly related to the TNBC, while BRCA2 mutations are related to the HR-positive/HER2-negative BC [5,6]. Furthermore, “BRCAAness” is the term used to describe tumors that are BRCA-proficient, however they behave as if they were deficient in DNA double-strand break repair mechanism (via homologous recombination) [7]. In addition, in patients with TNBC, the BRCAAness phenotype may be associated with BRCA mutations, BRCA1 promoter methylation, or low BRCA1 mRNA or protein expression [8]. As a consequence, such “vulnerable” tumors, which have alterations in BRCA1/2 genes, and thus, are unable to repair their DNA double-strand breaks (DSB) become dependent on single-stranded break (SSB) repair mechanism that is physiologically mediated by poly (ADP-ribose) polymerase (PARP) enzymes [8]. In essence, PARPs are a group of enzymes that transfer adenosine diphosphate (ADP) ribose parts to proteins, upon various signals, and take part in the cellular repair of DNA SSB [8]. In these circumstances, purposeful blocking of the PARP’s action (repair of DNA SSB) causes DNA DSB and replication fork collapse, resulting in cell death [8]. This creates a “perfect opportunity” for PARP inhibitors, as a class of targeted agents, for the treatment of patients with metastatic TNBC with BRCA1/2 mutations [8].

In the OlympiAD trial, which included patients with germline BRCA mutation and HER2-negative metastatic BC, olaparib (a PARP inhibitor) in monotherapy was compared to single-agent CHT of doctor’s choice (capecitabine, eribulin, or vinorelbine) (Table 1) [9,10]. The OlympiAD trial revealed an improvement in median PFS (7 versus 4.2 months) and ORR from 28.8 to 59.9%, among patients who received olaparib compared to those women, who received CHT [9,10]. Also, the safety of olaparib was acceptable, if indicated precautions and monitoring tests were timely performed (Table 2) [9,10]. Moreover, many patients had improved QoL in the olaparib group compared to the CHT group (33.7% vs. 13.4%, respectively) [10,11].

Similarly, in the EMBRACA trial, in patients with advanced BC and a gBRCA1/2 mutation (who received up to three prior lines of CHT), talazoparib (a PARP inhibitor) has revealed a better median PFS, compared to CHT of doctor’s choice (capecitabine, eribulin, gemcitabine, or vinorelbine) (8.6 vs. 5.6 months), and an improvement in ORR (from 27.7 to 62.2%) (Table 1) [12]. Moreover, among women in the talazoparib group, QoL and psycho-physical functioning level have been improved [13].

In the BROCADE-3 trial, Veliparib (a PARP inhibitor) has explored for the first time in combination with platinum-based CHT in patients with BRCA-mutated, HER2-negative metastatic BC (after no more than two previous lines of CHT and one prior platinum-based CHT). This trial assessing veliparib added to CHT (carboplatin and paclitaxel) is ongoing (Table 1) [14].

3. Immune checkpoints as a “double-edge sword” – How can we turn it to therapeutic strategies for patients with TNBC?

Physiologically, immune checkpoints are inhibitory
receptors that are “responsible” for preventing excessive damage to the tissues, which usually takes place during infections. Immune checkpoints are predominantly expressed on the surfaces of T cells and tumor cells, from which they conduct different “mediatory actions” [15]. Under such circumstances, blocking the T cell immunity causes a reduction of the cytotoxic T lymphocytes (CTL) activity and decreases the recruitment of regulatory T cells (Treg) myeloid derived suppressor cells (MDSC), and anti-inflammatory cells [16].

Programmed cell death 1 ligand 1 (PD-L1), which is an immunoglobulin superfamily haplotype type I transmembrane glycoprotein, contributes to cell apoptosis [16]. PD-L1 is widely expressed on the surface of lymphocytes, monocytes, natural killer (NK) cells, macrophages, and some other cells [16]. Similarly, programmed cell death protein-1 (PD-1), which is an inhibitory immune checkpoint that limits T-cell effector functions within tissues, is expressed on the surfaces of immune effector cells (e.g., T-cells, B cells, NK cells, dendritic cells (DCs), and tumor infiltrating lymphocytes (TILs)) [16].

An activation of PD-1 receptors on T lymphocytes and their binding to the ligands (PD-L1 and PD-L2) leads to blocking of the T cell’s functions. The PD-1/PD-L1 axis is “in charge” of precise regulation of T cell activation and prevention of tissue damage. Unfortunately, the PD-1/ PD-L1 axis represents also “a double-edge sword” that allows cancer cells to escape immune surveillance [16]. In practical terms, it causes suppression of the cytotoxic capability of T cells, which permits the tumor cells to escape cytotoxic reactions. As a consequence, malignant tumors are protected from the immune system attacks [16]. In this scenario, innovative immunomodulatory agents, such as immune checkpoints inhibitors, play a promising role of immunotherapeutic strategies for patients with advanced or metastatic TNBC [16].

4. Immune checkpoints inhibitors in metastatic TNBC

Notably, metastatic BC creates a specific microenvironment, where proliferation, apoptosis, and infiltration of the immune system cells occur simultaneously. Under these circumstances, tumor cells undergo apoptosis followed by phagocytosis, and tumor-specific antigens are expressed on the major histocompatibility complex (MHC) molecules by tumor-infiltrating antigen presenting cells (APC). Subsequently, APC can activate antigen-specific cytotoxic T lymphocyte (CTL) responses [16].

TNBC has a higher level of PD-L1 expression, and therefore, a blockade of PD-L1 by using immune checkpoint inhibitors can activate tumor-specific T-cell responses, causing increased anti-tumor activity and improving prognosis in patients with TNBC [16].

The use of the immune checkpoint inhibitors against PD-1 or PD-L1 have enriched a current therapeutic armamentarium for TNBC [16]. The cross-communication between PD-1 on T-cells and its ligands, PD-L1 and PD-L2, on neoplastic cells leads to T-cell exhaustion and conversion of T effector cells to immunosuppressive T regulatory (Treg) cells [16]. Subsequently, the immunotherapy directed against PD-1 or PD-L1, inhibits the “suppressive” action of the PD-1/PD-L1 axis. This in turn, causes the reactivation of cytotoxic T effector cells, releasing the anti-cancer “power” of the immune system [16].

5. Lessons learned from the IMpassion130 trial

Notably, in TNBC, expression of PD-L1 occurs mostly on tumor-infiltrating immune cells and contributes to poor anti-neoplastic immune responses [17,18]. This finding was an inspiration to evaluate the immune checkpoint inhibitor, an anti-PD-L1 agent - atezolizumab in combination with CHT agent (a nanoparticle albumin-bound (nab) paclitaxel) in the IMpassion130 trial in women with previously untreated advanced TNBC (Table 1) [17,18].

The IMpassion130 has led to approval of atezolizumab in combination with nab-paclitaxel for the treatment of patients with advanced or metastatic TNBC (who did not receive prior therapy for TNBC) (Table 1) [17,18]. The application of the checkpoint inhibitor with taxane-based CHT (blocking mitosis) was selected, since this combined therapy can increase the tumor-antigen release and magnify antitumor responses to the immune checkpoint inhibition [17,18].

In essence, the IMpassion130 trial has shown that the patients, whose TNBCs were positive for PD-L1 (about 41%) and received atezolizumab plus CHT had better outcomes compared to the ones treated with the nab-paclitaxel only (Table 1) [17,18].

Moreover, the combined therapy of atezolizumab and nab-paclitaxel has shown an acceptable safety and tolerability profile (Table 1) [17,18]. However, it has been recommended that all the patients receiving immunotherapy have to be closely monitored and well-educated about possible symptoms associated with the use of PD-L1 inhibi-
tors. In case of detection of any specific immune-mediated side effects, immediate intervention is required (Table 2)\textsuperscript{[17,18]}. It should be noted that the approval of atezolizumab in combination with nab-paclitaxel for the treatment of advanced or metastatic TNBC applies only to the patients, whose tumors express PD-L1 (staining of immune cells in ≥ 1% of tumor area, according to the Ventana diagnostic antibody SP142 test, which is the companion/complementary diagnostics for different subtypes of BC and other cancers)\textsuperscript{[17,18,19]}.

6. Immunotherapy in TNBC – promising signals from the KEYNOTE-086 and KEYNOTE-355 trials

According to the results of the KEYNOTE-086 trial, a PD-1 inhibitor, pembrolizumab, has shown durable antitumor activity (as a single-agent) in patients with both previously treated and untreated PD-L1-positive metastatic TNBC (Table 1)\textsuperscript{[20,21]}. Moreover, a safety profile of this anti-PD-1 antibody was manageable (Table 1)\textsuperscript{[20,21]}. Also, the ongoing KEYNOTE-355 trial, directly compares pembrolizumab (plus CHT of doctor's choice (e.g., nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin) to placebo plus CHT, as first-line therapy, among women with advanced or metastatic TNBC patients (Table 1)\textsuperscript{[22]}. The findings of the KEYNOTE-355 trial have been anticipated by research and clinical community. In the future, a detailed explanation of the immunologic mechanisms of patients, who most favorably responded to pembrolizumab can help identify a subgroup of women that may achieve the best possible outcomes upon monotherapy with pembrolizumab. In addition, further randomized trials of pembrolizumab in monotherapy or in combination therapy (e.g., with CHT or PARP inhibitors) for the treatment of women with metastatic TNBC are certainly merited.

7. Focus on Sacituzumab govitecan (IMMU-132) - a novel antibody–drug conjugate (ADC) – Do we have another treatment option for women with metastatic TNBC?

Sacituzumab govitecan (IMMU-132) is an antibody–drug conjugate (ADC) combining a humanized monoclonal antibody (that targets the human trophoblast cell-surface antigen 2 (Trop-2)) with SN-38 (an active metabolite of irinotecan, a topoisomerase I inhibitor), through the cleavable linker\textsuperscript{[23]}. Trop-2, a transmembrane calcium signal transducer that stimulates malignant cell growth is overexpressed in different epithelial cancers, including TNBC\textsuperscript{[24]}. Upon binding to Trop-2, SN-38 is transported to the tumor cells, and due to the cleavable linker, SN-38 is being released intracellularly (into the tumor itself) and extracellularly (into the tumor’s microenvironment), because of so-called bystander effect\textsuperscript{[25]}.

In this way, sacituzumab govitecan permits delivery of high concentrations of SN-38 to the tumor cells\textsuperscript{[26]}. Based on the findings of the IMMU-132-01 trial (an open-label, single-arm, multicenter trial, involving patients with various types of advanced solid tumors), the use of sacituzumab govitecan resulted in durable objective responses in women with metastatic TNBC (who previously received at least two anti-cancer treatments) (Table 1)\textsuperscript{[29]}.

In addition, objective responses were reported in women, who were given prior therapy with immune checkpoint inhibitors (e.g., PD-1 or PD-L1 inhibitors)\textsuperscript{[29]}. This may indicate that such a combination therapy can be useful, especially, since there was no cross-resistance with immunotherapy\textsuperscript{[29]}. Overall, IMMU-132 has revealed efficacy with a 33% response rate in a pretreated population of women with metastatic TNBC and its adverse effects were manageable (with applying necessary precautions) (Table 2)\textsuperscript{[29]}.

8. A spotlight on the PI3K-AKT-mTOR axis – Can we consider the use of AKT Inhibitors for TNBC?

Current advances in molecularly targeted agents have created some potential solutions to the most difficult to treat BC subtypes, including TNBC. It has been reported that so-called “druggable” mutations (related to the actionable gene changes) may affect therapeutic choices in order to more accurately tailor treatments to individual patients with TNBC\textsuperscript{[6,7,27,28]}. In particular, abnormalities of the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathway influence the carcinogenic processes in BCs and other malignancies\textsuperscript{[6,7,27]}. For instance, the PI3K/AKT/mTOR pathway is often distorted via activation of PIK3CA and AKT1, or loss of PTEN\textsuperscript{[6,7,27]}. However, the precise role of PIK3CA, AKT1, and PTEN alterations, as biomarkers of therapeutic response to targeted treatments (e.g., AKT inhibitors), still requires further assessment\textsuperscript{[6,7,27,28]}

Recently, the highly selective AKT inhibitor, ipatasertib, has been explored in combination with paclitaxel, among patients with metastatic TNBC, in the LOTUS trial (Table 1)\textsuperscript{[27]}. According to the reports from the LOTUS trial, the median PFS and OS were extended with ipatasertib, compared to placebo (Table 1)\textsuperscript{[27]}. In addition, in...
the subset of patients with PTEN-low tumors, the survival advantages of ipatasertib seemed to be even greater [27].

The PAKT trial has examined the addition of another AKT inhibitor, capivasertib, to first-line paclitaxel in women with metastatic TNBC [29]. Patients who received capivasertib had longer median PFS and median OS compared to the ones, who received placebo/paclitaxel, and such benefits were more pronounced in women with PIK3CA/AKT1/PTEN-altered tumors (Table 1) [29].

At present, two AKT inhibitors, ipatasertib and capivasertib, are being explored as potential first-line therapy for patients with metastatic TNBC, pending results from the clinical trials [27,29]. Also, these agents have been associated with some concerning adverse effects (e.g., diarrhea that needs to be carefully monitored and treated) (Table 1) [27,29].

9. Considerations of different avenues to deliver care for patients with BC - What can we see through the lens of COVID-19 pandemic?

At a time of anxiety and uncertainty due to the COVID-19 pandemic, both the patients with BC and the medical professionals experience several inconvenient changes superimposed on already difficult and complex issues of cancer management. Therefore, it is crucial to address some critical needs of both “partners in care”, patients and providers, possibly at the same time. Looking at the “bright side” of this situation, despite the adversities, the COVID-19 pandemic may create a chance to change some stereotypes and routines, at present and in the future. For instance, it has been reported that telemedicine visits are viewed by many patients as improvements to conducting clinical trials (e.g., no time spent of traveling, waiting, and limited exposure to infections) [30]. Also, more efficient study enrollment, data collection, or evaluations of adverse events via safe electronic technology, as well as direct shipment of study medications (e.g., oral formulations) or brochures to patients have been beneficial, and perhaps should be continued in the future [30]. This is in agreement with a consensus that has been reached regarding the modifications of BC guidelines during COVID-19 pandemic, according to which, only the necessary interventions should be performed, and otherwise, the workload at the medical institutions should be reduced [31].

Moreover, the recent European Society for Medical Oncology (ESMO) BC guidelines have addressed a wide spectrum of clinical problems and provided organized ways of diagnostic and therapeutic approaches in the COVID-19–era [32]. For instance, high-priority recommendations relay to patients, whose clinical status is unstable or tumor burden is life-threatening, medium-priority - to those, for whom postponing therapy beyond six weeks may decrease the probability of benefits from the interventions, and low-priority - to those, for whom the interventions can be delayed during the COVID-19 pandemic, without posing unnecessary health-related risks [32]. Based on the ESMO’s guidelines, tumor boards (involving multidisciplinary experts) should consider urgent oncology care, depending on detailed analysis of clinical and personal circumstances of individual patients, to improve their prognosis and QoL [32]. In particular, for women with a new diagnosis of localized BC, neoadjuvant CHT, targeted or hormonal therapies have been recommended [32]. Simultaneously, for patients with the metastatic BC, symptom-oriented monitoring, oral medications, and de-escalated maintenance therapy, need to be considered [32]. Furthermore, during the COVID-19 pandemic, offering to medical staff some basic support (e.g., adequate nutrition, rest, and help with personal needs), together with assuring precise communication channels, flexible diagnostic or therapeutic protocols, and sufficient medical equipment or facilities should result in improved professional efficiency and better control of this challenging situation [33]. In addition, it is essential to increase the patient’s and clinicians’ resilience to surrounding stressors, via implementing constructive coping skills and supportive approaches [34].

10. Conclusions and Future Research Directions in TNBC

TNBC is a very aggressive and heterogeneous subtype of BC. After many years of using cytotoxic CHT, some novel, molecularly targeted strategies bring some good news for the survival of patients with TNBC. In particular, elucidating molecular characteristics and targetable pathways allowed to re-shape the treatment landscape by making more precise choices of targeted therapies for individual patients with TNBC. In addition, accurate biomarkers need to be determined, to be able to choose the most appropriate candidates for such treatments and to estimate the risk of developing resistance to therapy, and typical adverse effects, due to specific anti-cancer treatments.

Currently approved targeted therapies for patients with BC, include Olaparib and talazoparib (PARP inhibitors) for gBRCA mutated HER2-negative metastatic BC, atezolizumab (immune checkpoint inhibitor) in combination with nab-paclitaxel for PD-L1-positive advanced or metastatic TNBC, and sacituzumab govitecan (an ADC)
for patients with metastatic TNBC who received at least two prior therapies. Moreover, potential innovative molecular targets, such as PIK3CA/AKT/PTEN pathway mutations have been detected and ongoing trials are assessing various agents, such as AKT inhibitors and some other options. It should be underscored that when tailoring the most optimal treatments for a given patient, clinicians need to incorporate relevant data from the recent clinical studies and adjust them to each patient’s medical and personal scenario. Moreover, such treatments should hopefully improve both the clinical outcomes and the QoL of women with metastatic TNBC. Importantly, the patient’s education and engagement should also enhance every treatment effect. Further clinical trials need to be focused on discovering the most optimal sequences or combinations of targeted therapies with other approaches (e.g., CHT, RT, surgery, or supportive care) that can augment the treatment’s efficacy and safety, as well as improve the patient’s survival. Also, whenever possible, tumor molecular profiling should be done at diagnosis and after TNBC recurrence or progression, to help with the most appropriate treatment plan.

References


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Table 1. Selected clinical trials of PARP inhibitors, immune checkpoint inhibitors, antibody-drug conjugate, and AKT inhibitors in patients with advanced or metastatic triple negative breast cancer

| Target therapy | Clinical trial phase, identifier | Trial’s main endpoints | Practical implications of the trial | Author, year [ref.]
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<tr>
<td>Olaparib PARP inhibitor</td>
<td>OlympiAD, phase III NCT02800622</td>
<td>m PFS prolonged by 2.8 ms in olaparib arm; m OS = 19.3 ms in olaparib arm vs. 17.1 ms in CHT arm</td>
<td>efficacy &amp; safety of olaparib vs. CHT (capcitabine, vinorelbin, or eribulin) in pts with gBRCA and HER2-neg metastatic BC; possible OS benefit with olaparib, in pts who did not receive CHT for metastatic BC</td>
<td>Robson et al. 2017, 2019 [9,10]</td>
</tr>
<tr>
<td>Talazoparib PARP inhibitor</td>
<td>EMBRACA phase III NCT01945775</td>
<td>m PFS prolonged by 3.5 ms in talazoparib arm; ORR doubled in talazoparib arm vs. CHT arm</td>
<td>efficacy &amp; safety of talazoparib vs. CHT (capcitabine, eribulin, gemcitabine or vinorelbine) in pts with gBRCA4 mutation, HER2-neg locally advanced or metastatic BC</td>
<td>Litton et al. 2018 [10]</td>
</tr>
<tr>
<td>Veliparib PARP inhibitor</td>
<td>BROCADE-3 phase III (ongoing) NCT021163694</td>
<td>in the subgroup analysis, in pts receiving veliparib as the 1-st-line therapy m PFS prolonged by 3.5 ms; 3-year PFS rate = 27.9% vs. 13.0% for pts on CHT</td>
<td>awaiting results of ongoing investigation of veliparib in combination with paclitaxel/carboplatin</td>
<td>Aun et al. 2019 [16]</td>
</tr>
<tr>
<td>Atezolizumab Anti-PD-L1 antibody</td>
<td>IMpassion130 phase III NCT02425891</td>
<td>PFS &amp; OS improved in PD-L1-positive pts; a trend of improved OS with atezolizumab in the ITT group (21.0 vs 18.7 ms) &amp; in the PD-L1-positive pts (25.0 vs 18.0 ms)</td>
<td>atezolizumab + nab-paclitaxel vs. placebo + nab-paclitaxel for pts with previously untreated advanced or metastatic TNBC; adding atezolizumab to 1-st-line CHT (nab-paclitaxel) prolonged m PFS in the ITT group (7.2 vs 5.5 ms) &amp; in pts with PD-L1-positive tumors (7.5 vs 5.0 ms); ORR was higher in the ITT group (56.0% vs 45.9%) and PD-L1-positive subgroup (58.9% vs 42.6%); the PD-L1 expression in immune cells is a predictor of response; in PD-L1-negative pts, there was no therapeutic effect of atezolizumab/nab-paclitaxel</td>
<td>Schmid et al. 2018,2020 [17,18]</td>
</tr>
<tr>
<td>Pembrolizumab Anti-PD-1 antibody</td>
<td>KEYNOTE-806 phase II NCT02447003</td>
<td>ORR- improved, safety-manageable</td>
<td>pembrolizumab monotherapy - as 1-st-line therapy for pts with PD-L1-positive advanced or metastatic TNBC ORR = 5.7% - in cohort A: pts previously-treated; ORR = 21.4% - in cohort B: pts previously untreated</td>
<td>Adams et al. 2019 [19]</td>
</tr>
<tr>
<td>Pembrolizumab Anti-PD-1 antibody</td>
<td>KEYNOTE-355 phase III (ongoing) NCT028191518</td>
<td>pending data analysis</td>
<td>comparison of pembrolizumab + CHT (nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin) to placebo + CHT in pts (previously untreated) with recurrent inoperable/metastatic TNBC</td>
<td>[21]</td>
</tr>
<tr>
<td>Target agent</td>
<td>Olaparib</td>
<td>Talazoparib</td>
<td>Atezolizumab</td>
<td>Sacituzumab govitecan</td>
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<td>Therapeutic class</td>
<td>PARP inhibitor</td>
<td>PARP inhibitor</td>
<td>IC inhibitor - monoclonal antibody</td>
<td>Antibody-drug conjugate</td>
</tr>
<tr>
<td>Main Indications for use in BC</td>
<td>for deleterious or suspected deleterious gBRCAm, HER2-negative metastatic BC, in pts who have been treated with CHT in the neoadjuvant, adjuvant, or metastatic setting</td>
<td>for pts with deleterious or suspected deleterious gBRCAm, HER2-negative, advanced or metastatic BC</td>
<td>used with nab-paclitaxel for pts with advanced or metastatic TNBC whose tumors express PD-L1</td>
<td>against Trop-2, delivers the cytotoxic SN-38</td>
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<tr>
<td>Adverse effects</td>
<td>Anemia, leukopenia, fatigue, nausea, vomiting, diarrhea, abdominal pain</td>
<td>Fatigue, nausea, headache, alopecia, back pain, anemia, neutropenia, thrombocytopenia, vomiting, diarrhea, decreased appetite</td>
<td>Alopecia, fatigue, peripheral neuropathies, nausea, diarrhea, anemia, constipation, headache, neutropenia, vomiting, decreased appetite, pyrexia, arthralgia</td>
<td>Neutropenia, anemia, nausea, vomiting, diarrhea, fatigue, increased AST, ALT, alkaline phosphatase, alopecia, &lt; Mg, Ca</td>
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<tr>
<td>Special precautions</td>
<td>Pneumonitis - interrupt treatment if pneumonitis is suspected; discontinue if it is confirmed; rare MDS/AML - if MDS/AML is confirmed, discontinue olaparib; combination of olaparib with other DNA damaging agents can increase myelosuppressive toxicity; Coadministration of CYP3A4 inhibitors can increase olaparib plasma concentrations (CYP3A inhibitors should be avoided)</td>
<td>Coadministration with amiodarone, carvedilol, verapamil, clarithromycin, or itraconazole should be avoided; but if these agents have to be used, the dose of talazoparib should be reduced accordingly</td>
<td>Immune-mediated pneumonitis or interstitial lung disease; administer prednisone, and taper it; elevated liver function tests, immune-mediated hepatitis; monitor for signs and symptoms of hepatitis, administer corticosteroids, followed by taper; immune-mediated colitis or diarrhea; if symptoms persist for &gt;5 days or recur, administer steroids</td>
<td>Premedicate for prevention of CHT-induced nausea and vomiting; Severe neutropenia may occur; withhold in case if ANC&lt;1,500/mm3 or neutropenic fever; consider G-CSF for secondary prophylaxis; start anti-infective treatment in pts with febrile neutropenia; Severe diarrhea can occur; monitor pts, give fluids/ electrolytes as needed; use atropine or loperamide (if no infection)</td>
</tr>
<tr>
<td>Important monitoring tests</td>
<td>CBC count for cytopenia - at baseline and then monthly; pts have to recover from hematological toxicity (e.g., due to previous therapy) before starting a PARP inhibitor</td>
<td>CBC count for cytopenia at baseline and then monthly; pts have to recover from hematological toxicity (e.g., due to previous therapy) before starting a PARP inhibitor</td>
<td>ALT, AST, and total bilirubin</td>
<td>CBC count periodically; in case of diarrhea, evaluate for infectious causes</td>
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**Table 2.** PARP inhibitors, immune checkpoint inhibitor, and antibody-drug conjugate approved for treatment of patients with advanced or metastatic triple negative breast cancer – the main indications, adverse effects and special precautions.

**Abbreviations:** AML, acute myeloid leukemia; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BC, breast cancer; BP, blood pressure; Ca, calcium; CBC, complete blood cell; CHT, chemotherapy; gBRCAm, germline BRCA-mutated; G-CSF, granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2; IC, immune checkpoint; MDS, myelodysplastic syndrome; Mg, magnesium; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed cell death ligand-1 protein; pts, patients; Trop-2, antitrophoblast cell-surface antigen 2.