

# Emerging treatment strategies for metastatic triple-negative breast cancer

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**Abstract:** Triple-negative breast cancer (TNBC) is a heterogeneous subtype of breast cancer that is often associated with an aggressive phenotype and a poor prognosis. Cytotoxic chemotherapy remains the mainstay of treatment for most patients with metastatic TNBC (mTNBC), but duration of response is often short and median overall survival is only 12–18 months. Therefore, it is critical to identify novel treatment strategies to improve outcomes for these patients. In this review article, we discuss recent advances in treatment strategies for patients with mTNBC including the use of immune checkpoint inhibitors, targeted therapies, and antibody–drug conjugates. For each topic, we summarize important preclinical and clinical data, discuss implications for clinical practice, and highlight future research directions.

**Keywords:** antibody–drug conjugates, emerging therapies, immunotherapy, metastatic triple-negative breast cancer

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## Introduction

Triple-negative breast cancer (TNBC) is a heterogeneous tumor type that is conventionally defined by the absence of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) gene amplification. TNBC accounts for 15–20% of all breast cancers and typically displays aggressive behavior, including earlier recurrences and a higher risk of developing metastatic disease with a preponderance of disease in viscera and brain.

Recent efforts to characterize TNBC tumors based on profiling of the genome, transcriptome, and immunologic microenvironment have increased our understanding of the molecular heterogeneity of TNBC.<sup>1–4</sup> Specifically, work by Lehmann demonstrated that TNBC can be divided into six subtypes based on gene expression profiles: basal-like (BL1 and BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM), and luminal androgen receptor (LAR), as well as an unspecified group (UNS).<sup>4</sup> BL1 and BL2 subtypes had higher expression of cell cycle and DNA damage response genes, M and MSL subtypes were

enriched in gene expression for epithelial–mesenchymal transition, and the LAR subtype was characterized by androgen receptor (AR) signaling. Refinement of this work divided TNBC into four subtypes – BL1, BL2, M, and LAR.<sup>2,3</sup> Using five publicly available neoadjuvant chemotherapy breast cancer gene expression datasets, the authors retrospectively evaluated chemotherapy response in more than 300 patients with TNBC and demonstrated that TNBC subtypes differ significantly in response to similar neoadjuvant chemotherapy with 41% of BL1 patients achieving a pathological complete response (CR) compared with 18% for BL2 and 29% for LAR.<sup>2</sup> Further work is needed to better understand the prognostic and therapeutic implications of these findings.

In terms of treatment options, unlike hormone receptor-positive (HR+) or HER2-positive breast cancer that can be treated with targeted therapies, there are fewer treatment options for patients with metastatic TNBC (mTNBC), and cytotoxic chemotherapy remains the mainstay of treatment for most patients. For patients with mTNBC, the duration of response to chemotherapy is often short

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and median overall survival (OS) is only 12–18 months. Therefore, the development of novel treatment strategies for mTNBC remains an area of unmet clinical need. In this review article, we discuss recent advances in treatment strategies for patients with mTNBC including the use of immune checkpoint inhibitors (ICIs), targeted therapies, and antibody–drug conjugates (ADCs). For each topic, we summarize important preclinical and clinical data, discuss implications for clinical practice, and highlight future research directions.

### Immunotherapy

Immunotherapy has revolutionized the treatment landscape for solid tumor oncology, leading to durable responses in many patients with metastatic disease. The most successful immunotherapeutic agents used to date are ICIs, which block immunosuppressive receptors like the programmed cell death 1 (PD-1), the programmed death-ligand 1 (PD-L1), and the cytotoxic T lymphocyte antigen 4 (CTLA-4) to improve the cytotoxic ability of tumor-infiltrating lymphocytes (TILs). There are several key characteristics of TNBC which suggest that it is more likely to respond to ICIs than other breast cancer subtypes. First, there are more TILs present in the TNBC tumor microenvironment (TME), which correlates with better response to ICI and improved prognosis.<sup>5–7</sup> Second, there are higher levels of PD-L1 expression in TNBC tumor and immune cells, providing a target for ICIs.<sup>8</sup> Third, data in multiple tumor types indicate that microsatellite instability and a high tumor mutational burden (TMB) increase neoantigens and result in a more robust immune response. A comparison of breast cancer subtypes demonstrated both high TMB and high immune infiltration occurred more frequently in TNBC compared with luminal breast cancers.<sup>9,10</sup> However, it is not clear whether TMB alone or in combination with immune gene expression profiling adds to the predictive values of ICI response in TNBC. Collectively, these data suggest that the immune system plays a particularly important role in the TNBC TME; hence, ICI therapy has been most extensively studied for this breast cancer subtype. In this section, we will discuss the use of ICI monotherapy and combination therapies for patients with mTNBC (also see Tables 1 and 2).

Of note, the definition of PD-L1 positivity varies based on the ICI. For pembrolizumab, PD-L1 positivity is determined by the combined positive

score (CPS), scored as the number of PD-L1-positive cells (including tumor cells, lymphocytes and macrophages) divided by the total number of tumor cells  $\times 100$  using the Dako 22 C3 antibody. For atezolizumab, PD-L1 positivity is determined by the percent of the tumor area covered by the area of PD-L1+ immune cells, using the Ventana SP142 antibody. The percent of tumors positive for PD-L1 is similar with SP142 1% and CPS 10 or more, but there is some discrepancy between PD-L1 antibody testing methods with incomplete overlap,<sup>11,12</sup> and future studies are needed to better understand clinical implications of these differences.

Importantly, ICI therapy is well tolerated by most patients, but has a risk of immune-related adverse events (IRAEs). It is important to monitor for IRAEs closely when these agents are used. Monitoring, presentation, and diagnosis of common IRAEs is shown in Table 3. If severe IRAEs occur, immunotherapy is stopped and steroids and/or other immunosuppressive agents are required.

### ICI monotherapy

Initial studies of ICIs in breast cancer evaluated the safety and efficacy of ICI monotherapy for mTNBC. In the phase Ib study KEYNOTE-012 (NCT01848834), 32 patients with both treatment-naïve and pretreated PD-L1-positive (defined as a CPS  $\geq 1$ ) mTNBC were treated with the PD-1 inhibitor pembrolizumab with an encouraging overall response rate (ORR) of 18.5%.<sup>13</sup> The larger follow-up KEYNOTE-086 (NCT02447003) phase II study evaluated two cohorts of patients with mTNBC. In cohort A, 170 patients with previously treated mTNBC were enrolled, including 105 (61.8%) with PD-L1-positive disease (CPS  $\geq 1$ ).<sup>14</sup> The ORR was a disappointing 5.3% in total and 5.7% in the PD-L1-positive population. Median progression-free survival (PFS) was 2.0 months. The most common grade  $\geq 3$  treatment-related adverse events (TRAEs) were diarrhea and increased alanine aminotransferase (ALT), and IRAEs occurred in 19.4% of patients, including hypothyroidism (11.8%) and hyperthyroidism (5.3%). In cohort B, 84 patients with treatment-naïve PD-L1-positive mTNBC were treated with pembrolizumab monotherapy with a more encouraging ORR of 21.4% and a median duration of response was 10.4 months, suggesting greater efficacy in the first-line metastatic setting.<sup>15</sup>

**Table 1.** Immune checkpoint inhibitor monotherapy and combination ICI + chemotherapy in mTNBC.

Trial/NCT number	Phase	No. of patients	Regimen	Prior lines of therapy for metastatic disease	Comparator arm	ORR, %	Median PFS, months	Median OS, months
ICI monotherapy								
KEYNOTE-012 NCT01848834	Ib	32	Pembro	Any number of prior treatment regimens	-	18.5	1.9	11.2
KEYNOTE-086A NCT02447003	II	170	Pembro	≥1	-	5.3	2.0	9
KEYNOTE-086B NCT02447003	II	84	Pembro	1-2	-	21.4	2.1	18
KEYNOTE-119 NCT02555657	III	622	Pembro	1-2	TPC	9.6 versus 10.6	2.1 versus 3.3	9.9 versus 10.8 HR 0.97
NCT01375842	I	116	Atezo	Any number of prior treatment regimens	-	1st line: 24% 2+ line: 6%	1.4	8.9 1st line: 17.6
JAVELIN NCT01772004	Ib	168 (58 mTNBC)	Avelumab	≥1	-	5.2 in patients with mTNBC	1.5	9.2
ICI + chemotherapy combinations								
NCT01375842	Ib	33	Atezo + Nab-pac	Recurrent and progressing for which no standard tx exists	Nab-pac	39.4	5.5	14.7
ENHANCE 1 NCT02513472	Ib/II-R	167	Pembro + Eribulin	0-2	-	23.4 (25.8 if no prior therapy, 21.8 if 1-2 prior therapies)	4.1	16.1
NCT03044730	II	30 (16 mTNBC)	Pembro + Cape	Any number of prior treatment regimens	-	13	4	15.4
TONIC NCT02499367	II	67	Nivo ± XRT or chemo (cyclo, cis, doxo)	At least one prior line of chemo in (neoadjuvant and/or metastatic setting)	Two-week waiting period before nivo	20	1.9	NA

(Continued)

Table 1. (Continued)

Trial/NCT number	Phase	No. of patients	Regimen	Prior lines of therapy for metastatic disease	Comparator arm	ORR, %	Median PFS, months	Median OS, months
IMpassion130 NCT02425891	III 1:1	902	Atezo + Nab-pac	0	Placebo + Nab-pac	ITT: 56.0 versus 45.9 PD-L1 + : 58.9 versus 42.6	ITT: 7.2 versus 5.5 HR = 0.80, $p = 0.002$ PD-L1 + : 7.5 versus 5.0 HR = 0.62, $p < 0.001$	ITT: 21.0 versus 18.7 HR = 0.87, $p = 0.077$ PD-L1 + : 25.4 versus 17.9 HR = 0.67, $p$ – not tested
IMpassion131 NCT03125902	III 2:1	651	Atezo + Pac	0	Placebo + Pac	63.4 versus 55.4	6.0 versus 5.7 HR = 0.82, $p = 0.20$	22.1 versus 28.3 HR = 1.11, $p = NA$
KEYNOTE-355 NCT02819518	III 2:1	847	Pembro + Nab-pac/ Pac/Gem-Carbo	0	Placebo + Nab-pac/ Pac/Gem-Carbo	53.2 versus 39.8	9.7 versus 5.6 in PD-L1 CPS $\geq 10$ HR = 0.66, $p = 0.0012$	23.0 versus 16.1 in PD-L1 CPS $\geq 10$ HR = 0.73, $p = 0.0093$
ICI + targeted therapy combinations								
MEDIOLA NCT02734004	II	34	Durvalumab + olaparib (PARPi)	Any number of prior treatment regimens	-	All cohort: 63.3 TNBC 58.8	All cohort: 8.2 TNBC: 4.9	All cohort: 21.5 TNBC 20.5
KEYNOTE-162 (TOPACIO) NCT02657889	I/II	55	Pembro + niraparib (PARPi)	Phase I: 0-4 Phase II: 0-2	-	Overall: 21 gBRCAm: 47	gBRCAm: 8.3	NA
NCT03800836	Ib	140	Ipatasertib (AKTi), atezo, pac, or nab-pac	0-2 (varies by cohort)	-	73%	NR	NR

II-R, phase II randomized; AKTi, AKT inhibitor; atezo, atezolizumab; cape, capecitabine; carbo, carboplatin; cis, cisplatin; CPS, combined positive score; cyclo, cyclophosphamide; doxo, doxorubicin; gBRCAm, germline BRCA-mutated; gem, gemcitabine; HR, hazard ratio; ICI, immune checkpoint inhibitors; ITT, intention-to-treat population; mTNBC, metastatic triple-negative breast cancer; NA, not available; nab-pac, nab-paclitaxel; nivo, nivolumab; NR, not reached; ORR, objective response rate; OS, overall survival; pac, paclitaxel; PARPi, parp inhibitor; PD-L1 +, programmed death-ligand 1-positive; pembro, pembrolizumab; PFS, progression-free survival; TPC, treatment of physician's choice; XRT, radiation.

**Table 2.** Select ongoing trials of ICIs plus chemotherapy and/or targeted therapies and novel immunotherapy agents in mTNBC.

Trial/NCT number	Phase	Regimen	Prior lines of therapy for metastatic disease	Comparator arm	Primary endpoint
ICI + chemotherapy combinations					
IMpassion132 NCT03371017	III	Chemo (Gem + Carbo or Cape) + Atezo	0	Chemo (Gem + Carbo or Cape) + placebo	OS (PD-L1+) and OS (mITT)
MK-7339-009/ KEYLYNK-009 NCT04191135	II/III	Induction: Pembro + Gem + Carbo (4-6X) then maintenance Pembro + Gem + Carbo	0	Induction: Pembro + Gem + Carbo (4-6X) then maintenance Pembro + Olaparib	PFS, OS
ICI + targeted therapy combinations					
DORA NCT03167619	II	Olaparib + Durv	0-2	Olaparib	PFS
InCITe NCT03971409	II	Lipo doxo/avelumab; binimetinib/lipo dox/avelumab; Sacituzumab govitecan/avelumab	≤2 prior chemo ≤1 prior ICI	-	Best ORR
ETC TN NCT02849496	II	Arm 1: Olaparib Arm 2: Olaparib + Atezo	Any number of prior treatment regimens	-	PFS
BEGONIA NCT03742102	II	Pac + Durv ± Capivasertib or danvatirsen (STAT3i) or oleclumab (anti-CD73)	0	-	Incidence of AEs, lab findings
Novel immunotherapy agents					
NCT00349934	I	IMP321 (Lag 3 inhibitor)	0	-	Safety, pharmacodynamic parameters
NCT03742349	IB	LAG525 (Lag 3 inhibitor_ + spartalizumab (anti-PD-1) + NIR178, capmatinib, MCS110, or canakinumab	0-2; neoadjuvant or adjuvant chemo counts as one prior line	-	AEs
NCT04616248	I	CDX-1140 (CD 40 agonist) + CXD-301 (recombinant FIt3 ligand), Poly-ICLC, radiotherapy	Any number of prior treatment regimens	-	AEs
AC, doxorubicin/cyclophosphamide; AEs, adverse events; atezo, atezolizumab; cape, capecitabine; carbo, carboplatin; chemo, chemotherapy; durv, durvalumab; EC, epirubicin/cyclophosphamide; EFS, event-free survival; gem, gemcitabine; HR, hazard ratio; ICI, immune checkpoint inhibitor; Lipo doxo, liposomal doxorubicin; mITT, modified intention-to-treat population; mTNBC, metastatic triple-negative breast cancer; N/A, not applicable; Nab-pac, nab-paclitaxel; ORR, objective response rate; OS, overall survival; pac, paclitaxel; pCR, pathologic complete response; PD-1, programmed cell death 1; PD-L1 +, programmed death-ligand 1-positive; PFS, progression-free survival.					

**Table 3.** Monitoring, presentation, and diagnosis of common IRAEs.

Toxicity	Monitoring	Presentation	Diagnosis
Thyroid	<ul style="list-style-type: none"> <li>Check TSH and free T4 at baseline and every 4–6 weeks during ICI therapy</li> </ul>	<ul style="list-style-type: none"> <li>Hypothyroidism</li> <li>Hyperthyroidism</li> <li>Myxedema</li> <li>Thyroid storm</li> </ul>	<ul style="list-style-type: none"> <li>Check TSH, free T4. Consider TSH receptor antibodies if Graves disease is suspected</li> <li>Check the morning cortisol level for concurrent adrenal insufficiency</li> </ul>
Adrenal insufficiency	<ul style="list-style-type: none"> <li>Check TSH and free T4 at baseline and every 4–6 weeks on ICI</li> <li>Consider baseline ACTH and cortisol in high-risk patients</li> </ul>	<ul style="list-style-type: none"> <li>Hypophysitis (causes headache, dizziness, nausea)</li> <li>Dysfunction of thyroid, adrenal, or gonadal axis</li> </ul>	<ul style="list-style-type: none"> <li>Check morning cortisol and ACTH, TSH, free T4, LH, FSH, testosterone (men), estradiol (women)</li> <li>Imaging: pituitary MRI</li> </ul>
Dermatologic	<ul style="list-style-type: none"> <li>Complete skin and mucous membrane examination</li> </ul>	<ul style="list-style-type: none"> <li>Rash, pruritus, bullous dermatitis</li> <li>Dermatomyositis</li> <li>Dermal hypersensitivity reaction</li> <li>Sweet syndrome</li> <li>Pyoderma gangrenosum</li> <li>DRESS</li> <li>SJS/TEN</li> </ul>	<ul style="list-style-type: none"> <li>Complete skin examination</li> <li>Rule out alternative etiologies of dermatologic disorders (e.g. infection, other drug rash, systemic illness causing dermatologic manifestations)</li> <li>Consider skin biopsy</li> </ul>
Colitis	<ul style="list-style-type: none"> <li>Inquire about baseline bowel habits and assess for diarrhea and abdominal pain with each cycle</li> </ul>	<ul style="list-style-type: none"> <li>Diarrhea</li> <li>Fecal urgency</li> <li>Abdominal pain or cramping</li> </ul>	<ul style="list-style-type: none"> <li>Assess frequency of diarrhea</li> <li>Rule out infection. Check C diff, CMV DNA PCR, stool ova and parasites, stool culture</li> <li>Consider CT abdomen/pelvis</li> <li>Consider GI consultation for EGD/colonoscopy with biopsies</li> </ul>
Hepatitis	<ul style="list-style-type: none"> <li>Check LFTs at baseline and with every cycle of ICI therapy (q2–3 weeks)</li> </ul>	<ul style="list-style-type: none"> <li>Elevation of AST/ALT</li> <li>Fulminant hepatitis</li> </ul>	<ul style="list-style-type: none"> <li>Check LFTs, CMP.</li> <li>Rule out other etiologies of liver disease with viral serologies, ask about alcohol use and other medications, consider autoimmune workup</li> <li>CT abdomen/pelvis to evaluate for liver metastases and rule out obstruction</li> <li>Consider liver biopsy</li> </ul>
Pneumonitis	<ul style="list-style-type: none"> <li>Inquire about any new respiratory symptoms with each cycle</li> </ul>	<ul style="list-style-type: none"> <li>Shortness of breath</li> <li>Cough</li> <li>Respiratory failure</li> </ul>	<ul style="list-style-type: none"> <li>Consider CT chest</li> <li>Consider infectious workup: nasal swab, sputum culture</li> <li>Consider bronchoscopy with BAL and consider transbronchial lung biopsy</li> </ul>

ACTH, adrenocorticotropic hormone; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BAL, bronchoalveolar lavage; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; DRESS, drug rash with eosinophilia and systemic symptoms; EGD, esophagogastroduodenoscopy; FSH, follicle-stimulating hormone; GI, gastroenterology; ICI, immune checkpoint inhibitor; IRAEs, immune-related adverse events; LH, luteinizing hormone; LFT, liver function test; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SJS/TEN, Stevens–Johnson syndrome or toxic epidermal necrolysis; T4, thyroxine; TSH, thyroid-stimulating hormone.

Supporting this hypothesis, the phase III KEYNOTE-119 study (NCT02555657) randomized 622 patients with mTNBC who had received 1–2 prior lines of therapy to receive single-agent pembrolizumab *versus* single-agent chemotherapy of physician’s choice (capecitabine,



eribulin, gemcitabine, or vinorelbine), and found no improvement in ORR, PFS, or OS with pembrolizumab monotherapy *versus* chemotherapy.<sup>16</sup> In the overall population, median OS was 9.9 months for the pembrolizumab group and 10.8 months for the chemotherapy group [hazard ratio (HR) 0.97, 95% confidence interval (CI) 0.82–1.15]. In participants with a CPS of 1 or more, median OS was 10.7 months for the pembrolizumab group and 10.2 months for the chemotherapy group (HR 0.86, 95% CI 0.69–1.06,  $p=0.073$ ). In an exploratory analysis, the median OS in patients with CPS  $\geq 20$  was 14.9 months with pembrolizumab *versus* 12.5 months with chemotherapy.<sup>17</sup> In patients treated with pembrolizumab, the presence of a greater proportion of TILs was associated with better clinical outcomes.

In addition to studies of pembrolizumab, other ICI therapies have also been evaluated. A phase I trial evaluated the efficacy of the PD-L1 inhibitor atezolizumab (NCT01375842) in patients with mTNBC.<sup>6</sup> Among 116 evaluable patients, the ORRs were higher in the first line (5 of 21, 24%) than in the second line or greater (6 of 94, 6%). In the first line, median OS was 17.6 months. Patients with PD-L1 expression of at least 1% tumor-infiltrating immune cells had higher ORRs and longer OS (12% and 10.1 months, respectively) than those with less than 1% tumor-infiltrating immune cells (0% and 6.0 months, respectively). In the phase Ib JAVELIN trial (NCT01772004), 168 patients with metastatic breast cancer (MBC), including 58 patients with TNBC, were treated with the PD-L1 inhibitor avelumab.<sup>18</sup> In this heavily pretreated population, the ORR was 3.0% overall and 5.2% in patients with mTNBC. Collectively, these studies suggest that ICI monotherapy has limited therapeutic potential in patients with mTNBC, with response rates ranging from 5% in pretreated patients to 24% in treatment-naïve patients with PD-L1-positive disease, with the possibility of improved outcome with PD-L1 enrichment. Therefore, recent efforts have focused on the use of ICI in combination with other agents, primarily with chemotherapy, and in the first-line setting.

There is also increasing evidence that patients with high TMB, defined as 10 or more mutations per megabase, are more likely to benefit from ICI therapy. Approximately 10% of patients with MBC have high TMB, so the use of ICI therapy in this patient population is of particular interest

as it may result in durable responses. Based on data from KEYNOTE-158,<sup>19</sup> pembrolizumab received accelerated approval for the treatment of patients with metastatic solid tumors with high TMB, regardless of the specific tumor type. In breast cancer, the NIMBUS trial (NCT03789110) treated 30 women with metastatic HER2-negative breast cancer with high TMB (at least nine mutations per megabase) with up to three prior lines of chemotherapy with low-dose ipilimumab and nivolumab. Preliminary results were presented at SABCS in 2021.<sup>20</sup> More patients with hormone receptor-positive (HR+) disease compared with TNBC had a high TMB (21 *versus* 9). At a median follow-up of 9.7 months, the ORR rate was 16.7% (5/30); six (20.0%) had stable disease and three (10%) were not evaluable for response. Of note, three of the responders had a TMB at least 14 mutations per megabase and the five patients with a TMB of 14 mutations per megabase or higher achieved a longer median PFS (9.5 months *versus* 1.4 months) and OS (not reached *versus* 8.8 months) than those with lower TMB; the numbers are very small. There were no grade 4 or 5 events, and the most common adverse events were fatigue, diarrhea, anemia, and anorexia, similar to those seen in other tumors treated with the combination of nivolumab and ipilimumab. Although this study provides interesting data regarding response to immunotherapy in breast cancers with a high TMB, it does not address the question about whether dual therapy is better than ICI monotherapy in this patient population.

Of note, the current understanding of mechanisms of acquired resistance to ICIs is remarkably limited. Resistance to ICIs may initially be classified as (1) primary resistance (i.e. patients who do not respond to ICIs at all) and (2) acquired resistance (i.e. patients who have a period of initial response, followed by progression of disease).<sup>21</sup> To confront the challenge of primary resistance, ICIs have been combined with other agents, as discussed in the next few sections and noted above. In contrast, less is known about how to circumvent the challenge of acquired resistance, but this remains an active area of research.

#### *Combination therapy with ICI and chemotherapy*

Given the low clinical response of ICI monotherapy or combination therapy in most patients with breast cancer, subsequent studies evaluated the

combination of ICI with chemotherapy. Preclinical data have demonstrated that chemotherapy can induce tumor antigen release and potentially increase TILs which may stimulate a greater antitumor immune effect,<sup>22,23</sup> increasing the enthusiasm for this combination treatment strategy.

*Phase I and II studies of ICI and chemotherapy combinations.* Several phase I and II studies have evaluated ICI and chemotherapy combinations. In a phase Ib trial of atezolizumab and nab-paclitaxel (NCT01375842) in 33 patients with pre-treated mTNBC, the ORR was 39.4%, median PFS was 5.5 months, and median OS was 14.7 months.<sup>24</sup> In the phase Ib/II ENHANCE1 trial (NCT02513472), 167 patients with mTNBC who had received 0–2 prior lines of therapy were treated with the combination of pembrolizumab and the microtubule inhibitor eribulin.<sup>25</sup> In this study, the ORR was 25.8% for patients with no prior systemic anticancer therapies ( $n=66$ ) and 21.8% for patients with 1–2 prior systemic anticancer therapies ( $n=101$ ). In another phase II study (NCT03044730), 30 patients with MBC (16 with mTNBC, 14 with HR+/HER2– MBC) were treated with pembrolizumab and capecitabine with a median PFS and OS of 4 and 15.4 months, respectively,<sup>26</sup> similar to historic controls treated with capecitabine alone. In the first stage of the phase II TONIC trial (NCT02499367), 67 patients with mTNBC were randomized to receive a short induction (irradiation, cyclophosphamide, cisplatin, doxorubicin, or no induction) followed by nivolumab. The ORR was 20%, with higher responses in the doxorubicin (ORR 35%) and cisplatin (ORR 23%) cohorts.<sup>27</sup> Doxorubicin or cisplatin induction resulted in upregulation of immune-related genes involved in PD-1/PD-L1 and T-cell cytotoxicity pathways. These data suggest that short-term low-dose doxorubicin and cisplatin could induce a more favorable TME and increase the likelihood of response to anti-PD-1 therapy in TNBC, which is currently under investigation. In addition, the Synergy study is a phase I/II study of paclitaxel plus carboplatin and durvalumab with or without oleclumab, a monoclonal antibody targeting CD73, for previously untreated locally recurrent inoperable or mTNBC (NCT03616886). Preliminary results were presented at ESMO in 2020: 0 of six patients experienced dose-limiting toxicity and four patients had a clinical benefit at week 24.<sup>28</sup> Results of the phase II study are forthcoming.

### *Phase III studies of ICI and chemotherapy combinations*

*Atezolizumab.* The phase III IMpassion130 study (NCT03371017) randomized 902 patients with unresectable locally advanced or mTNBC to receive either atezolizumab plus nab-paclitaxel versus placebo plus nab-paclitaxel in the first-line setting.<sup>29</sup> In the intention-to-treat (ITT) analysis, the median PFS was 7.2 months with atezolizumab plus nab-paclitaxel versus 5.5 months with placebo plus nab-paclitaxel (HR 0.80; 95% CI 0.69–0.92,  $p=0.002$ ). Among the 41% of patients with PD-L1-positive tumors (defined as SP142  $\geq 1\%$ ), the median PFS was 7.5 and 5.0 months, respectively (HR 0.62, 95% CI 0.49–0.78,  $p<0.001$ ). The hierarchical statistical plan was designed to allow evaluation of OS in the PD-L1-positive cohort only if there was a significant difference in the ITT group. There was no significant improvement in OS in the ITT population, but the difference in OS in the PD-L1-positive cohort was clinically significant and therefore was reported as a descriptive analysis. In the final analysis, OS was improved with the addition of atezolizumab by 7.5 months in the PD-L1-positive subgroup (25.4 versus 17.9 months, stratified HR 0.67).<sup>30</sup> Hypothyroidism was the most common irAE reported with the addition of atezolizumab compared with placebo (17.3% versus 4.3%). Pneumonitis occurred more commonly in the atezolizumab arm than in the placebo group (3.1% versus 0.2%). Chemotherapy-related toxicity, such as cytopenias and peripheral neuropathy, was not increased with the addition of atezolizumab. Treatment was discontinued because of toxicity in 15.9% of patients treated with atezolizumab versus 8.2% of those in the placebo arm. TME analysis demonstrated that PD-L1 immune-inflamed tumors and PD-L1 basal-like immune-activated tumors showed the highest sensitivity to immunotherapy, whereas LAR tumors did not benefit from the addition of atezolizumab.<sup>31</sup> The results of this study lead the US Federal Drug Administration (FDA) and the European Commission to provide accelerated approval for atezolizumab and nab-paclitaxel for the treatment of PD-L1-positive mTNBC.

However, another phase III study, IMpassion131 (NCT03125902), also assessed the efficacy of atezolizumab in patients with mTNBC, randomizing 651 patients 2:1 to receive atezolizumab or placebo combined with weekly paclitaxel as first-line therapy.<sup>32</sup> At the primary PFS analysis, the addition of atezolizumab to paclitaxel did not



improve PFS or OS in either the ITT or PD-L1-positive population (in PD-L1-positive: PFS 6.0 months *versus* 5.7 months; OS 22.1 months *versus* 28.3 in atezolizumab + paclitaxel *versus* placebo + paclitaxel, respectively). Of note, the OS in the PD-L1-positive control population receiving paclitaxel alone was longer than any other first-line study of patients with mTNBC. Given the inability to confirm the OS benefit from atezolizumab demonstrated in IMpassion130, Roche withdrew the indication for atezolizumab with nab-paclitaxel as treatment for patients with mTNBC whose tumors express PD-L1 in consultation with the US FDA in August 2021, although the combination is still approved in many countries.

The reasons for the inconsistency between the results of IMpassion130 and IMpassion131 are unclear. It is possible that the differential use of steroids between the trials played a role, potentially reducing ICI efficacy. However, steroids were used in KEYNOTE-355, which demonstrated efficacy when pembrolizumab was added to chemotherapy, as discussed in the next section. Alternatively, it is possible that paclitaxel may be an inferior chemotherapy partner in patients with mTNBC who have already been treated with paclitaxel in the early-stage setting. Finally, it is possible that patient characteristics not included in standard stratification factors differed between cohorts in the trials and could have impacted results. In countries where atezolizumab is still approved, clearly nab-paclitaxel is the appropriate chemotherapy partner.

**Pembrolizumab.** The KEYNOTE-355 study (NCT02819518) randomized 847 patients with mTNBC 2:1 to receive physician's choice of chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin) with either pembrolizumab or placebo in the first-line setting.<sup>33</sup> Eligible patients either had *de novo* mTNBC or relapsed at least 6 months from treatment in the early-stage setting (compared with 12 months for the IMpassion trials). In the 38% of patients whose tumors were PD-L1 positive defined as a CPS  $\geq$  10, the addition of pembrolizumab to chemotherapy significantly improved both PFS and OS (PFS: 9.7 *versus* 5.6 months, HR 0.66;  $p=0.0012$ ; OS 23.0 *versus* 16.1 months, HR 0.73;  $p=0.0093$ ). Both ORR (53.2% *versus* 39.8%) and duration of response (19.3 *versus* 7.3 months) were improved with pembrolizumab in PD-L1+ (CPS  $\geq$  10) mTNBC.<sup>34,35</sup> In the pembrolizumab arm, 26.5%

of patients experienced IRAEs (any grade), most commonly hypothyroidism (15.8%) and hyperthyroidism (4.3%). Grade 3–6 immune-mediated toxicity was 5.3% in the pembrolizumab arm and 0.0% in the placebo arm, and more patients discontinued treatment because of adverse events in the pembrolizumab arm. Based on these data, the combination of pembrolizumab with physician's choice of chemotherapy (weekly paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin) received accelerated approval for patients with PD-L1+ (CPS  $>$  10) mTNBC by the US FDA in November 2020 and final approval in July 2021.

**Checkpoint inhibitors in the early-stage setting.** Several studies have evaluated the combination of ICI and chemotherapy in the early-stage setting as described here briefly, as these data may inform our understanding of ICI efficacy in mTNBC. In stage II and III TNBC, the large phase III KEYNOTE 522 trial (NCT03036488) demonstrated improvement in both pathologic complete response (pCR) and event-free survival (EFS) with the addition of pembrolizumab to neoadjuvant chemotherapy and continued in the adjuvant setting, leading to regulatory approval of this treatment by the FDA in July 2021. KEYNOTE 522 randomized 1174 patients with early-stage TNBC to receive neoadjuvant paclitaxel/carboplatin followed by anthracycline/cyclophosphamide with both in combination with pembrolizumab *versus* placebo; blinded pembrolizumab or placebo was continued for an additional nine cycles after surgery.<sup>36</sup> pCR was assessed in the first 602 patients and was increased by 13.6% with pembrolizumab (pCR 64.8% *versus* 51.2%,  $p < 0.001$ ). At a median follow-up of 39.1 months, EFS was improved in patients who received pembrolizumab. The 3-year EFS was 84.5% with pembrolizumab/chemotherapy compared with 76.8% with chemotherapy alone (HR 0.63, 95% CI 0.48–0.82,  $p=0.00031$ ), and improvement of 7.7%<sup>30</sup> Interestingly, outcome was very good in patients achieving a pCR, regardless of the treatment arm, but EFS was also improved in patients who did not achieve a pCR receiving pembrolizumab compared with those receiving placebo. As expected, use of pembrolizumab resulted in immune toxicity, with three associated deaths. Clearly early diagnosis and careful management is required to ensure best outcomes with the combination of ICI and chemotherapy. Based on these results, in July 2021, the US FDA approved pembrolizumab for the treatment of patients with high-risk early-stage TNBC in combination with

chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery.

The smaller phase III IMpassion031 study (NCT03197935) randomized 333 patients with early-stage TNBC to receive atezolizumab or placebo plus nab-paclitaxel followed by anthracycline/cyclophosphamide then surgery, with unblinded atezolizumab to complete 1 year of therapy postoperatively.<sup>37</sup> pCR was improved by 17% with atezolizumab (pCR 58% *versus* 41%,  $p=0.0044$ ). Interestingly, PD-L1 status did not predict improved pCR in either trial, or EFS in KEYNOTE 522. The large phase III NASBP B-59/GeparDouze trial randomized 1500 patients with high-risk early-stage TNBC to receive atezolizumab or placebo with neoadjuvant chemotherapy and continuing postsurgery to complete 1 year of therapy. Results are expected in 2022–2023.

Finally, the phase II GeparNUEVO study (NCT02685059) randomized 174 patients to receive the ICI durvalumab or placebo with neoadjuvant nab-paclitaxel followed by epirubicin/cyclophosphamide. pCR, the primary endpoint, was numerically but not significantly increased with durvalumab.<sup>38</sup> However, with longer follow-up, durvalumab significantly increased invasive disease-free survival (DFS), distant DFS, and OS.<sup>38</sup> These intriguing data, taken in the context of KEYNOTE 522, suggest that patients who achieve a pCR may not need continued ICI postsurgery, although further analyses are clearly required.

One important outstanding question is defining the role of additional immunotherapy in the metastatic setting for patients who received ICIs in the neoadjuvant and/or adjuvant setting and then subsequently develop metastatic disease. For example, future studies are needed to evaluate whether the disease-free interval, time to rechallenge with ICI, or the specific ICI agent (continue the prior agent *versus* treating with a different ICI) affect response and resistance in the metastatic setting.

*Ongoing studies of ICI and chemotherapy combinations in mTNBC.* Additional studies evaluating the combination of ICIs and chemotherapy for mTNBC, as well as novel sequencing and immune induction strategies, are ongoing (Table 2). For example, IMpassion132 (NCT03371017)

is evaluating whether first-line atezolizumab plus chemotherapy will improve outcomes compared with chemotherapy alone in patients with mTNBC that recurs within 1 year of adjuvant therapy. Future studies are needed to determine the optimal chemotherapy partners, the timing and sequencing of ICI administration, and whether there are predictive biomarkers that can be used to understand which patients will derive the most benefit from the addition of ICI to chemotherapy.

#### *ICI and targeted therapy combinations*

Given that most patients with mTNBC do not appear to benefit from the addition of ICIs to chemotherapy, there is great interest in improving both PD-L1 expression and TILs with targeted therapy combinations. In the targeted section below, we will discuss combination approaches; completed and ongoing studies of targeted therapies and ICI are included in Table 1 and Table 2 respectively.

#### *Novel systemic immunotherapy agents*

Efforts are ongoing to identify additional novel immunologic targets that can enhance the efficacy of ICI and/or provide independent benefit. For example, emerging data suggest a possible role for lymphocyte-associated gene 3 (LAG3) inhibitors. LAG3 is an inhibitory receptor that is mainly found on activated immune cells and coexpressed with other inhibitory receptors like PD-1.<sup>39,40</sup> In a phase I study, the combination of IMP321, a fusion recombinant inhibitor of LAG3, was combined with paclitaxel in the first-line metastatic setting (mTNBC and HR+ MBC), demonstrating acceptable toxicity.<sup>41</sup> Subsequently, a phase II trial studied IMP321 and paclitaxel in patients with HR+ MBC (NCT02614833); preliminary data from the run-in phase suggested that IMP321 enhanced antigen-presenting cell (APC) and T-cell activation.<sup>42</sup> There is also interest in understanding if the combination of PD-1 and LAG3 inhibition is synergistic, as *in vivo* studies demonstrate enhanced benefit with this combination.<sup>43</sup> For example, there is a phase Ib clinical trial studying the safety and efficacy of a PD-1 inhibitor (spartalizumab) and an LAG3 inhibitor (LAG525) in combination with another investigational drug (NIR178, capmatinib, MCS110, or canakinumab) in patients with mTNBC (NCT03742349).

Another interesting novel immunotherapy strategy is the use of CD40 agonists. CD40 is an immune costimulatory receptor expressed by APCs.<sup>44</sup> In early phase clinical trials, CD40 monoclonal antibodies demonstrated favorable antitumor responses in the treatment of melanoma, mesothelioma, pancreatic adenocarcinoma, and lymphoma.<sup>45–50</sup> In breast cancer, there is a trial underway evaluating the anti-CD40 agent CDX-1140 in combination with radiation therapy and other immunomodulatory agents in patients with unresectable or MBC (all subtypes) (NCT04616248). One concern with the use of CD40 agonists is the potential for hepatotoxicity and cytokine release syndrome.<sup>45</sup> To limit systemic toxicities, intratumoral injection of CD40 agonists is being studied in early phase trials (NCT02379741), although it is unclear how local infiltration alone will affect efficacy.

Magrolimab is another novel antibody of interest, targeting CD47. CD47 is a macrophage immune checkpoint referred to as the ‘do not eat me’ signal, enabling cancer cells to evade the immune system. Initial studies in hematologic malignancies are encouraging, and trials in TNBC are just beginning.

Several other immunotherapy agents are also being studied in early phase clinical trials. For example, anti-CD47 antibodies prevent tumor cells from escaping macrophage-mediated phagocytosis.<sup>51</sup> 4-1BB agonists bind to the 4-1BB costimulatory receptor and activate antitumor lymphocytes.<sup>52</sup> Ox40 agonists bind to the Ox40 protein receptor and trigger a T-cell and cytokine response.<sup>53</sup> Most of these agents are undergoing initial testing across various tumor types, and the future of these agents in the treatment of breast cancer is uncertain.

#### *Intratumoral agents and other emerging immunotherapy strategies*

There is also interest in studying the safety and efficacy of intratumoral therapies, which can increase local drug concentration, directly cause malignant cell apoptosis, and also have an immunotherapy effect through activation of local and systemic immune responses.<sup>54</sup> For example, talimogene laherparepvec (T-VEC) is a modified herpes simplex virus (HSV) that has been studied in the treatment of cancer.<sup>55–57</sup> In early-stage breast cancer, there are data that the combination of T-VEC and neoadjuvant chemotherapy is safe and feasible.<sup>58</sup> There are ongoing studies evaluating the

combination of T-VEC and chemotherapy or endocrine therapy for patients with unresectable, recurrent, or metastatic HER2-negative disease (NCT03554044). Besides oncolytic viruses, there has also been interest in directly injecting immune modulating agents into the TME either alone or in combination with systemic immunotherapy. For example, tavokinogene telseplasmid (tavo) is a plasmid encoding interleukin (IL)-12, which is a pivotal regulator of innate and adaptive immunity.<sup>59</sup> There is currently a phase II trial evaluating the safety and efficacy of intratumoral tavo in combination with systemic pembrolizumab in patients with inoperable locally advanced or mTNBC (KEYNOTE-890/OMSI-141, NCT03567720). Preliminary results from 11 of the planned 25 patients were presented at the San Antonio Breast Cancer Symposium in 2018 and 3 of the 11 patients had a partial response (ORR 27.3%).<sup>60</sup>

In addition, other emerging immunotherapy strategies include the use of anticancer vaccines, bispecific T-cell engagers (BITEs), and chimeric antigen receptor (CAR) T-cell therapy. Ongoing studies are underway to evaluate the safety and efficacy of these strategies alone or in combination with ICIs or other novel immunotherapy agents.

#### **Targeted therapies**

Targeted therapies are drugs that block the growth of malignant cells by interfering with a specific molecule/pathway that is required for cell proliferation, growth, and survival. Breast cancer cells may overexpress certain receptors that can activate cell growth, so using agents that specifically block these pathways can prevent tumor growth. These can be germline mutations that are present in somatic and tumor cells, or acquired mutations may be found in tumor cells. Targeted therapies have the potential to specifically target malignant cells with increased efficacy and decreased toxicity, and can often be combined with chemotherapy and/or ICIs to more effectively control malignant proliferation. In this section, we will discuss the use of targeted therapies as monotherapy and in combination with other therapies to treat mTNBC (also see Table 4).

#### *PARP inhibitors for patients with germline and somatic BRCA-mutant breast cancer*

Breast cancers associated with *BRCA1* or *BRCA2* pathogenic mutations occur in approximately 5% of breast cancers, and up to 20% of patients with

**Table 4.** Targeted therapies in mTNBC.

Trial/NCT number	Phase	No. of patients	Regimen	Prior lines of therapy for metastatic disease	Comparator arm	ORR, %	Median PFS, months	Median OS, months
PARP inhibitors								
OlympiAD NCT02000622	III	302	Olaparib	0–2	Chemo (cape, erib, vino)	59.9 versus 28.8	7.0 versus 4.2 HR = 0.58, <i>p</i> = 0.0009	19.3 versus 17.1 HR = 0.90, <i>p</i> = 0.513
EMBRACA NCT01945775	III	431	Talazoparib	0–3	Chemo (cape, gem, erib, vino)	62.6 versus 27.2	8.6 versus 5.6 HR = 0.54, <i>p</i> < 0.0001	19.3 versus 19.5 HR = 0.848, <i>p</i> = 0.17
AKT inhibitors								
LOTUS NCT02162719	II	124	Ipatasertib + pac	0	Pac plus placebo	ITT: 40 versus 32 PIKCA/ AKT-1/ PTEN altered: 50% versus 44	ITT: 6.2 versus 4.9 HR = 0.60, <i>p</i> = 0.037 PIKCA/AKT-1/ PTEN altered: 9.0 versus 4.9 HR = 0.44, <i>p</i> = NA	ITT: 25.8 versus 16.9 HR = 0.80 PIKCA/AKT-1/ PTEN altered: 25.8 versus 22.1 HR = 1.13
PAKT NCT02423603	II	140	Capivasertib + pac	No prior chemo for metastatic disease. No prior PI3Ki, AKIi, mTORi	Pac plus placebo	ITT: 34.8 PIKCA/ AKT-1/ PTEN altered: 35.3%	ITT: 5.9 versus 4.2 HR = 0.74, <i>p</i> = 0.06 PIKCA/AKT-1/ PTEN altered: 9.3 versus 3.7 HR = 0.30, <i>p</i> = 0.01	ITT: 19.1 versus 13.5 HR + 0.70, <i>p</i> = 0.085 PIKCA/AKT-1/ PTEN altered: 19.1 HR = 0.58
IPATunity130, cohort A NCT03337724	III	255	Ipatasertib + pac	No prior chemo for metastatic disease. No prior PI3Ki, AKIi, mTORi	Pac plus placebo	39 versus 35	7.4 versus 6.1 HR + 1.02, <i>p</i> = 0.9237	NR (ongoing)
MEK inhibitors								
COLET NCT02322814	II	Cohort I 106	Cobimetinib + pac	0	Pac plus placebo	38.3 versus 20.9	5.5 versus 3.8	NA
Tyrosine kinase inhibitors								
FUTURE-C-PLUS NCT04129996	II	48	Camrelizumab + nab-pac + famitinib	0	n/a	NR (ongoing)	NR (ongoing) 9-month PFS 60.2%	NR (ongoing)
AKTi, AKT inhibitor; cape, capecitabine; carbo, carboplatin; chemo, chemotherapy; gem, gemcitabine; HR, hazard ratio; ITT, intention-to-treat population; mTNBC, metastatic triple-negative breast cancer; mTORi, mTOR inhibitor; NA, not available; nab-pac, nab-paclitaxel; NR, not reported; ORR, objective response rate; OS, overall survival; pac, paclitaxel; PFS, progression-free survival; PI3Ki, PI3-kinase inhibitor; vino, vinorelbine.								

TNBC. Poly(ADP-ribose) polymerase (PARP) is critical for repairing single-stranded DNA damage, so PARP inhibitors have been studied in patients with germline *BRCA1* or *BRCA2* mutations.

The phase 3 OlympiAD study (NCT02000622) enrolled 302 patients with HER2-negative MBC and a pathogenic germline *BRCA1* or *BRCA2* mutation and randomized them 2:1 to receive olaparib 300 mg BID or physician's choice of



single-agent chemotherapy (with capecitabine, eribulin, or vinorelbine).<sup>61</sup> Median PFS was significantly longer in the olaparib arm compared with the standard therapy arm (7.0 *versus* 4.2 months) and response rate was also significantly higher in the olaparib group (59.9% *versus* 28.8%). The rate of grade  $\geq 3$  adverse events was lower in the olaparib group than in the standard therapy group (36.6% *versus* 50.5%), with anemia (16.1%) and neutropenia (9.3%) being the most common grade  $\geq 3$  adverse events in the olaparib arm. Based on this study, olaparib was FDA approved in 2018 for the treatment of HER2-negative MBC in patients with a germline *BRCA1* or *BRCA2* pathogenic mutation. Of note, recent data also indicate that olaparib is effective in the early-stage setting. The Olympia trial (NCT02032823) randomized 1836 patients with high-risk early-stage breast cancer and pathogenic or likely pathogenic *BRCA1* or *BRCA2* germline mutations to receive 1 year of adjuvant olaparib *versus* placebo.<sup>62</sup> The addition of adjuvant olaparib improved 3-year invasive DFS by 8.8 percentage points (85.9% in the olaparib group *versus* 77.1% in the placebo group; HR 0.58,  $p < 0.001$ ). Future studies are needed to determine whether there is a role for PARP inhibitors in the metastatic setting if patients have already received one of these agents in the adjuvant setting.

In addition to olaparib, other PARP inhibitors are also under investigation. In the phase III EMBRACA study (NCT01945775), 431 patients with advanced HER2-negative breast cancer and a pathogenic germline *BRCA1* or *BRCA2* mutation were randomized to receive the PARP inhibitor talazoparib *versus* standard single-agent physician's choice of therapy (capecitabine, eribulin, gemcitabine, or vinorelbine).<sup>63</sup> Median PFS was significantly longer in the talazoparib group compared with the standard therapy group (8.6 *versus* 5.6 months). The ORR was higher in the talazoparib group compared with the standard therapy group (62.6% *versus* 27.2%). Grade 3 and 4 nonhematologic adverse events occurred in 32% of patients in the talazoparib arm *versus* 38% of patients in the standard therapy arm; grade 3 and 4 hematologic adverse events (mainly anemia) occurred in 55% *versus* 38% of the groups, respectively. Patient-reported outcomes favored the use of talazoparib, with patients reporting a significant improvement in quality of life and a delay in the time to clinically meaningful deterioration according to both the global health status-quality-of-life and breast symptoms scales. Given

the efficacy of PARP inhibitors in the aforementioned studies, it is important to obtain germline *BRCA* testing on all patients with early-stage and mTNBC, regardless of patient age and family history, given the implications for treatment.

There are also studies underway evaluating the safety and efficacy of combining a PARP inhibitor with cytotoxic chemotherapy, other targeted therapies, and/or ICIs. In particular, the combination of PARP inhibitors with ICIs is a promising area of research. Preclinical work in a *BRCA*-deficient mTNBC mouse model demonstrated that PARP inhibitors activate the stimulator of interferon gene (STING) pathway, which increases type 1 interferons and infiltration of intertumoral T-cells,<sup>64</sup> potentially offering a synergistic effect with ICI. In the phase II MEDIOLA trial (NCT02734004), 34 patients with germline *BRCA1* or *BRCA2* mutations and HER2-negative MBC were treated with a combination of the PD-L1 inhibitor durvalumab and olaparib until disease progression.<sup>65,66</sup> The primary efficacy endpoint of disease control at 12 weeks was achieved in 24 patients (80%), the median duration of response was 9.2 months, and the median PFS was 8.2 months. Eleven of the 34 patients experienced  $\geq$  grade 3 TRAEs, of which the most common were anemia ( $n = 4$ ), neutropenia ( $n = 3$ ), and pancreatitis ( $n = 2$ ). In the phase I/II TOPACIO/KEYNOTE-162 study (NCT02657889), 55 patients with advanced or mTNBC were treated with pembrolizumab plus the PARP inhibitor niraparib.<sup>67</sup> In 15 evaluable patients with tumor *BRCA* mutations, the ORR was 47% and median PFS was 8.3 months; in 27 patients with *BRCA* wildtype tumors, the ORR was 11% and median PFS was 2.1 months. The most common  $\geq$  grade 3 TRAE was anemia (18%). Therefore, the authors concluded that the combination of niraparib plus pembrolizumab provided promising antitumor activity, with higher response rates in those with tumor *BRCA* mutations. Several additional studies are ongoing, such as the phase II DORA study (NCT03167619)<sup>68</sup> which is evaluating the combination of olaparib and durvalumab in the first- or second-line setting for HER2-negative germline *BRCA mutant* MBC and KELYNK-009 (NCT04191135)<sup>69</sup> which is evaluating the combination of olaparib, chemotherapy (gemcitabine plus carboplatin), and pembrolizumab as first-line therapy in patients with locally recurrent inoperable TNBC or mTNBC (with or without pathogenic *BRCA1* or *BRCA2* germline mutations).



Unfortunately, primary resistance to PARP inhibitors as well as acquired resistance with prolonged PARP inhibitor administration remains major challenges. Homologous recombination repair restoration is the predominant reason for PARP inhibitor resistance, but other factors such as reversion mutations, epigenetic modification, restoration of ADP-ribosylation, and pharmacological alteration can all play a role as well.<sup>70</sup> Potential strategies to overcome PARP inhibitor resistance is an active area of research; use of inhibitors early in the treatment course may help.

Of note, in addition to PARP inhibitors, cytotoxic chemotherapy with platinum salts is also an effective therapy for patients with *BRCA1* or *BRCA2* mutations. In the phase III TNT study, 376 patients with untreated mTNBC were randomized to receive carboplatin or docetaxel. In the unselected population, these agents were equivalent (ORR 31.4% versus 34.0%, respectively) but in the 43 patients with a germline *BRCA* mutation, carboplatin was associated with double the ORR compared with docetaxel [68% ( $n = 25$ ) versus 33% ( $n = 18$ ), respectively].<sup>71</sup> Although this small subset suggests superiority of carboplatin in terms of response, PARP inhibitors are associated with less toxicity overall, and the numbers were too small to evaluate any potential impact of sequencing on survival. Subsequent studies have evaluated the combination of carboplatin and olaparib, including in *BRCA* wildtype patients. For example, a phase I/Ib study evaluated the safety and efficacy of carboplatin plus olaparib in patients with sporadic TNBC, demonstrating that it was safe and tolerable with modest activity;<sup>72</sup> further evaluation is warranted to determine if there are predictive biomarkers to identify which patients with wildtype *BRCA* mutations had response.

#### Targeted therapies for patients with *PIK3A*, *AKT1*, and *PTEN* somatic mutations

Approximately 15–20% of patients with TNBC have *PIK3CA/AKT1/PTEN* mutations, so there has also been interest in targeting this pathway with AKT inhibitors (AKTi). Two randomized phase II trials have evaluated the combination of AKTi with paclitaxel in mTNBC: LOTUS (NCT02162719)<sup>73,74</sup> which evaluated the combination of paclitaxel plus ipatasertib or placebo, and PAKT (NCT02423603)<sup>75</sup> which evaluated the combination of paclitaxel plus capivasertib or placebo. Based on encouraging results from these

studies, the phase III IPATunity130 study (NCT03337724) evaluated the combination of ipatasertib and paclitaxel in patients with *PIK3CA/AKT1/PTEN*-altered advanced or mTNBC (cohort A,  $n = 255$ ) or HR+, HER2 negative (cohort B,  $n = 201$ ). Interim results from cohort A demonstrated that the ORR was similar between the ipatasertib and paclitaxel versus the placebo and paclitaxel arms (47% versus 45%) and there was no difference in PFS (7.4 versus 6.1 months, respectively).<sup>76</sup> The ongoing phase III CAPItello trial (NCT03997123) is evaluating a different AKTi, capivasertib in combination with paclitaxel in unselected patients with mTNBC.

In addition, AKTi are also being studied in combination with ICI. In a recent phase 1b study (NCT03800836), the triplet combination of ipatasertib, atezolizumab, and paclitaxel or nab-paclitaxel was evaluated in patients with advanced and mTNBC. Preliminary efficacy data demonstrated an ORR of 73% in the first 26 patients.<sup>77</sup> We await data from arm 2 of the BEGONIA trial (NCT03742102), evaluating capivasertib, in combination with paclitaxel and durvalumab.

#### Other targeted therapies under investigation

Another promising treatment strategy involves targeting the mitogen-activated protein kinase (MAPK) pathway, which may be important in immune regulation. In preliminary results from cohort 1 of the phase II COLET study, the addition of the MEK inhibitor cobimetinib to paclitaxel improved PFS compared with paclitaxel alone in 106 patients with advanced TNBC (5.5 versus 3.8 months, HR 0.73, 95% CI 0.43–1.24).<sup>78</sup> In a second cohort of the COLET study, cobimetinib and atezolizumab were combined with either paclitaxel or nab-paclitaxel in patients with mTNBC. Preliminary results from 63 patients demonstrated an ORR of 34% in the paclitaxel arm and 29% in the nab-paclitaxel arm.<sup>79</sup> Other trials are ongoing, such as InCITE/TBCRC047 (NCT03971409), which includes one arm that is evaluating the efficacy of the PD-L1 antibody avelumab and liposomal doxorubicin with or without the MEK inhibitor binimetinib in patients with advanced or mTNBC.

Another phase II study FUTURE C-PLUS (NCT04129996) is currently studying the combination of the anti-PD-1 antibody camrelizumab, nab-paclitaxel, and famitinib (a tyrosine kinase inhibitor targeting vascular endothelial

growth factor receptor-2 [VEGFR-2], platelet-derived growth factor receptor [PDGFR], and c-kit) in patients with the immunomodulatory subtype of mTNBC. Preliminary data presented at ASCO 2021 were notable for a 9-month PFS of 60.2%;<sup>80</sup> duration of response and OS data are not yet mature.

Notch inhibitors are another targeted therapy which are under investigation in patients with mTNBC. Notch signaling is a highly evolutionarily conserved pathway involved in cell development and survival.<sup>81</sup> Preclinical studies have shown that targeting the Notch pathway can prevent or reverse treatment resistance through the reduction or elimination of breast cancer stem cells, and thus may be an important therapeutic target.<sup>82</sup> However, the study of Notch inhibitors in the clinic has been complicated by dose-limiting gastroesophageal toxicity for some agents.<sup>83</sup> In a phase I pharmacologic and pharmacodynamic study of the gamma secretase (Notch) inhibitor MK-0752, 103 patients with advanced solid tumors were treated with escalating doses of an oral notch inhibitor.<sup>84</sup> Weekly dosing was generally well tolerated and resulted in strong modulation of a Notch gene signature, so rational combination trials are currently underway to maximize clinical benefit in combination with other agents.

### ADCs

Aside from ICI and targeted therapies, another treatment strategy for mTNBC is the use of ADCs. ADCs are composed of a monoclonal antibody linked to a cytotoxic small molecule payload, engineered to deliver the small molecule preferentially to malignant cells. This novel treatment approach combines the specificity of the small molecule with the potency of the cytotoxic agent to improve cancer treatment. Sacituzumab govitecan is the first ADC approved for the treatment of mTNBC, and there are encouraging data from other emerging ADCs based on clinical trials. In this section, we will summarize the existing literature about ADCs for the treatment of mTNBC and highlight emerging areas of research (also see Table 5).

#### *Sacituzumab govitecan*

Sacituzumab govitecan-hziy is a first-in-class ADC that combines a humanized monoclonal antibody to the human trophoblast cell-surface antigen 2 (Trop-2) conjugated by a cleavable

linker to SN-38, the active metabolite of irinotecan. The trop-2 receptor is ubiquitously expressed on 90% of TNBC cells, among other subtypes of BC and other malignancies.<sup>85,86</sup> SN-38 binds to the topoisomerase I cleavage complex on DNA, ultimately causing S-phase-specific cell death.

In a single-arm phase I/II study NCT01631552, 108 patients with heavily pretreated mTNBC (median five prior lines of therapy, range 1–12) received 10 mg/kg of sacituzumab govitecan on days 1 and 8 in a 21-day cycle.<sup>86,87</sup> The ORR was 33.3%, the median PFS was 5.5 months, and the median OS was 13.0 months. Importantly, patients appeared to derive benefit from sacituzumab govitecan, regardless of age, receipt of prior ICIs, and number of prior lines of therapy, although subgroups were too small to be able to make statistically significant conclusions.

To confirm these findings, the open-label phase III ASCENT trial (NCT02574455) enrolled 529 patients with refractory or mTNBC who had received at least two prior lines of chemotherapy (including a taxane) in the metastatic setting and patients were randomized to receive either sacituzumab govitecan or to physician's choice of single-agent chemotherapy (choice of eribulin, capecitabine, vinorelbine, or gemcitabine). Sacituzumab govitecan demonstrated a significant improvement in median PFS (5.6 *versus* 1.7 months,  $p < 0.0001$ ), median OS (12.1 *versus* 6.7 months,  $p < 0.0001$ ), and ORR (35% *versus* 5%) over standard chemotherapy.<sup>88</sup> The most common  $\geq 3$  TRAEs in the sacituzumab govitecan arm *versus* standard chemotherapy were neutropenia (51% *versus* 33%), diarrhea (10.5% *versus* <1%), anemia (8% *versus* 5%), and febrile neutropenia (6% *versus* 2%). Of note, in a subgroup analysis, sacituzumab govitecan improved ORR and PFS in the small subset of patients with stable brain metastases (PFS 2.8 *versus* 1.6 months; ORR 3% *versus* 0%).<sup>89</sup> Biomarker analysis demonstrated that efficacy may be independent of Trop-2 expression, although numbers in the Trop-2 low group were too low to make a definitive conclusion. By subgroup, PFS for sacituzumab *versus* chemotherapy for Trop-2 high was 6.9 *versus* 2.5 months, for Trop-2 medium was 5.6 *versus* 2.2 months, and for Trop-2 low was 2.7 *versus* 1.6 months.<sup>90</sup> Sacituzumab govitecan received accelerated approval for the treatment of patients with mTNBC who have received at least one prior line of therapy for advanced disease based on the phase I/II data, which was then

**Table 5.** Antibody–drug conjugates in mTNBC.

Drug	Target	Antibody	Linker-payload	Trial name/ NCT number	No. of patients	Phase	Patient cohort	Regimen	Prior lines of therapy for metastatic disease	Comparator arm	ORR (%)	PFS (months)	OS (months)
Sacituzumab govitecan	Trop-2	RS7	CL2A-SN-38	NCT01631552	108	I/II	mTNBC	Saci	≥2	-	33.3	5.5	12
Trastuzumab deruxtecan (DS-8201A)	HER2	Anti-HER2 IgG	Peptide linker with DXd	ASCENT/ NCT02574455	529	III	mTNBC	Saci	≥2 (including a taxane)	Chemo (eribulin/cape/vnr/gem)	35 versus 5	5.6 versus 1.7 HR = 0.41, p < 0.001	12.1 versus 6.7 HR = 0.48, p < 0.001
				NCT04468061	1NR	II	mTNBC	Saci ± Pembro	0	-	-	NR	NR
Datopotamab deruxtecan (Dato-DXd)	Trop-2	IgG1	DXd	DESTINY-Breast04/ NCT03734029	NR	III	HER2-low MBC <sup>a</sup>	DS-8201a	1–2	Chemo (cape/eribulin/gem/pac/nab-pac)	NR	NR	NR
				PanTumor01/ NCT03401385	NR	I	mTNBC, NSCLC	Dato-DXd	Refractory or intolerable of standard tx; treated with T-DM1	-	34 TNBC	NR	NR
Ladiratuzumab vedotin (SGN-LIV1a)	LIV-1	hLIV22	Vc-MMAE	NCT01969643	NR	I	MBC	SGN-LIV1A	No prior cytotoxic chemo	-	32	0.94	NR
Anti-CA6-DM4 (SAR566658)	CA6	DS6	SPDB-DM4	NCT03424005	NR	Ib/II	mTNBC	SGN-LIV1A + atezo, cape	0–1	Cape	NR	NR	NR
				NCT03310957	NR	I/II	mTNBC	SGN-LIV1A + pembro	No prior cytotoxic chemo	-	NR	NR	NR
U3-1402	HER3	Patritumab	Peptide linker with DXd	NCT01156870	NR	I	Solid tumors expressing CA6 in ≥30% tumor cells with IHC 2/3+	SAR566658	Refractory or intolerable of standard tx	-	35–60	NR	NR
				NCT02984683	NR	II	CA6+ TNBC	SAR566658	1–3	-	NR	NR	NR
AVID100	EGFR	MAB100	DM1	NCT03094169	NR	Ia/IIa	TNBC, HNSCC, NSCLC	AVID100	Refractory or intolerable of standard tx	-	NR	NR	NR
CAB-ROR2 (BA3021)	Ror2	CAB	Undisclosed	NCT03504488	NR	I/II	NSCLC, TNBC, sarcoma	BA3021	Refractory or intolerable of standard tx	-	NR	NR	NR

AC, doxorubicin/cyclophosphamide; atezo, atezolizumab; cape, capecitabine; DXd, etecan derivative; EGFR, epidermal growth factor receptor; gem, gemcitabine; HER2, human epidermal growth factor receptor 2; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; IHC, immunohistochemistry; ISH, *in situ* hybridization; MBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; nab-pac, nab-paclitaxel; NR, not resulted; NSCLC, non-small cell lung cancer; ORR, objective response rate; pac, paclitaxel; pembro, pembrolizumab; PFS, progression-free survival; saci, sacituzumab govitecan; T-DM1, ado-trastuzumab emtansine; vnr, vinorelbine.  
<sup>a</sup>Low-HER2 expression defined as IHC 2+/ISH- or IHC 1+ (ISH- or untested).

converted to full approval based on data from the ASCENT study.

Sacituzumab govitecan is currently being studied in a number of settings and in various combinations, including in the post-neoadjuvant setting, in HR+ MBC, and in combination with ICI. For example, the TROPICS-02 trial is evaluating sacituzumab govitecan *versus* treatment of physician's choice for the treatment of HR+ HER2-negative MBC (NCT03901339).<sup>1</sup> Another study is evaluating the efficacy of sacituzumab govitecan plus pembrolizumab *versus* sacituzumab govitecan alone in patients with PD-L1-negative treatment-naïve mTNBC (NCT04468061).

Of note, despite the efficacy of ADCs, resistance unfortunately does occur. Mechanisms of resistance include resistance to the individual components of the ADC, including the monoclonal antibody and the cytotoxic drug.<sup>91</sup> In addition, optimal efficacy of the ADC requires endocytic uptake of the antibody into the cell and chemical or enzymatic cleavage of the cytotoxic agent in the lysosomes. Therefore, defects in internalization and trafficking pathways of the drug, impaired lysosomal function, and/or drug efflux pumps can reduce drug efficacy. Strategies to circumvent these challenges are currently under evaluation.

#### *Trastuzumab deruxtecan*

HER2-targeted therapies have significantly improved survival in patients with HER2-positive breast cancer. Interestingly, novel ADCs against HER2 are showing activity in patients with HER2-negative breast cancer with low HER2 expression, so-called 'HER2-low' [i.e. immunohistochemistry (IHC) 1+ or 2+/*in situ* hybridization (ISH) not amplified]. The clinical and molecular features of HER2-low breast cancer have not yet been fully elucidated.<sup>94</sup> In a retrospective clinicopathological study including 3689 patients, the proportion of HER2-low was higher in HR+ disease (65.4%) than in TNBC (36.6%).<sup>92</sup> In HR+ disease, *ERBB2* and luminal-related genes were expressed more frequently in HER2-low than in HER2 0, but there was no difference in gene expression in patients with TNBC based on the HER2 level. In another retrospective observational study, Agostinetti *et al.* evaluated 804 breast cancers and identified 410 HER2-low tumors. HER2-enriched tumors were more frequent in HER2-low/HR- and HER2-low/HR+ subtypes, compared with HER2-negative/HR- and HER2-negative/HR+ subtypes, respectively (13.7%

*versus* 1.6% and 1.2% *versus* 0.5%, respectively).<sup>93</sup> Further work is needed to better understand the biology of HER2-low disease.

Trastuzumab deruxtecan (T-DXd, formerly DS-8201A) is a humanized antibody against HER2 linked to a topoisomerase I inhibitor, ete-can derivative (DX-8951 derivative, DXd), which is a potent topoisomerase inhibitor. The first-in-human study of T-DXd enrolled patients with breast, gastric, or gastroesophageal carcinoma (regardless of HER2 status) (NCT02564900).<sup>95,96</sup> In the dose escalation study performed at two centers in Japan, 24 patients were enrolled including 8 with low-HER2-expressing tumors (IHC 1+ or 2+, ISH negative). Patients with HER2 IHC 3+ had the best response, but there were two patients with HER2-low disease who responded as well. In the dose expansion study, patients with advanced/metastatic HER2-low breast cancer (~20% of TNBC) were enrolled. The confirmed ORR by central review was 20/54 patients (37%, 95% CI 24.3–51.3%) with median duration of response of 10.4 months. Common grade 3 or 4 TRAEs included neutropenia, thrombocytopenia, leukopenia, hypokalemia, increased aspartate aminotransferase (AST), decreased appetite, and diarrhea. Three patients treated at 6.4 mg/kg suffered fatal events associated with T-DXd-induced pneumonitis/interstitial lung disease; current data suggest this toxicity can be reduced by careful monitoring and mitigation strategies. Based on encouraging results of this study, the phase II DESTINY-Breast01 (NCT03248492) enrolled 184 patients with HER2-positive unresectable and/or MBC who had received previous treatment with trastuzumab emtansine and demonstrated an ORR of 60.3%,<sup>97</sup> leading to accelerated FDA approval in December 2019 for patients with unresectable or metastatic HER2-positive breast cancer who had received two or more prior anti-HER2-based regimens in the metastatic setting. Most recently, the phase III DESTINY-Breast03 compared T-DXd and T-DM1 in the second-line setting for HER2-positive unresectable or MBC. Initial results were presented at ESMO in 2021; T-DXd showed a marked improvement in PFS compared with T-DM1.<sup>98</sup> Updated results from exploratory subgroup analysis of the study demonstrated that T-DXd induced PFS and ORR improvements *versus* T-DM1 across patients irrespective of hormone receptor status, prior pertuzumab, number of prior lines of therapy, presence or absence of visceral disease, or presence of brain metastases.<sup>99</sup>



Given the promising clinical benefit of T-DXd in HER2-positive breast cancer, this agent is now being studied in patients with the newly defined HER2-low biomarker. In patients with HER2-low unresectable or MBC, the phase III DESTINY-Breast04 (NCT03734029) evaluated the efficacy of trastuzumab deruxtecan compared with physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel). The trial has completed accrual, and results are expected in 2022.

#### *Datopotamab deruxtecan*

Datopotamab deruxtecan (Dato-DXd) is an ADC directed at TROP2 conjugated to DXd, a potent topoisomerase I inhibitor payload. The phase I TROPION-PanTumor01 study (NCT03401385) was a first-in-human study enrolling patients with mTNBC, HR+ MBC, and non-small cell lung cancer who had relapsed on standard therapies or for whom no standard treatment was available. In mTNBC, cohort data from 44 patients with TNBC treated with Dato-DXd demonstrated an ORR of 34% in all patients with TNBC and 52% in patients with TNBC who did not receive prior treatment with a Topo I inhibitor-based ADC ( $n = 27$ ).<sup>100,101</sup> TRAEs occurred in 33% of patients, with grade 3 TRAEs including stomatitis (13%), fatigue (4%), and anemia (4%). A phase III trial is planned in TNBC and is underway in HR+ disease.

#### *Ladiratumumab vedotin (SGN-LIV1a)*

Ladiratumumab vedotin is a humanized antibody targeting the zinc transporter LIV-1 conjugated with monomethyl auristatin E (MMAE), a microtubule-disrupting agent. LIV-1 is expressed on multiple tumor types, and is expressed on nearly 70% of mTNBC cells.<sup>102</sup> The payload, MMAE, is a synthetic analogue of dolastatin 10, a natural antimetabolic drug produced by the sea hare *Dolabella auricularia* causing G2/M phase cell cycle arrest. A phase I study evaluated the safety, tolerability, and pharmacodynamics of ladiratumumab vedotin in patients with LIV1-positive advanced or MBC (NCT01969643). Among 44 patients with mTNBC in the combined dose escalation and expansion cohorts, the ORR was 32% (14 PR) and the PFS was 11.3 weeks.<sup>103</sup> The most common TRAEs were nausea (53%), fatigue (45%), and diarrhea (43%). Peripheral sensory neuropathy is a dose-limiting TRAE, and occurred in 20% of patients. Weekly dosing is

currently being evaluated as a mechanism to preserve efficacy and reduce toxicity. Ladiratumumab vedotin is also being evaluated in combination with pembrolizumab (NCT03310957)<sup>104</sup> and atezolizumab (NCT03424005).

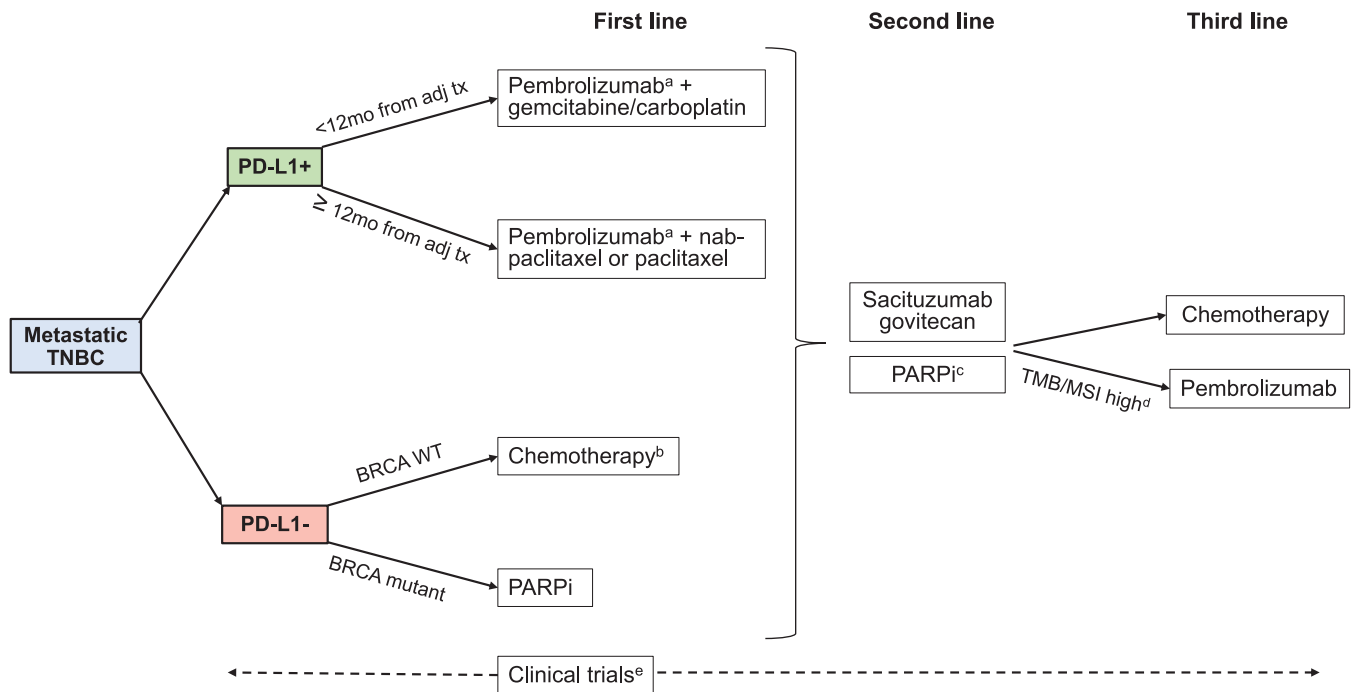
#### *Other ADCs under investigation*

There are also other ADCs that are under evaluation in early phase clinical trials that have exciting potential. For example, SAR566658 is a humanized DS6 antibody that is directed against the tumor-associated protein sialoglycocone CA6 and linked to DM4 (a derivative of maytansine). A phase 1 study enrolled 114 patients, including patients with breast cancer with CA6 expression, and demonstrated a reasonable toxicity profile.<sup>105</sup> A subsequent study evaluated the safety and efficacy of SAR566658 in patients with CA6-positive mTNBC (NCT02984683), but results have not yet been reported. Other promising ADCs under investigation include patritumab deruxtecan (U3-1402) (NCT02980341), AVID100 (NCT03094169), and CAB-ROR2 (BA3021) (NCT03504488). Future studies are needed to determine the safety and efficacy of these agents in patients with breast cancer.

#### **Sequencing therapy in mTNBC**

Sequencing therapies in mTNBC remain an ongoing question; generally treatments demonstrating survival benefits (i.e. ICI) are preferred in the subsets with benefit, and decisions about therapy should balance benefit and toxicity. Figure 1 depicts a potential treatment paradigm based on current data. For patients whose tumors are PD-L1 negative and *BRCA* wildtype, chemotherapy is the appropriate first-line therapy. For patients whose tumors are PD-L1 negative who have a germline *BRCA* mutation, PARP inhibitors are an important option in the first-line setting. For patients whose tumors are PD-L1 positive and have developed recurrent disease within 1 year from completing adjuvant therapy, pembrolizumab in combination with gemcitabine and carboplatin is recommended as first-line therapy. If recurrence occurs 12 months or more since completing adjuvant therapy, pembrolizumab in combination with nab-paclitaxel or paclitaxel is recommended as first-line therapy, and PARP inhibitors for those with germline *BRCA* mutations should be considered as second-line therapy. Sacituzumab govitecan can be chosen in the second line for patients developing metastatic disease within a year of completing





**Figure 1.** Shown is a treatment paradigm for metastatic triple-negative breast cancer (TNBC) based on current data.

Abbreviations: MSI, microsatellite instability; PARPi, PARP inhibitor; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden; tx, treatment; WT, wildtype.

- Pembrolizumab is the only approved immune checkpoint inhibitor for mTNBC in the United States; atezolizumab can also be used in countries where regulatory approval has been retained. For pembrolizumab, PD-L1 positivity is determined by the combined positive score (CPS), scored as the number of PD-L1 positive cells (including tumor cells, lymphocytes and macrophages) divided by the total number of tumor cells  $\times 100$  using the Dako 22C3 antibody. For atezolizumab, PD-L1 positivity is determined by the percent of the tumor area covered by the area of PD-L1+ immune cells, using the Ventana SP142 antibody.
- See National Comprehensive Cancer Guidelines [nccn.org] for recommended chemotherapy regimens.
- PARPi can be used in the second line if the patient has a germline *BRCA* 1 or 2 mutation and PARPi not used in the first line.
- Pembrolizumab can be used as monotherapy if the patient is TMB/MSI high [ $\geq 10$  mutations/megabase (mut/Mb)].
- Clinical trials should be considered as any line of therapy if available.

adjuvant therapy, or in the third line for those with *de novo* or late relapsing disease. Clinical trials should be considered at every step, and options should be carefully investigated. Third-line treatment options include sequential chemotherapy or of course clinical trials; patients with a high TMB or microsatellite instability can be treated with pembrolizumab as a single agent.

## Conclusion

Historically, patients with mTNBC have a poor prognosis and chemotherapy-resistant disease with limited treatment options; novel treatment strategies are desperately needed. Recent studies have demonstrated efficacy of immunotherapy with ICI in combination with chemotherapy in patients whose tumors or tumor immune cells express PD-L1. Other promising strategies include ICI combinations with other novel

immunotherapy agents or targeted therapies. PARP inhibitors, AKTi, and MEK inhibitors are being evaluated in various combinations in certain subsets of patients with mTNBC, and PARP inhibitors have demonstrated efficacy in patients with germline *BRCA* mutations. ADCs are a promising treatment strategy with sacituzumab govitecan demonstrating marked efficacy in resistant mTNBC. Additional ADCs are under active investigation. Further studies are needed to clarify the most effective sequencing of these therapies, and whether combination therapies can increase the efficacy of these agents to improve outcomes for patients with mTNBC.

## Author contributions

**Laura A. Huppert:** Writing – original draft.

**Ozge Gumusay:** Writing – original draft.

**Hope S. Rugo:** Writing – review & editing.

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