

# Combining Immune Checkpoint Inhibitors With Chemotherapy for the Treatment of Metastatic Triple-Negative Breast Cancer: An Overview for Managed Care Professionals

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## HIGHLIGHTS

- › Current Treatment Landscape and Emerging Therapies for Metastatic Triple-Negative Breast Cancer
- › Impact of Emerging Clinical Trends on Overall Cost of Care and the Role of the Managed Care Pharmacist
- › CE Sample Posttest

# Combining Immune Checkpoint Inhibitors With Chemotherapy for the Treatment of Metastatic Triple-Negative Breast Cancer: An Overview for Managed Care Professionals

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## Intended Audience

Managed care payers, pharmacy directors, pharmacy benefit managers, specialty pharmacy directors, and any other pharmacist and/or healthcare professional interested in scientific advances for combination therapies in the treatment of metastatic triple-negative breast cancer.

## Activity Overview

Triple-negative breast cancer (TNBC) accounts for 15% to 20% of all newly diagnosed breast cancers and is a particularly aggressive type of breast cancer that is associated with poorer prognosis than other subtypes. The heterogeneity of TNBC and lack of specific molecular targets make it challenging to treat. Although TNBC is responsive to cytotoxic chemotherapy, duration of response is short, and relapses are common. Compared with other types of breast cancers, the increased expression of PD-L1 in some TNBCs makes it a good target for immune checkpoint inhibitor (ICI) therapy. However, use of combination ICI plus chemotherapy in patients with TNBC that express PD-L1 has shown promising results. Costs associated with metastatic TNBC have continued to increase with advancements in treatment. Examining current guideline recommendations and utilizing value frameworks to evaluate impact to stakeholders will be key for managed care pharmacists to fully comprehend how these emerging treatment regimens fit into current and evolving treatment paradigms. Pharmacists and managed care professionals need to work together to manage resource utilization to optimize patient outcomes and promote value-based care in oncology.

## Statement of Educational Need

Treatment options for triple-negative breast cancer (TNBC) have historically been limited by high rates of treatment failure after traditional cytotoxic chemotherapy and disease recurrence as well as significant toxicities for patients. TNBC is associated with low overall survival. However, research has indicated that some TNBCs express PD-L1, making it a good target for immune checkpoint inhibitors (ICIs). In recent years, new research has focused on investigating combination strategies of chemotherapy with ICIs, with early results demonstrating improved

clinical benefit. Pharmacists must be familiar with patient-specific factors determining therapy selection, as disease progression may require modifications to therapy plans. Despite the potential therapy benefits with combination regimens, growing availability of biologic agents and increased patient survival will have significant financial implications that managed care professionals must consider when determining medical drug spending. Pharmacists must recognize where combination regimens that include ICIs fit within established treatment guidelines to limit treatment discordance, which has been associated with higher costs. Managed care professionals also need to remain informed about results from clinical trials and cost-effectiveness studies of chemotherapy/ICI combination regimens, as these results will inform decisions of coverage and formulary placement of ICIs for patients with metastatic TNBC. Equipped with knowledge of emerging combination chemotherapy/ICI treatment advances in metastatic TNBC, managed care pharmacists and professionals will be prepared to establish strategies and interventions to optimize future access to value-based care.

## Educational Objectives

Upon completion of this activity, participants will be able to:

- Analyze emerging clinical data involving the use of immune checkpoint inhibitor (ICI)/chemotherapy combination regimens for the treatment of metastatic triple-negative breast cancer (mTNBC).
- Determine how emerging ICI/chemotherapy combinations will fit into the future treatment paradigm for mTNBC.
- Examine the impact of ICI/chemotherapy treatment combinations on the overall cost of care for mTNBC.
- Identify strategies and interventions that improve cost of care and enhance the value of treatments in mTNBC.

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### OVERVIEW

Through this supplement to *The American Journal of Managed Care*<sup>®</sup>, managed care professionals will increase their knowledge of combination therapies in the therapeutic landscape of triple-negative breast cancer.

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# Current Treatment Landscape and Emerging Therapies for Metastatic Triple-Negative Breast Cancer

Nelly G. Adel, PharmD, BCOP, BCPS

## Introduction

Worldwide, breast cancer is the most frequently diagnosed cancer in women. In the United States, it accounts for 30% of all cancers in women and is the second leading cause of cancer-related mortality, surpassed only by lung cancer. In 2021, an estimated 284,200 new cases of breast cancer and 44,130 deaths related to breast cancer will have occurred, representing 15% of all new cancer cases and 7.3% of all cancer deaths.<sup>1,2</sup>

Breast cancer is highly heterogeneous at the molecular level, characterized by the presence of discrete subtypes with distinct clinical behaviors. Several molecular biomarkers, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression have been incorporated into the breast cancer diagnostic staging system and impact therapy selection.<sup>3</sup> Triple-negative breast cancer (TNBC) is a subgroup of breast cancer lacking expression of all three of these biomarkers; defined more specifically by the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) as tumors that have less than 1% cellular expression of ER and PR, as determined by immunohistochemistry (IHC), and HER2 expression of 0 or 1+ by IHC or 2+ by IHC. An IHC result of 2+ is considered equivocal, which indicates the need to undergo a more accurate testing with fluorescence in situ hybridization; this will determine whether the tumor is HER2 positive or HER2 negative.<sup>4,5</sup>

## TNBC

### Epidemiology and Prevalence

TNBCs account for approximately 15% to 20% of all newly diagnosed breast cancers. Incidence rates in non-Hispanic Black women are almost double the rates compared with other racial/ethnic groups, which may account for the fact that they experience 40% higher breast cancer-associated death rates.<sup>6,7</sup>

Breast cancer as a whole is most common in middle-aged and older women, with a median age at diagnosis of 62 years.<sup>8</sup> There is a significant increase in incidence of breast cancer after the age of 40 and a bimodal age frequency distribution, with peaks near 45 and 65 years.<sup>9</sup> By contrast, TNBC is more prevalent in younger women (<50

## ABSTRACT

A lack of therapeutically targetable molecular alterations and its aggressive nature make triple-negative breast cancer (TNBC) a challenging disease. Chemotherapy is standard of care for most patients with metastatic disease, but median overall survival is less than 18 months. Unravelling the molecular underpinnings of TNBC revealed it to be a potentially highly immunogenic subtype within a more broadly immunologically inert cancer type, suggesting that it may respond to immunotherapy. An urgent need for new therapies is being filled in part by recent successes with immune checkpoint inhibitors (ICIs) targeting the programmed cell death receptor 1 and programmed death ligand 1 (PD-L1). Although single-agent ICIs had limited activity, exploration of rational combinations has yielded 2 new FDA approvals for atezolizumab and pembrolizumab in combination with chemotherapy, leading to a new standard of care for patients with PD-L1-positive disease. Two FDA-approved companion diagnostic PD-L1 assays are available to identify patients eligible for immunotherapy treatment, but other biomarkers of response are also being examined. Ongoing clinical trials are also evaluating a range of targeted therapies as combination partners, which may have immunomodulatory effects in addition to their main mechanism of action, complementing the activity of ICIs. This article will evaluate the current and emerging clinical trends in the use of ICIs as part of combination regimens in the treatment of patients with metastatic TNBC.

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For author information and disclosures, see end of text.

years), which presents a challenge as it often occurs in women who are not part of breast cancer screening programs, thus patients are diagnosed with more advanced stages of the disease. When it does occur in women undergoing regular screening, TNBC usually presents as an interval cancer (occurring between 2 mammograms).<sup>10</sup>

Along with younger age and Black race, a number of other risk factors associated with TNBC have been identified. These include the presence of a mutation in the breast cancer susceptibility genes, *BRCA1* and *BRCA2*; up to 20% of patients with TNBC harbor a *BRCA1/2* mutation.<sup>11</sup> Notably, mutations in *BRCA1/2* occur in approximately 2.5% of the Ashkenazi Jewish population, which puts them at high risk for developing TNBC.<sup>12</sup> The penetrance of breast cancer at age 70 among *BRCA1* mutation carriers in this population is 46% and for *BRCA2* mutation carriers, it is 26%.<sup>13</sup> Studies have also found that reproductive factors, including multiparity, young age at first pregnancy, and obesity are associated with an increased risk of TNBC, whereas breastfeeding may be associated with a reduced risk of TNBC.<sup>10,14-16</sup>

### Prognosis and Pathogenesis

TNBC has historically been considered a single-disease entity, with diagnosis dependent on accurate assessment of the status of ER, PR, and HER2; “omics” technologies have revealed substantial complexity and heterogeneity at the molecular level. Breast cancers as a whole can be categorized into 4 major gene expression-based subtypes: luminal A (ER+, PR+, HER2-), luminal B (ER+, PR+, HER2+), HER2-enriched (ER-, PR-, HER2+), and basal-like (ER-, PR-, HER2-, CK5/6 and EGFR+).<sup>17-19</sup> The majority of TNBCs fit into the basal-like subtype, but the remainder are distributed across the other subtypes.<sup>20</sup> Meanwhile, studies have further elucidated at least 4 different gene expression-based TNBC subtypes: 2 basal subtypes (BL1 and BL2), a mesenchymal subtype (M), mesenchymal stem-like (MSL), immunomodulatory (IM) and a luminal androgen receptor (LAR) subtype.<sup>21</sup> While these insights have yet to translate into clinical utility, they help to explain much of the variation in natural history and clinical behavior observed in TNBCs.

Most TNBCs are high-grade invasive ductal carcinomas with a high proliferative rate. Clinically, they are a particularly aggressive type of breast cancer, associated with poorer prognosis than other subtypes. TNBC accounts for approximately 5% of all cancer-related deaths annually<sup>22</sup> and has one of the lowest 5-year relative survival rates, just 11.5% for patients with distant metastases.<sup>23</sup> TNBC is a chemo-sensitive disease, with some of the highest pathologic complete response rates to neoadjuvant chemotherapy among breast cancer subtypes<sup>24</sup>; however, they have a higher rate of early recurrence and distant metastasis, particularly to the brain and lungs. Relapse rates peak between 3 and 5 years post-surgery and the risk of death following recurrence is higher in patients with TNBC compared with other types of breast cancer.<sup>10</sup> The progress

in understanding the heterogeneity of this disease has opened the door for new therapeutic strategies.

## Metastatic TNBC (mTNBC)

### Current Standard of Care

The lack of molecular targets in TNBC makes it challenging to treat and, in patients with locally recurrent inoperable or metastatic disease, chemotherapy remains the standard of care. No agent is specifically approved for TNBC, but chemotherapies that are approved for metastatic breast cancer are also used in the setting of TNBC. The National Comprehensive Cancer Network (NCCN) recommends either anthracyclines or taxanes as preferred first-line treatment options for patients who have not previously received these agents as neoadjuvant or adjuvant treatment.<sup>25</sup> The NCCN guidelines detail the doses for preferred chemotherapy regimens. Patients with *BRCA1/2* mutations can receive poly(ADP-ribose) polymerase (PARP) inhibitors or platinum-based (cisplatin or carboplatin) chemotherapy, based on the results of phase 3 clinical trials that demonstrated the efficacy of these agents, which exploit the DNA repair defects in tumors with *BRCA1/2* mutations.<sup>25</sup> The current guideline-recommended approach is single-agent chemotherapy, as combination chemotherapy has not been shown to prolong survival and is associated with an increased risk of toxicity. However, combination chemotherapy may be appropriate for patients with extensive disease or rapid progression of the disease with multiple organ involvement or who need rapid control of symptoms or disease.<sup>25</sup>

### Second Line and Beyond

In patients who experience progression following first-line therapy, the recommended treatment strategy is for sequential use of other single-agent chemotherapy regimens, without treatment breaks, for as long as it is tolerated. Several options are available for later-line treatment in patients who have progressed and no longer tolerate chemotherapy.<sup>25</sup> The trophoblast cell-surface antigen 2 (Trop-2)-targeted antibody-drug conjugate, sacituzumab govitecan, designed to provide targeted delivery of SN-38, the active metabolite of irinotecan, is approved in this setting.<sup>26,27</sup> In patients with high levels of microsatellite instability (MSI), deficient mismatch repair (dMMR), or high tumor mutational burden (TMB), the PD-1-targeted immunotherapeutic agent pembrolizumab is approved as monotherapy.<sup>25</sup> However, it should be noted that the tumor agnostic approval of pembrolizumab in patients with these biomarkers is based on clinical trials that did not include patients with TNBC.<sup>28,29</sup> **Figure 1** summarizes NCCN guideline-recommended standard of care for mTNBC.<sup>25</sup>

In a meta-analysis of phase 3 clinical trials of chemotherapy in the first-line setting for metastatic breast cancer, the pooled overall response rate (ORR) was 23% and median overall survival (OS) was 17.5 months. As patients progress, the efficacy of chemotherapy

becomes even more limited, with a pooled ORR of 11% reported in a recent meta-analysis.<sup>30</sup> Responses are generally short lived and chemotherapy is associated with toxicity that can impact patient quality of life; thus, there is an urgent need for new therapies to improve outcomes for patients with mTNBC.

### The Evolving Immunotherapy Landscape

T cells, the cytotoxic effectors of the immune system, are able to recognize abnormal cellular antigens present on cancer cells and mount an antitumor immune response against them. In the absence of cancer, T-cell activation is closely regulated by multiple mechanisms, including signaling through inhibitory receptors, dubbed immune checkpoints, that prevent autoreactivity against the body's own cells. Among the best-known immune checkpoints are programmed cell death PD-1 and its ligands PD-L1 and PD-L2. PD-1 is expressed on the surface of T cells, B cells, and natural killer cells, and interaction with its ligands, which are expressed on antigen-presenting cells, inhibits the T-cell response leading to loss of T-cell function. Cancer cells can modulate immune checkpoint signaling (PD-L1 is frequently expressed on tumor cells and immune cells in the tumor microenvironment, for example), thereby evading the immune system by downregulating T-cell cytotoxic activity.<sup>31</sup>

Immunotherapy, designed to reinvigorate the antitumor immune response, has been one of the major breakthroughs of the past decade in cancer research. Immune checkpoint inhibitors (ICIs), particularly monoclonal antibodies targeting PD-1 and PD-L1, are among the most successful types of immunotherapy, eliciting durable

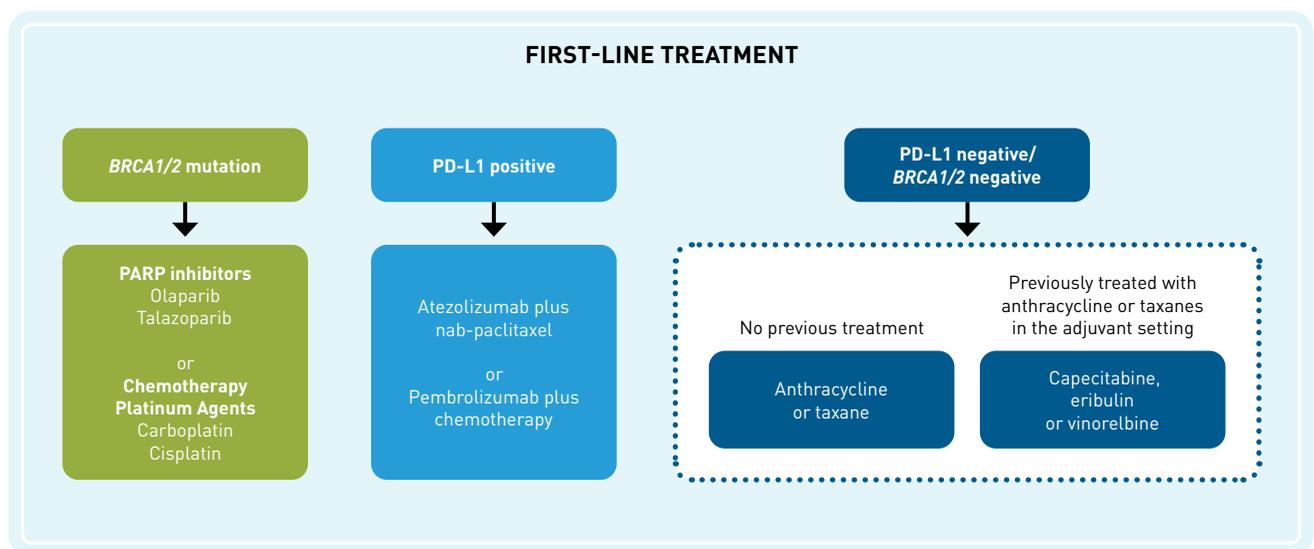
clinical responses across a range of solid tumor types. Despite their success, many patients do not benefit from ICI treatment, which has, in part, been attributed to differences in the immunogenicity of tumors. So-called "hot" tumors are characterized by infiltration of T cells into the tumor microenvironment, molecular signatures of immune activation, and increased PD-L1 expression levels, which has been shown to correlate with improved responses to ICIs.<sup>31-33</sup>

Historically, breast cancer has been considered a "cold" tumor; however, a better understanding of the molecular underpinnings of this disease has revealed that some subtypes are more immunogenic than others. TNBC presents a rational target for ICIs for a number of reasons, including its higher mutational load (meaning a greater number of neoantigens), increased number of tumor-infiltrating immune cells, and high PD-L1 expression levels. ICIs have been explored in numerous clinical trials in patients with mTNBC, but demonstrated limited single-agent activity. The focus has now shifted to exploring rational combination therapy in an effort to boost their effectiveness.<sup>34,35</sup>

### Immunotherapy in Combination With Chemotherapy

Optimal combination strategies are designed to capitalize on additive or even synergistic activity between drugs with complementary mechanisms of action. In addition, with immunotherapy, combination regimens are also designed to exploit the potential immunomodulatory properties of the partner drug. The precise immunomodulatory properties of chemotherapy vary according to the specific agent but, in general, their cytotoxic activity causes

**FIGURE 1.** Initial Approach to Treatment for mTNBC<sup>25</sup>



mTNBC, metastatic triple-negative breast cancer; PD-L1, programmed death ligand 1.

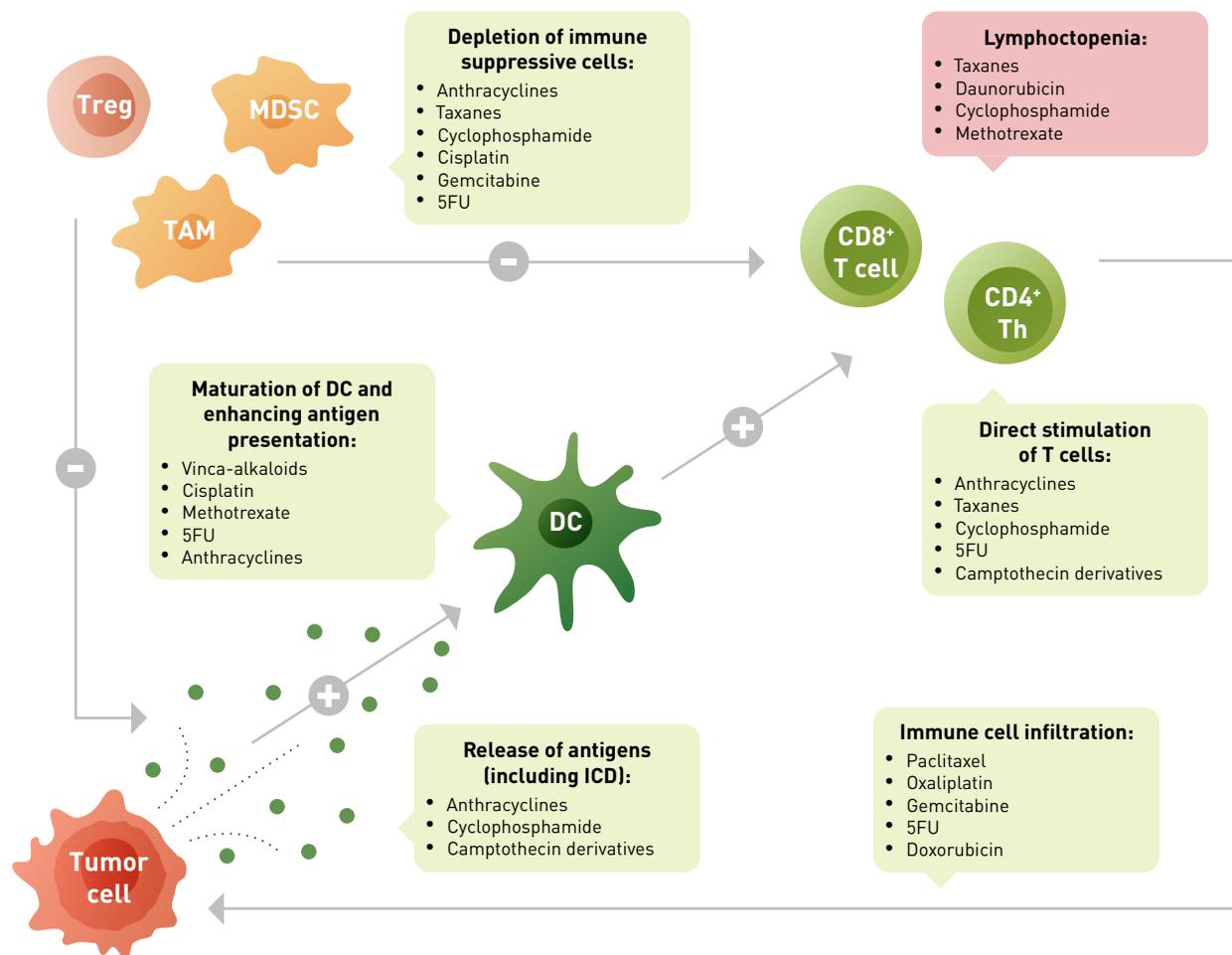
tumor-associated antigens to be released into the circulation as cancer cells are destroyed, which can prime the antitumor immune response and boost responses to immunotherapy. In addition, chemotherapy specifically, the topoisomerase inhibitors, antimicrotubule agents, alkylating agents, and antimetabolites deplete immunosuppressive cells, such as regulatory T cells and myeloid-derived suppressor cells, making the tumor microenvironment more amenable to immunotherapy (Figure 2).<sup>37</sup>

*A New Standard of Care: Atezolizumab plus nab-Paclitaxel*

The combination of ICIs with chemotherapy in mTNBC has proved much more successful than single-agent ICIs and has yielded approval of 2 new treatment regimens by the FDA, shaping a new standard

of care specifically in patients with PD-L1 expression. Following promising results from a phase 1 clinical trial,<sup>38</sup> the combination of the PD-L1 inhibitor atezolizumab and nanoparticle albumin-bound paclitaxel (nab-paclitaxel) was evaluated in the randomized phase 3 IMpassion130 trial. Patients (N = 451) were randomized 1:1 to receive atezolizumab 840 mg intravenously (IV) on days 1 and 15 in combination with nab-paclitaxel 100 mg/m<sup>2</sup> IV on days 1, 8, and 15 in 28-day cycles or placebo plus nab-paclitaxel. In an initial analysis, used to support FDA approval in 2019, the combination improved progression-free survival (PFS) compared with placebo plus chemotherapy in both the overall population (hazard ratio [HR], 0.80; 95% CI, 0.69-0.92; P = .002) and patients with PD-L1-positive tumors (defined as those with ≥1% PD-L1 expression on

**FIGURE 2.** Immunomodulatory Effects of Chemotherapy<sup>36</sup>



DC, dendritic cells; 5-FU, 5-fluorouracil; ICD, immunogenic cell death; MDSC, myeloid-derived suppressor cell; TAM, tumor-associated macrophages; Th, T-helper cell; Tregs, regulatory T cells.

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tumor-infiltrating immune cells as a percentage of tumor area) (HR, 0.62; 95% CI, 0.49-0.78;  $P < .001$ ) (Table 1<sup>35,39-47</sup>). Results from a second interim analysis were recently published; although median OS was numerically higher with the addition of atezolizumab, this did not cross the threshold for statistical significance (HR, 0.86; 95% CI, 0.72-1.02;  $P = .078$ ). However, exploratory analyses suggested a significant improvement in OS in the PD-L1–positive population (HR, 0.71; 95% CI, 0.54-0.94). Grade 3/4 adverse effects (AEs) occurred in 49% of atezolizumab-treated patients compared with 43% of patients in the placebo group, most commonly neutropenia, peripheral neuropathy, decreased neutrophil count, and fatigue.<sup>39</sup>

The combination of atezolizumab and nab-paclitaxel is included in the NCCN guidelines as a category 1 preferred treatment option

for the initial treatment of mTNBC in patients with PD-L1–positive disease, as determined by an FDA-approved companion diagnostic.<sup>25</sup>

#### *Atezolizumab plus Paclitaxel*

As nab-paclitaxel is not universally available, a randomized phase 3 trial was conducted to determine if paclitaxel could be used in its place in combination with atezolizumab in patients with previously untreated mTNBC (IMpassion131). A total of 651 patients were randomized 2:1 to receive atezolizumab 840 mg IV on days 1 and 15 plus paclitaxel 90 mg/m<sup>2</sup> IV on days 1, 8, and 15 of 28-day cycles or placebo plus paclitaxel. Unexpectedly, using paclitaxel with atezolizumab did not improve PFS or OS in either the overall population or in patients with PD-L1–positive disease (Table 1<sup>35,39-47</sup>).

**TABLE 1.** Overview of ICI Combination Therapy Trials in Metastatic TNBC<sup>35,39-47</sup>

Clinical trial identifier	Phase	Treatment arms	Stratification	Results		
				ORR (%)	mPFS (mo)	mOS (mo)
<b>Chemotherapy</b>						
IMpassion130 (NCT02425891)	3	Nab-paclitaxel + atezolizumab vs nab-paclitaxel + placebo	Overall	56 vs 46	7.2 vs 5.5	21 vs 18.7
			PD-L1+	NA	7.5 vs 5	25 vs 18.7
IMpassion131 (NCT03125902)	3	Paclitaxel + atezolizumab vs paclitaxel + placebo	Overall	54 vs 47	5.7 vs 5.6	19.2 vs 22.8
			PD-L1+	63 vs 55	6 vs 5.7	22.1 vs 28.3
KEYNOTE-355	3	Pembrolizumab + chemotherapy vs chemotherapy + placebo	Overall	NA	7.5 vs 5.6	NA
			PD-L1 CPS $\geq 1$	NA	7.6 vs 5.6	NA
			PD-L1 CPS $\geq 10$ PD-L1 CPS $\geq 20$	NA	9.7 vs 5.6 9.5 vs 5.4	NA
ENHANCE-1	2	Pembrolizumab + eribulin	Overall	23.4	4	16
			PD-L1+ (First-line setting)	34	6.1	21
			PD-L1+ (1-2 prior therapies)	24.4	4.1	14
TONIC	2	Radiation cyclophosphamide, cisplatin, or doxorubicin + nivolumab	Fewer than 3 lines of therapy	35%		
<b>PARP Inhibitors</b>						
TOPACIO/KEYNOTE-162 (NCT02657889)	1/2	Niraparib + pembrolizumab	Overall	21	2.3	NA
			BRCAm	47	8.3	NA
			BRCA wt	11	2.1	NA
MEDIOLA (NCT02734004)	1/2	Olaparib + durvalumab after 4-week run-in of olaparib	Germline BRCAm	58.8	4.9	20.5
<b>AKT Inhibitors</b>						
NCT03800836	1	Paclitaxel vs nab-paclitaxel + ipatasertib + atezolizumab	PD-L1+ or –	36 vs 13	7.2 vs 6.6	NA
<b>MEK Inhibitors</b>						
COLET (NCT02322814)	2	Nab-paclitaxel vs paclitaxel + cobimetinib + atezolizumab	Overall	29 vs 34.4	7 vs 3.8	NR vs 11
			PD-L1+	33 vs 44	NA	NA

CPS, combined positive score; ICI, immune checkpoint inhibitor; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; PD-L1, programmed death ligand 1; NA, not applicable; NR, not reported; TNBC, triple-negative breast cancer.

The reasons for this continue to be explored, but it has been suggested that increased use of steroid premedication to decrease the AEs of paclitaxel in IMpassion131 may have been partly to blame, by blunting the effects of atezolizumab.<sup>48</sup> The FDA issued an alert to warn clinicians not to use paclitaxel in place of nab-paclitaxel in this setting.<sup>49</sup> The ongoing randomized phase 3 IMpassion132 study (NCT03371017) is exploring the combination of atezolizumab with other types of chemotherapy (capecitabine or gemcitabine/carboplatin) for previously untreated mTNBC that recurs 12 months or less after completion of standard neoadjuvant chemotherapy.<sup>50</sup>

### *Pembrolizumab plus Chemotherapy*

The PD-1 inhibitor pembrolizumab is also being tested in combination with chemotherapy in various ongoing clinical trials. In the randomized, phase 3 KEYNOTE-355 study, pembrolizumab in combination with chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine plus carboplatin) improved PFS compared with placebo plus chemotherapy (HR, 0.65; 95% CI, 0.49-0.86;  $P = .0012$ ; Table 1<sup>35,39-47</sup>) in the first-line treatment of patients with mTNBC, securing FDA approval for this combination in patients with PD-L1-positive disease defined as combined positive score (CPS) of greater than or equal to 10 in late 2020. In the trial, 847 patients were randomized 2:1 to receive pembrolizumab 200 mg IV every 3 weeks plus chemotherapy or placebo plus chemotherapy. The median PFS was 9.7 months with pembrolizumab-chemotherapy and 5.6 months with placebo-chemotherapy in patients with CPS of greater than or equal to 10. However, the median PFS was 7.6 and 5.6 months among patients with CPS of greater than or equal to 1, thus proving pembrolizumab treatment effect is increased with PD-L1 enrichment. The most common AEs included anemia (49% vs 46%), neutropenia (41% vs 38%), and nausea (39% vs 41%), and grade 3 and higher AEs occurred in 68% and 67% of patients, respectively. OS follow-up is ongoing.<sup>41</sup> Additional data demonstrated that key secondary end points (ORR, duration of response, and disease control rate) also favored the pembrolizumab/chemotherapy combination and that the PFS benefit was observed regardless of the type of chemotherapy used.<sup>51</sup> These data are currently utilized in the updated NCCN guidelines to reflect that this combination is a category 1 recommendation for patients who are eligible for immunotherapy treatments.

Another notable ongoing trial is the phase 1b/2 ENHANCE-1/KEYNOTE-150 study (NCT02513472), which is evaluating the combination of pembrolizumab and eribulin in patients with mTNBC previously treated with two or fewer systemic therapies. Patients were divided into PD-L1-positive and PD-L1-negative subgroups and by number of previous therapies; first-line setting (stratum 1, no prior therapy,  $N = 60$ ) and second-line setting (stratum 2, 1-2 prior therapies,  $N = 89$ ). No new safety signals were seen and treatment-emergent AEs were fatigue (66%), nausea (65%), peripheral

sensory neuropathy (41%), alopecia (40%), and constipation (37%). Dose and schedule of eribulin was 1.4 mg/m<sup>2</sup> IV on day 1 and day 8, dose and schedule of pembrolizumab was 200 mg as a flat dose IV on day 1, both in 21-day cycles.<sup>52</sup>

### *Nivolumab plus Chemotherapy*

Based on preclinical research suggesting that there is immune modulatory properties for chemotherapy and irradiation, an adaptive, noncomparative phase 2 trial (TONIC study) was designed to look at this theory followed by nivolumab.<sup>53,54</sup> Sixty-seven patients with mTNBC were randomized to receive nivolumab without induction or with 2-week low-dose induction, or with irradiation ( $3 \times 8$  Gy), or cyclophosphamide, or cisplatin or doxorubicin, all followed by nivolumab. The ORR in the full cohort was 20%. The majority of responses were observed in the cisplatin (ORR, 23%) and doxorubicin (ORR, 35%) cohorts. After doxorubicin and cisplatin induction, there was an upregulation of immune-related genes involved in PD-1-PD-L1 and T-cell cytotoxicity pathways. The clinical and translational data of this study indicate that short-term doxorubicin and cisplatin may induce a more favorable tumor microenvironment and increase the likelihood of response to PD-1 blockade in TNBC, supporting further trials addressing these combinations.<sup>46</sup>

## Emerging Immunotherapy Combinations

### Immunotherapy in Combination With Targeted Therapies

ICI-targeted therapy combinations are also emerging as potential strategies to improve response rates and potentially reduce toxicity in mTNBC, with several phase 1 and 2 trials reporting results (Table 1<sup>35,39-47</sup>).

### *ICIs plus PARP Inhibitors*

The *BRCA1/2* genes encode proteins that are central to the repair of DNA double-strand breaks via the homologous recombination pathway of DNA repair. PARP enzymes are involved in the repair of single-strand breaks via base excision repair. *BRCA1/2*-deficient tumors become more heavily dependent on PARP-mediated pathways of repair, opening up a therapeutic vulnerability in breast cancers with homologous recombination deficiencies such as *BRCA1/2* mutations.<sup>55</sup> Several PARP inhibitors are approved for use in the approximately 15% of patients with mTNBC who harbor *BRCA1/2* mutations.<sup>56</sup> Studies have revealed that PARP inhibitors upregulate the expression of PD-L1 on tumor cells, and clinical trials are underway to explore potential synergy between PARP inhibitors and ICIs.<sup>57,58</sup>

In the open-label phase 1/2 TOPACIO/KEYNOTE-162 trial (NCT02657889), 55 patients with mTNBC were treated with niraparib 200 mg PO once daily and pembrolizumab 200 mg IV on day 1 of 21-day cycles. The combination demonstrated significant activity,

especially among patients with *BRCA1/2* mutations and appeared safe, with a tolerable safety profile. Grade 3 or higher AEs included anemia, thrombocytopenia, and fatigue.<sup>59</sup> In the phase 1/2 MEDIOLA trial (NCT02734004), a combination of durvalumab (a PD-L1 inhibitor) and olaparib demonstrated significant activity and was well tolerated. Patients with various advanced solid tumors were treated with a 4-week run-in of olaparib 300 mg PO twice daily, followed by olaparib at the same dose in combination with durvalumab 1500 mg IV every 4 weeks until disease progression or unacceptable toxicity. The trial included 34 patients with metastatic, HER2-negative, germline *BRCA1/2*-mutated breast cancer; 30 were eligible for activity analysis showing a disease control at 12 weeks. Anemia and neutropenia were the most common AEs. These results give further opportunities to study the combination of these agents in larger trials.<sup>44</sup>

### *ICIs plus PI3K/AKT Inhibitors*

The PI3K/AKT pathway is one of the most frequently dysregulated in cancer and has emerged as a mechanism of resistance to a range of different cancer therapies, including ICIs.<sup>33</sup> An ongoing phase 1b clinical trial (NCT03800836) is evaluating the triplet combination of AKT inhibitor ipatasertib (400 mg) PO on days 1-21, atezolizumab (840 mg) IV on days 1 and 15, and paclitaxel IV (80 mg/m<sup>2</sup>, arm A) or nab-paclitaxel IV (100 mg/m<sup>2</sup>, arm B) on days 1, 8, and 15 of 28-day cycles. Data for these 2 arms are outlined in Table 1.<sup>35,39-47</sup> Two additional arms evaluated sequential regimens beginning with doublet therapy followed by the third agent on day 15 (ipatasertib plus paclitaxel adding in atezolizumab, arm C; atezolizumab plus paclitaxel adding in ipatasertib, arm D). In the overall population that included 114 patients, the ORR was 54% and median PFS was 7.2 months. There was no consistent trend in subgroup analyses according to PD-L1 expression or PI3K/AKT pathway alteration status.<sup>45</sup> A phase 3 clinical trial of this combination has been initiated (NCT04177108).

Another notable ongoing clinical trial is the phase 2 MARIO-3 study, which is examining a triple combination of atezolizumab, nab-paclitaxel, and eganelisib, a PI3K gamma inhibitor. This combination was recently granted fast track designation by the FDA for the first-line treatment of advanced/mTNBC.<sup>60</sup> Among 13 evaluable patients enrolled to date, 100% exhibited tumor reduction, regardless of PD-L1 status; ORR was 69.2% in the overall population and 100% in 5 PD-L1-positive patients.<sup>61,62</sup>

### *ICIs plus MEK Inhibitors*

The mitogen-activated protein kinase (MAPK) pathway is frequently dysregulated in cancer, which prompted the development of small-molecule inhibitors of components of this pathway, such as MEK. In preclinical studies, MEK inhibitors have been shown to have immunomodulatory effects.<sup>63</sup> In the phase 2 COLET trial, the MEK inhibitor cobimetinib was added to first-line paclitaxel

for the treatment of patients with mTNBC but did not improve PFS.<sup>64</sup> However, an exploratory biomarker analysis suggested that cobimetinib increased immune infiltration within the tumor microenvironment<sup>65</sup> and, as such, a second part of the COLET trial began enrolling patients to be treated with a triplet of atezolizumab 840 mg IV on day 1 and 15, cobimetinib 60 mg PO on days 3-23, and paclitaxel IV 80 mg/m<sup>2</sup> (cohort 2) or nab-paclitaxel IV 100 mg/m<sup>2</sup> (cohort 3) on days 1, 8, and 15 of 28-day cycles. Data for 62 evaluable patients are presented in Table 1.<sup>35,39-47</sup>

## Biomarkers for Immunotherapy Response

### PD-L1 Expression

Another way to maximize patient outcomes with ICIs is to identify reliable predictive biomarkers to select patients most likely to benefit. Cancer cells and tumor-infiltrating immune cells have been shown to overexpress the PD-L1 protein, including 20% to 30% of patients with TNBC,<sup>66</sup> and clinical trials have shown a correlation between higher levels of PD-L1 expression and efficacy of ICIs. Thus, the utility of PD-L1 as a potential predictive biomarker has been extensively studied.<sup>67-69</sup>

Both FDA-approved combination regimens in mTNBC are restricted to patients with PD-L1-positive tumors, and 2 antibody-based companion diagnostics for immunohistochemical analysis are available. The PD-L1 IHC 22C3 pharmDx (Dako North America) is approved for selecting patients for treatment with pembrolizumab, using a cutoff of CPS of 10 or greater. The Ventana PD-L1 (SP142) assay (Roche Diagnostics) is approved by the FDA for use with atezolizumab in mTNBC. In this case, the cutoff is an immune cell (IC) score of 1% or more. [Figure 3](#)<sup>70</sup> and [Table 2](#)<sup>70</sup> describe the scoring algorithms in more detail.

Although PD-L1 expression is currently the most important biomarker in clinical practice in TNBC, it faces numerous limitations. It does not reliably predict response, as some studies demonstrated responses in patients with PD-L1-negative tumors; thus, using these cutoffs may be missing patients who could benefit from ICIs. Other limitations include high levels of inter-observer variability, heterogeneity of PD-L1 expression within a tumor, differential PD-L1 expression level between the primary tumor and distant metastases, and variability in the antibodies and scoring systems used.<sup>24</sup>

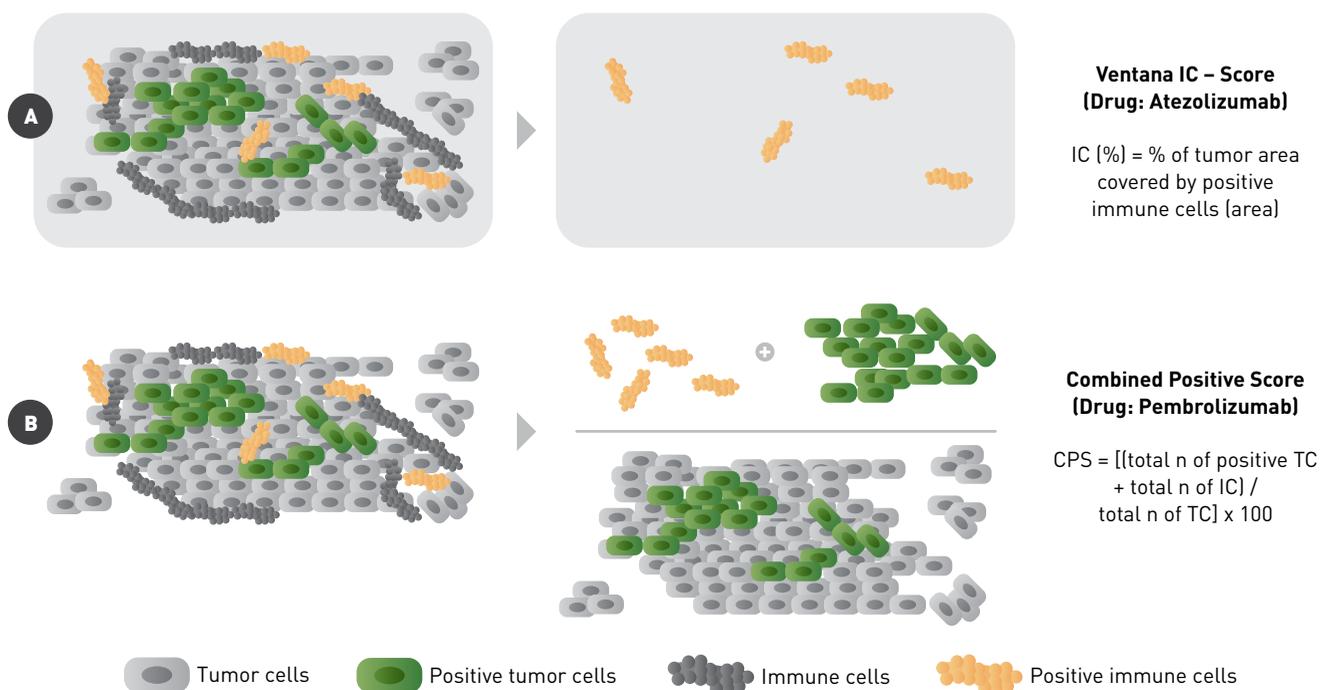
### Mismatch Repair Deficiencies

Mismatch repair (MMR) is an essential cellular mechanism of repair for DNA mismatches (alignment of 2 non-complementary bases), which can occur as a result of DNA damage, errors in DNA replication, or defects in other repair processes. Defects in MMR, which frequently occur in cancer cells due to mutations in the genes that govern DNA repair processes, cause DNA mismatches to go unrepaired, which can lead to the accumulation of mutations in the genome and drive the development of MSI—fluctuations in the

length of repetitive sequences of DNA within the genome. dMMR or MSI-high tumors usually display many DNA mutations, which can serve as antigens that stimulate the immune system. Numerous studies have demonstrated that dMMR tumors are more responsive to ICIs, which resulted in the approval of pembrolizumab in patients with dMMR/MSI-high in both the refractory or metastatic solid tumors, the first approval of its kind for a tumor agnostic

indication.<sup>68,71</sup> The most commonly used methods to detect dMMR and MSI-high are to examine the expression of specific proteins involved in MMR by IHC or by DNA sequencing using polymerase chain reaction or next-generation sequencing (NGS). There are currently no specific FDA-approved assays, but a number of companies provide MSI-high/dMMR testing and companion diagnostics continue to be approved postmarketing.<sup>29,68</sup>

**FIGURE 3.** PD-L1 Scoring Algorithms Applied in TNBC<sup>70</sup>



[A] The Ventana SP-142 assay measures PD-L1 expression in tumor-infiltrating immune cells and generates an IC-Score [%]. This score is required to assess first-line treatment eligibility with atezolizumab plus nab-paclitaxel for patients with metastatic TNBC; patients are eligible for treatment if the cutoff of 1% is exceeded. [B] The PD-L1 IHC 22C3 pharmDx assay generates a combined positive score (CPS) by measuring PD-L1 expression in both the tumor cells and tumor-infiltrating immune cells. This score is required to assess first-line treatment eligibility with pembrolizumab and chemotherapy in patients with metastatic TNBC; patients are eligible if they meet or exceed the cutoff of 10.

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**TABLE 2.** Scoring Algorithm for Various Diagnostic Assays<sup>70</sup>

Drug	Approved PD-L1 assay	Algorithm basis	Staining characteristics
Atezolizumab	Ventana PD-L1 (SP142)	Immune cell score (IC) Cutoff IC ≥ 1%	Low tumor cell staining Developed for immune cell staining Dot-ant-like staining platform
Pembrolizumab	PD-L1 IHC 22C3 pharmDx	Combined positive score (CPS) Cutoff CPS ≥ 10	Homogeneous tumor cell staining Mostly weak staining intensity

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## Tumor Mutation Burden (TMB)

TMB, defined as the number of mutations per megabase, has also emerged as a highly promising and clinically validated biomarker. Evaluating TMB allows assessment of the global spectrum of mutations across a given tumor and could provide a more comprehensive assessment of patients who might respond to ICIs than dMMR/MSI, which are just two of the many phenotypes that can cause hypermutable tumors. Studies have demonstrated that subsets of patients with high TMB exist across almost all cancer types and that assessing TMB through whole-exome sequencing or NGS can predict response to ICIs. Patients with high TMB experience improved outcomes following ICIs, it is thought as a result of the production of a greater number of antigenic peptides that provoke an antitumor immune response.<sup>68,72</sup> The FDA recently approved pembrolizumab for use across cancers with high TMB (defined as having at least 10 mutations/Mb), marking the first approval using this biomarker and another tumor agnostic indication for pembrolizumab. Foundation Medicine's FoundationOne CDx assay was approved as a companion diagnostic.<sup>68,72</sup>

## Conclusions

The development of novel treatments for mTNBC remains a significant unmet need. ICIs are a promising new option for patients with PD-L1-positive disease and are already shaping a new standard of care in combination with chemotherapy. With a number of ongoing studies reporting promising preliminary data for other ICI-chemotherapy and ICI-targeted therapy combination strategies, the stage is set for the treatment of mTNBC to further evolve over the next few years. Although PD-L1 expression is an established biomarker to select patients for treatment with ICIs, there are limitations to its use and there is a need to investigate additional biomarkers to predict response. In better understanding new and emerging treatment options and challenges and concerns regarding their use, managed care professionals can help to ensure optimal outcomes for patients with this challenging tumor type. ■

*The FDA is holding a public meeting of the Oncologic Drugs Advisory Committee (ODAC) on April 27-29 to discuss multiple indications from different drugs granted accelerated approval that have since reported results from a confirmatory trial that have not verified clinical benefit. One of the indications listed on the agenda for discussion is atezolizumab in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors express PD-L1.<sup>73</sup>*

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# Impact of Emerging Clinical Trends on Overall Cost of Care and the Role of the Managed Care Pharmacist

Rebecca Tombleson, PharmD, BCOP

## Introduction

In the United States, breast cancer accounts for 30% of all cancers in women and is the second leading cause of cancer-related mortality. An estimated 284,200 new cases and 44,130 deaths associated with breast cancer are expected in 2021.<sup>1</sup> Triple-negative breast cancer (TNBC) refers to a subtype of breast cancer that does not express estrogen, progesterone, or human epidermal growth factor receptor (HER2) and represents approximately 20% of all breast cancers.<sup>2</sup> Owing to the aggressive nature of metastatic TNBC (mTNBC), median overall survival in this population is estimated at 18 months or less and represents an urgent need for novel treatments to improve survival.<sup>3</sup>

Atezolizumab was approved for use on March 8, 2019, in combination with nab-paclitaxel (protein-bound) for adults with locally advanced or mTNBC whose tumors express programmed death ligand 1 (PD-L1) (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering  $\geq 1\%$  of the tumor area). It should be noted that atezolizumab is not approved in combination with paclitaxel. Interim analysis from the IMpassion131 trial showed that treatment with atezolizumab plus paclitaxel did not significantly reduce progression-free survival compared with placebo plus paclitaxel. Additionally, overall survival results also favored paclitaxel plus placebo as well.<sup>4</sup> Pembrolizumab in combination with chemotherapy was approved before completion of the KEYNOTE-355 phase 3 trial for locally recurrent unresectable or mTNBC whose tumors express PD-L1 combined positive score (CPS) greater than or equal to 10. KEYNOTE-355 investigators found that pembrolizumab and chemotherapy (nab-paclitaxel; paclitaxel; or gemcitabine plus carboplatin) provided a significant increase in progression-free survival compared with chemotherapy and placebo. Longer-term clinical follow-up trial data are planned to establish full benefits.<sup>5</sup> Each of the regimens described above is indicated in the front line or subsequent setting of mTNBC both per FDA-labeled indication and National Comprehensive Cancer Network (NCCN) guidelines, changing the landscape of treatment in significant ways both clinically and economically. PD-L1 testing is now considered necessary per NCCN guidelines for all patients

## ABSTRACT

The cost of metastatic triple-negative breast cancer (mTNBC) continues to rise; before the use of immune checkpoint inhibitors in mTNBC, cumulative costs of treatment ranged from \$51,070 for patients not treated with chemotherapy, up to \$143,150 for patients who received three or more regimens. For those with programmed death ligand 1 (PD-L1)-positive mTNBC, expanding treatments continue to be approved for combination first-line therapy. Both combination atezolizumab with nab-paclitaxel and pembrolizumab with chemotherapy have been recently approved for this population under accelerated approval. Managed care pharmacists should continue to emphasize evidence-based treatment that is consistent with National Comprehensive Cancer Network guidelines, as non-concordance has been associated with increased costs and worsened outcomes. There are several tools that can be used to assess the value of treatment, with significant heterogeneity among frameworks. Innovative programs that have the potential to decrease costs should be considered when evaluating payment models.

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For author information and disclosures, see end of text.

diagnosed with either hormone-receptor or HER2-negative breast cancer based on these new indications.<sup>6</sup>

### Rising Cost of Cancer Therapy

Costs associated with mTNBC have continued to increase with evolving treatments. One study by Aly and colleagues utilized the Surveillance, Epidemiology, and End Results (SEER)-Medicare database from 2004 to 2011 to estimate overall survival, treatment, and economic burden of elderly patients (mean, 76.8 years old) with mTNBC.<sup>7</sup> Patients were divided into the following groups: no chemotherapy (NC), one regimen (1R), two regimens (2R), or three or more regimens (3R+). A total of 625 patients met the study inclusion and exclusion criteria. Forty-nine percent (n = 308) of patients in this study did not receive any chemotherapy treatment. Of the remaining patients, 161 received 1 regimen, 88 patients received 2 regimens, and 68 patients received 3 or more regimens.

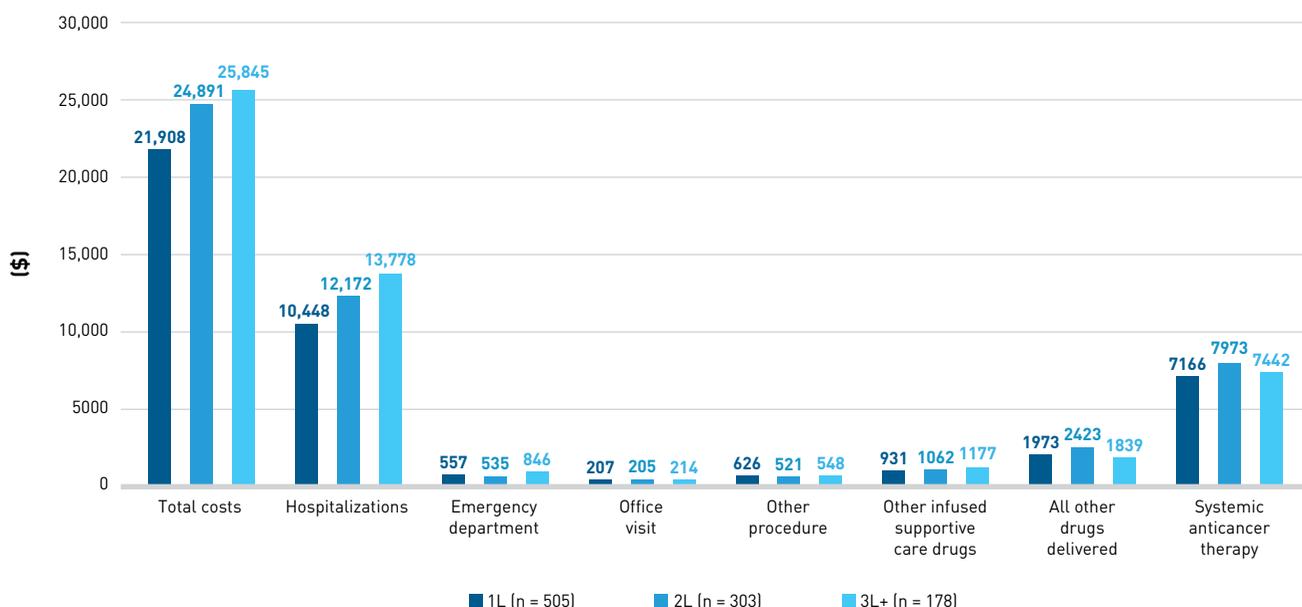
As the line of therapy increased, the rate of single-agent use decreased for both 2R (47%) and 3R+ (59%). The cumulative cost of treating patients continued to increase from \$51,070 for patients not treated with chemotherapy, up to \$143,150 total cumulative costs for patients who received 3R+. Inpatient and physician office visits were the main driver of per-patient per-month costs across all groups.<sup>7</sup>

While per-patient per-month costs were lower in the higher regimen groups compared with NC, median overall survival was lowest in the NC group and increased with later lines of treatment.

Median overall survival for NC was 3.5 months and increased as the number of regimens increased from 1R (7.1 months), 2R (16.0 months), and 3R+ (25.3 months).<sup>7</sup> It should be noted that this study was conducted before the approval of immune checkpoint inhibitor (ICI)-based regimens, which are associated with higher costs when compared with the chemotherapy regimens identified in this study.

Another retrospective study that reviewed the monthly cost of treating mTNBC used the electronic medical record and billing data from the Vector Oncology Data Warehouse, which stores data from 9 oncology practices throughout the United States.<sup>8</sup> Unlike the previous study, this study included patients who were on average much younger (mean, 56.6 years old) and were diagnosed with mTNBC from 2010 to 2016. This evaluation was divided similar to the previous study: first line (1L), second line (2L), and third or later line (3L+). A total of 505 patients were included in this analysis. The mean cost of treatment was calculated with all patients eligible for each line of treatment, and included inpatient, outpatient, and all cancer-related medication. Total mean 1L costs were \$21,908 per month and increased to \$24,891 in the 2L group and \$25,845 in the 3L+ group. A majority (>50%) of monthly costs were attributed to hospitalizations and emergency department visits, while less than one-third of the total cost was associated with anticancer therapy. The mean monthly patient costs are summarized in the **Figure**.<sup>8</sup> The time period in which these data were assessed was also before the approval of atezolizumab and pembrolizumab combination

**FIGURE.** Mean Monthly Patient Healthcare Cost by Line of Therapy (\$USD)<sup>8</sup>



1L, first line; 2L, second line; 3L+, third or later line through the first of transfer to hospice, end of record, or 3 months prior to death.

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regimens in mTNBC and may not be truly reflective of the costs that eligible patients with mTNBC may presently experience.<sup>8</sup>

Other studies have also supported hospitalizations as a major cost driver in patients with mTNBC. One claims-based study of 4617 patients from 2012 to 2019 found that these patients had a mean of 2.4 hospitalizations per patient per year, with an associated cost of \$57,115 per patient per year. Reasons for hospitalization included chemotherapy-related adverse effects (AEs), disease progression, and breast-related surgeries.<sup>9</sup>

### Cost-effectiveness of ICI Treatment for mTNBC

The cost-effectiveness of PD-L1 agents in combination with chemotherapy in mTNBC is limited. No cost-effectiveness data were identified regarding pembrolizumab combination with chemotherapy due to its recent approval. Several different cost-effective analyses have been conducted with regard to atezolizumab plus nab-paclitaxel, but traditional cost-effectiveness thresholds may not complete the whole picture, as methodologies differed in these studies.<sup>10,11</sup>

In one study, investigators looked at the cost-effectiveness of atezolizumab plus nab-paclitaxel compared with nab-paclitaxel alone. In patients who were PD-L1 positive, atezolizumab plus nab-paclitaxel increased overall cost by \$120,800 and 0.11 quality-adjusted life-year (QALY) gained compared with just nab-paclitaxel. This corresponded to an incremental cost-effectiveness ratio (ICER) of \$1,101,000 per QALY gained, which was higher than the traditionally accepted ICER threshold of \$150,000 per QALY gained. Study authors concluded that atezolizumab plus nab-paclitaxel was not cost-effective compared with nab-paclitaxel for treatment of mTNBC positive for PD-L1.<sup>10</sup>

A second cost-effectiveness analysis noted that atezolizumab plus nab-paclitaxel added an additional \$149,465 and 0.762 QALY gained on top of nab-paclitaxel in patients with PD-L1-positive mTNBC. This resulted in an ICER of \$196,073 per QALY gained. This number, while lower than other calculations, is still above traditional ICER thresholds of cost-effectiveness. In patients who had an unknown PD-L1 status, the cost-effectiveness of atezolizumab plus nab-paclitaxel increased to an ICER of \$281,448 per QALY gained. These results support that atezolizumab plus nab-paclitaxel was more cost-effective in a population that was PD-L1 positive compared with one that was PD-L1 status unknown.<sup>11</sup> Notably, treatment guidelines only support the use of this combination in patients with PD-L1-positive disease.<sup>6</sup>

### Evidence-Based Guidelines

Current NCCN guidelines recommend atezolizumab and nab-paclitaxel combination therapy and pembrolizumab in combination with chemotherapy as category 1 preferred regimens for the initial treatment in patients with PD-L1-positive mTNBC.<sup>6</sup> As previously

noted, this addition of atezolizumab to nab-paclitaxel increased the mean cost by approximately \$120,800.

Treatment adherence to NCCN guidelines is critical for high-quality care. A 2020 retrospective cohort study of 16,858 women with TNBC between 2004 and 2016 found patients with nonadherent care had worse disease-specific survival compared with those who received NCCN-adherent treatment. In this cohort using the California Cancer Registry, 32.5% of patients with TNBC received NCCN-adherent care ( $P < .0001$ ). Nonadherent care was associated with an increase in disease-specific mortality (HR, 1.21; 95% CI, 1.11-1.31;  $P < .0001$ ). Patient populations less likely to receive guideline-adherent care included non-Hispanic Black patients, Hispanic patients, and patients of lowest and lower-middle socioeconomic status.<sup>12</sup>

Managed care organizations can consider clinical pathways to ensure adherence to guideline recommendations. Clinical pathways are management tools defined as protocols that are evidence-based specific to type of cancer and stage.<sup>13</sup> Pathways have been successful in optimizing guideline-concordant care through either internal or external incentivization. In one example of Anthem's Cancer Care Quality Program, providers receive an additional financial incentive for each patient who is treated in accordance with approved clinical pathways. It was noted that within the first 6 months after implementation, the clinical pathway adherence was 63% for breast, 72% for colorectal, and 63% for lung cancers.<sup>14</sup> Evidence-based clinical pathway adherence has been the cornerstone of many programs that seek to encourage providers to prescribe regimens consistent with appropriate guidelines both in terms of outcomes and cost mitigation; an example of this will be discussed in relation to the Oncology Care Model (OCM).

### Cost of Supportive Care: A Driver of Total Costs

One major consideration of cost in patients receiving chemotherapy includes immune-related AEs (irAEs), which can include a wide range of systemic effects including, but not limited to, colitis, pneumonitis, neurological conditions, and endocrinopathies.<sup>15</sup> The irAE rates known per clinical trials are noted first. Authors of IMpassion130 noted that between study arms, the overall incidence of treatment-related AEs was well balanced; however, the study arm that included atezolizumab and nab-paclitaxel saw an increased rate of grade 3-4 events (40% vs 30%) and serious AEs (13% vs 7%) when compared with nab-paclitaxel and placebo. Notably, 16% of patients in the study arm experienced an AE leading to treatment of any study drug, whereas only 8% of patients discontinued treatment for this reason in the placebo arm. With specific mention to irAEs, while these did occur at a higher rate in the atezolizumab arm, there were only a few patients who required discontinuation for irAEs alone. KEYNOTE-355 authors noted, not surprisingly, a higher rate of irAEs with an overall rate of 26% in the study arm

compared with 6% in the placebo arm. Similarly, rates of grade 3-4 irAEs were seen in 5% of patients in the study arm compared with none in the placebo arm. Authors noted that treatment-related AEs grade 3 or higher were similar across study and placebo arms (68% and 67%, respectively). While treatment discontinuation due to AEs was not captured in KEYNOTE-355, both this study and IMpassion130 appear to demonstrate a unique but overall reasonably tolerated AE profile with regard to the approved study arms. There are presently limited data to assess the frequency with which irAEs occur in the setting of mTNBC and it is with anticipation we look to real-world evidence and publication of the irAEs as these regimens are used with increasing frequency. In the absence of this specific evidence in this setting owing to each regimen's relatively recent approval, we will further attempt to quantify some of these real-world irAEs.<sup>3,5</sup>

In an observational study that used the Premier Healthcare Database, a total of 13,030 patients on an ICI were identified from 2015 to 2017. These patients had non-small cell lung cancer, renal cell carcinoma, urothelial carcinoma, or Merkel cell carcinoma. Of the patients identified, 51% experienced at least 1 irAE, with a total of 15,277 distinct irAEs. Health-related costs were assessed up to 90 days after a reported irAE. The mean cost for inpatient irAEs was \$21,219 and the mean cost for outpatient irAEs was \$5951. The most expensive irAEs on average included transverse myelitis (\$80,976), toxic epidermal necrolysis (\$69,115), and myocarditis (\$45,341). Although this study did not include patients with mTNBC treated with atezolizumab or pembrolizumab, it does illustrate the increased cost burden associated with treating patients with an ICI. This may be an increasingly burdensome problem in the midst of the COVID-19 pandemic and patients who are in geographically rural areas. Limited access to specialist care may decrease timely referrals for irAEs. It is especially crucial that patients who start ICI therapy are appropriately monitored to ensure timely referral to care.<sup>16</sup>

Another concern regarding irAEs has been the rate of ICI discontinuation. From clinical trials of ICI monotherapy, discontinuation associated with irAEs was noted to be up to 13%.<sup>17</sup> One small study demonstrated an interesting interpretation of study discontinuation with 61 patients with non-small cell lung cancer, 22.4% of patients on nivolumab (n = 9/40) and 42.9% of patients on pembrolizumab (n = 9/21) had to discontinue therapy due to irAEs. Importantly, in this small study, the majority of irAEs appeared to be related to the presence of interstitial lung disease that then was associated with the development of drug-related interstitial lung disease and death in some cases, underscoring the need for consideration of this diagnosis in combination with treatment decisions. None of the patients in this study went on to rechallenge with an ICI after the onset of drug-related interstitial lung disease; however, the study goes on to note that the patients who required treatment discontinuation due to irAE development had significantly better

outcomes than those who discontinued treatment for other reasons. The paradoxical outcomes of this study highlight the need to better understand how efficacy of ICI relates to treatment discontinuation and underlying patient- and disease-specific medical history.<sup>18</sup>

Current American Society of Clinical Oncology (ASCO) and NCCN guidelines for the management of irAEs are comprehensive and include monitoring recommendations for each type of potential irAE. In general, ICI therapy should be continued in mild cases of irAEs. For those that progressed to grade 2 or higher, ICIs were recommended to be stopped temporarily or discontinued indefinitely depending on type of irAE and severity.<sup>17,19</sup> Providers may also consider rechallenging ICI treatment after an irAE after individualized assessments of risk versus benefit. A study evaluated the rate of subsequent irAEs after an initial grade greater than or equal to 2 irAEs in 180 patients with varied types of cancer. After the rechallenge on an ICI, 38.9% experienced a subsequent grade greater than or equal to 2 irAEs. It was also observed that lower rates of irAE were associated with rechallenge with the same ICI.<sup>20</sup> For patients who use an ICI, irAEs not only have the potential to increase costs but may also drive the need for a new treatment dependent on the severity of the irAE.

## Payer Considerations

Due to the rapidly changing treatment landscape for mTNBC, managed care pharmacists should be cognizant of current treatment guidelines published through the NCCN. When selecting an agent for formulary inclusion, agents for cancer treatment are generally covered for appropriate indications and guideline recommendations. However, in the case of preferring one ICI over the other for the treatment of mTNBC, no comparative head-to-head studies have been conducted to determine which regimen may be superior. Although both agents have demonstrated efficacy in mTNBC, longer-term follow-up and real-world efficacy and safety data are needed to help providers and patients make the best-informed decision on treatment selection.

Besides cost to payers, managed care pharmacists should take into consideration the financial burden and quality-of-life impacts on the patient. Financial toxicity has been associated with psychological stress, potential delay of care, nonadherence to therapy, and worsening outcomes. Proactive identification of these patients is crucial to risk mitigation of treatment failure. Patients who are identified as higher risk for financial toxicity through evaluation of social determinants to health should be provided appropriate resources and follow-up to ensure adherence.<sup>21</sup>

## The Managed Care Pharmacist's Role in Cost Management

The cost of treating mTNBC will continue to increase as new treatment modalities are developed. Managed care pharmacists may

assist with many functions such as optimization of evidence-based prescribing, formulary management, and ensuring adherence to NCCN guidelines. Through innovative payment models such as the OCM, managed care organizations strive to improve clinical care of patients while simultaneously managing costs.<sup>22</sup>

### Strategies to Address Costs of Therapy

The cost of treating mTNBC will continue to increase as new treatment modalities are approved and improve overall survival and progression-free survival. Managed care pharmacists should focus not just on the direct drug spend on anticancer agents, but also on how to optimize treatment in a way that improves patient efficacy and safety outcomes while managing cost. Means of optimizing treatments include the previously discussed clinical pathways to incentivize concordance with evidence-based guidelines. As non-concordance with NCCN and evidence-based guidelines are associated with overall more costs, clinical pathways may help to encourage appropriate utilization.<sup>23</sup> As mentioned previously, the managed care pharmacist may also play a role in ensuring that AEs are minimized through the proactive treatment planning to prevent neutropenia or nausea/vomiting and through close monitoring for the development of irAEs that may lead to hospitalization if not managed assertively.

Value-based frameworks may be of assistance to patients and providers when discussing treatment options. These frameworks attempt to incorporate values and outcomes that are patient centered

but relevant to various stakeholders such as additional years of life, disease-free survival, functionality, AEs, and total cost of care.

The ASCO Value Framework was initially developed to help form the shared decision between provider and patient that weighed clinical benefit versus risk of treatment. Additionally, the European Society of Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS) has been used by clinicians to estimate the magnitude of clinical benefit observed in trials from a score of 0 (negligible) up to 4-5 (substantial).<sup>24</sup> It has been observed that the ASCO and ESMO tools are similar in how they assess benefit and incorporate toxicity. The major difference is that ESMO does not incorporate cost whereas ASCO does.<sup>25</sup> NCCN evidence blocks are easy to visualize and interpret snapshots of data that reflect treatment, quality of data, and cost. This tool can be used by providers with patients to help determine preference of treatments.<sup>26</sup>

The Memorial Sloan Kettering Cancer Center DrugAbacus is a tool that is aimed at providers to allow them to compare drug prices weighted by preference (eg, toxicity, rarity, unmet need). Another tool that allows for cost comparisons between agents are Institute for Clinical and Economic Review (ICER) evaluations. These evaluations target managed care organizations and policymakers to provide a value-based price assessment. It presents data as an ICER, or cost per QALY gained. This helps managed care organizations determine the cost-effectiveness of regimens based on study outcomes and cost.<sup>26</sup> The [Table](#)<sup>26</sup> provides a brief summary of key characteristics of these tools.

**TABLE.** Summary of Key Characteristics of Value-based Frameworks<sup>26</sup>

	ASCO	NCCN	MSKCC	ICER	ESMO
Target audience	Patient Provider	Patient Provider	Provider Policymaker	Payer Policymaker	Payer Policymaker
Evidence input	1 clinical trial	All relevant clinical data	1 clinical trial (pivotal trial for first indication)	Clinical trial data and manufacturer data	1 study
Health benefit included?	Yes	Yes	No	Yes	Yes
Cost to patient included?	Yes	No	No	No	No
Cost to healthcare Included?	No	Total costs	Yes	ICER and budget impact	No
Pros	Simple clinical benefit score that is cancer specific	Quick visual snapshot of efficacy, safety, quality of evidence, consistency of evidence, and cost	Allows user to assess reasonable cost of drugs based on characteristics (eg, rarity)	Focused on providing payers tools of cost-effectiveness	Simple clinical benefit score, able to be used by policymakers
Cons	Not appropriate for payer or policymaker decisions, only incorporates 1 trial	Not appropriate for payer or policymaker decisions	Does not incorporate clinical benefit, limited drugs available for assessment	Not appropriate for individual patient decisions and not cancer specific	Does not incorporate cost into scoring, only incorporates 1 trial

ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; ICER, Institute for Clinical and Economic Review; MCBS, Magnitude of Clinical Benefit Scale; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network.

## Challenges of Implementing New Payment Models

One of the most storied payment models for oncology is the OCM, which began its 5-year pilot in 2016. This model is a fee-for-service payment model with additional monthly enhanced oncology service (MEOS) payments and performance-based payments incentives. Some successes of OCM implementation were that many practices that participated implemented or considered treatment pathway software that was guideline concordant. Additionally, providers noted that practices adopted from the OCM (eg, increased palliative care specialists, enhanced advance care planning, enhanced outpatient services) have improved patient care, and believed patients were better informed regarding their treatment. Results of available data have demonstrated no significant impact on spending, hospitalizations, or emergency department visits for those patients who received active treatment.<sup>27</sup> The Oncology Care First (OCF) program is slated to launch following the completion of OCM and is intended to improve on specific elements of OCM to further incentivize the prescription of high-value, evidence-based care.

A recent study attempts to quantify whether OCM episodic cost savings may be realized and maximized through the use of voluntary pathways from quarter 1 of 2017 through quarter 1 of 2019. Authors concluded that a reduction in spend when utilizing evidence-based clinical pathways within a value-based care model is possible after seeing a less-rapid increase in drug spend (18.6% vs 34.4%) and a percentage decrease in drug spend (13.5% vs 0.1%) in a non-OCM center compared with an OCM center, respectively. While the study did include patients receiving ICIs, this was more in populations with diseases other than mTNBC in which reasonable substitutions could be made that decreased costs such as combinations utilizing paclitaxel instead of nab-paclitaxel in appropriate patients.<sup>28</sup>

There are, as mentioned throughout this article, very little data that tie back to ICI use in mTNBC owing to the recent approvals; however, cost savings could be realized through implementation of and adherence to evidence-based clinical pathways. For example, ensuring that these ICI-based regimens are only utilized in those patients known to benefit with the aforementioned PD-L1 levels could provide significant cost savings owing to the specificity with which these regimens must be used and the extraordinary costs associated with each. Further, both KEYNOTE-355 and IMpassion130 have demonstrated that not all patients diagnosed with mTNBC will benefit from these interventions owing to PD-L1 expression. Ensuring that only patients presently known to benefit from these treatments will receive them results in myriad benefits: the patient is kept from receiving a treatment that will likely not help them or provide a survival benefit; the patient avoids costs for the aforementioned treatment and any resulting AEs; lastly, a reduction in healthcare utilization costs overall are only a small sample of the many ways in which treatment that is prescribed on-evidence produces better results for a variety of stakeholders across the medical spectrum and society overall.

Future considerations may include a hospital at-home program or other innovative practices in appropriate patients. Regardless of the type of payment model used, managed care pharmacists should continue to evaluate the cost savings and potential decrease of healthcare resource utilization.<sup>22</sup>

## Conclusions

As the cost of mTNBC treatment rises, combination ICIs are recommended for first-line therapy in patients who are PD-L1 positive. Both combination atezolizumab with nab-paclitaxel and pembrolizumab with chemotherapy are FDA approved for this population. Treatment decisions should be based on evidence-based guidelines, as non-concordance with them has been associated with increased drug costs and worsened outcomes. Care must be taken to validate that these new and novel ICI-based regimens are appropriately utilized based on available literature and evidence. Real-world evidence especially seeks to further explain the nuances with which these treatments may be implemented effectively. With set costs, it becomes imperative as clinicians to focus on the appropriate use of these drugs in patients with specific PD-L1 expression in order to both streamline use and ensure the avoidance of costly off-label prescribing practices that result in tremendous cost both financially and clinically. Pharmacists should be aware that costs will continue to increase for the treatment of mTNBC and use the tools available to help the provider and patient understand their choices through utilization of value frameworks and adherence to evidence and guidelines where applicable. ■

*The FDA is holding a public meeting of the Oncologic Drugs Advisory Committee (ODAC) on April 27-29 to discuss multiple indications from different drugs granted accelerated approval that have since reported results from a confirmatory trial that have not verified clinical benefit. One of the indications listed on the agenda for discussion is atezolizumab in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors express PD-L1.<sup>29</sup>*

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# Combining Immune Checkpoint Inhibitors With Chemotherapy for the Treatment of Metastatic Triple-Negative Breast Cancer: An Overview for Managed Care Professionals

**Release date:** April 15, 2021

**Expiration date:** October 15, 2021

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## Sample of Online Posttest

Choose the best answer for each of the following:

1. **A 54-year-old postmenopausal woman is diagnosed with metastatic triple-negative breast cancer (mTNBC). Mutation testing shows *BRCA1* and *BRCA2* negativity. Her tumor expresses programmed death ligand 1 (PD-L1) with a combined positive score (CPS) of 60. What is the most appropriate first-line treatment for her?**
  - A. Pembrolizumab, carboplatin, and gemcitabine
  - B. Olaparib
  - C. Nab-paclitaxel
  - D. Sacituzumab govitecan
2. **When using the Ventana PD-L1 (SP142) assay as a companion diagnostic, what cutoff of PD-L1 positivity is required for treatment with a combination of atezolizumab and nab-paclitaxel?**
  - A. Immune cell (IC)  $\geq 1\%$
  - B. CPS  $\geq 10$
  - C. IC  $\geq 5\%$
  - D. CPS  $\geq 1$
3. **AN is a 40-year-old woman with PD-L1–positive mTNBC. Her oncologist has recommended a combination of atezolizumab and paclitaxel. Which of the following statements is correct?**
  - A. The recommended treatment is the preferred standard of care regimen for this patient.
  - B. The patient should undergo germline *BRCA1/2* mutation testing to determine if this is the best course of treatment.
  - C. Paclitaxel is not recommended in combination with atezolizumab in this setting based on the results of the IMpassion131 study in which there was no survival benefit.
  - D. Paclitaxel is a safe and efficacious alternative to nab-paclitaxel in this setting.
4. **Which of the following triplet combinations that includes a PI3K gamma inhibitor has recently been granted fast track designation by the FDA for first-line treatment of locally advanced or mTNBC?**
  - A. Atezolizumab plus nab-paclitaxel plus olaparib
  - B. Durvalumab plus olaparib plus paclitaxel
  - C. Atezolizumab plus nab-paclitaxel plus eganelisib
  - D. Nivolumab plus ipilimumab plus nab-paclitaxel
5. **The ongoing phase 3 KEYNOTE-355 study is evaluating the combination of pembrolizumab and chemotherapy in patients with mTNBC. Which statement relating to this trial is correct?**
  - A. The combination of pembrolizumab and chemotherapy improved overall survival compared with placebo and chemotherapy.
  - B. The combination improved progression-free survival compared with placebo plus chemotherapy, but overall survival follow-up is ongoing and data have not yet been reported.
  - C. There was a trend toward improved overall survival in patients with PD-L1–positive disease treated with pembrolizumab and chemotherapy compared with those treated with placebo and chemotherapy.
  - D. The study is not powered to detect overall survival differences between arms as it is designed to evaluate noninferiority.

- 6. Which of the following is a result of adhering to evidence-based clinical pathways for mTNBC?**
- A. All patients with mTNBC will benefit from immune checkpoint inhibitor (ICI) treatment.
  - B. Patients avoid treatments that will not likely provide a survival benefit.
  - C. Patients incur higher out-of-pocket costs due to adverse effects.
  - D. There is an increase of healthcare resource utilization for patients without PD-L1 expression.
- 7. Non-concordance with National Comprehensive Cancer Network treatment guidelines has been associated with which of the following?**
- A. Increased overall survival
  - B. Increased overall disease-free progression
  - C. Increased patient out-of-pocket costs
  - D. Decreased patient out-of-pocket costs
- 8. Which of the following statements is true regarding immune-related adverse effects (irAEs)?**
- A. Discontinuation due to irAEs in clinical trials for mTNBC was less than 2%.
  - B. Grade 3-4 irAEs in both IMpassion130 and KEYNOTE-355 were lower in the treatment arm compared with placebo.
  - C. irAEs are a major driver of supportive care costs in ICI treatment.
  - D. Patients who experience an irAE should never rechallenge ICI treatment.
- 9. Which statement is true regarding cost-effectiveness of ICIs for mTNBC?**
- A. Atezolizumab plus nab-paclitaxel was shown to have an incremental cost-effectiveness ratio (ICER) below the \$100,000 threshold and is therefore cost-effective treatment.
  - B. Both pembrolizumab plus chemotherapy and atezolizumab plus nab-paclitaxel are equally cost-effective treatment options.
  - C. Current evidence suggests that atezolizumab plus nab-paclitaxel is not cost-effective at this current price.
  - D. There was insufficient information to determine cost-effectiveness of any ICI treatment regimen for mTNBC.
- 10. Which statement is NOT true when developing utilization management for ICI combination therapy for mTNBC?**
- A. Managed care pharmacists should only consider direct drug spend when making formulary decisions for these agents.
  - B. Criteria should consider the maximum number of infusions per cycle, and the total duration of acceptable treatment.
  - C. Non-concordance with treatment guidelines has been associated with increased out-of-pocket costs.
  - D. Testing for PD-L1 prior to treatment initiation is necessary.







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