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ABOUT COVER

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Overview of recent advances in metastatic triple negative breast cancer

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Abstract

Metastatic triple negative breast cancer (TNBC) has an aggressive phenotype with a predilection for visceral organs and brain. Best responses to chemotherapy are predominately in the first line. Recent studies have demonstrated improved progression free survival with the combination of atezolizumab/pembrolizumab and chemotherapy in programmed death-ligand 1 positive metastatic TNBC. However, a recent trial in a similar population showed no benefit for atezolizumab and paclitaxel which led to a Food and Drug Administration alert. Two phase III trials (OLYMPIAD and BROCADE3) demonstrated a benefit in progression free survival (PFS) but not overall survival in patients with BRCA-associated metastatic TNBC treated with Olaparib or Talazoparib respectively. For those treated with Talazoparib, the time to deterioration in health related-quality of life was also longer compared to chemotherapy. The BROCADE3 trial demonstrated that the combination of a platinum and veliparib increased PFS in first-line metastatic TNBC but at the cost of increased toxicity. There are no head-to-head comparisons of a poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPi) and platinums. There are unanswered questions regarding the role of PARPi maintenance after platinum therapy as is standard of care in BRCA-associated ovarian cancer. Other areas of therapeutic interest include targeting aberrations in the phosphoinositide 3-kinase pathway, protein kinase B, mammalian target of rapamycin or utilising antibody drug conjugates. This review focusses on recent and emerging therapeutic options in metastatic TNBC. We searched PubMed, clinicaltrials.gov and recent international meetings from American Society of Clinical Oncology, San Antonio Breast Cancer Conference and the European Society of Medical Oncology.

Key Words: Triple negative breast cancer; Immunotherapy; Poly (adenosine diphosphate-ribose) polymerase inhibitors; Breast cancer

Core Tip: Despite recent advances, chemotherapy remains integral to the management of advanced triple negative breast cancer. Immunotherapy and poly (adenosine diphosphate-ribose) polymerase inhibitors have shown much promise but have yet to demonstrate a proven overall survival benefit in this disease. Antibody drug conjugates and other targeted therapies may ultimately prove to be the next frontier in treating this illness.

INTRODUCTION

Triple negative breast cancer (TNBC) accounts for approximately 15% of breast cancers and is characterised by the absence of expression of the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2 receptor (HER2) expression[1-3].

Triple negative breast cancers are most often high grade invasive ductal carcinomas which are characterised by an aggressive clinical phenotype. There are some rarer histological subtypes such as adenoid cystic carcinoma of the breast that is associated with an excellent prognosis.

Even for those with localised disease, approximately 25% of patients will relapse with distant metastasis. For patients with advanced or stage IV disease, the median overall survival (OS) is in the region of 12 mo with fewer than 20 % of patients alive at four-years. This is in stark contrast to ER-positive/PR-positive/HER2-negative (ER +/PR +/HER2-) disease where the median OS is closer to 36 mo and an estimated 40% of patients are alive at four years.

TNBC disproportionately effects younger women and black women, with these groups three-times as likely to be diagnosed with TNBC[4,5]. It has been estimated that 170000 women worldwide are diagnosed with TNBC each year of a total of 1 million breast cancer diagnoses[6]. It is also the most common breast cancer subtype in patients who carry a mutation in the *BRCA1* gene.

Advances in the treatment of HER2-positive breast cancer have resulted in clinical outcomes similar to those with ER+/PR+/HER2- disease however advances in triple negative breast cancer have been much slower[7]. In this article, we will review the biological features of advanced TNBC and explore the expanding treatment options for this aggressive disease.

CLINICAL FEATURES OF METASTATIC TNBC

Only 5% of patients with TNBC present with *de novo* metastatic disease[8]. The majority of patients unfortunately relapse following treatment with curative intent. The biological features of TNBC result in a unique clinical phenotype. It is characterized by a propensity for visceral and brain metastases, absence of bone metastases and typically early relapse (< 3 years).

Data from a Canadian breast cancer cohort with 180 TNBC (1601 in total cohort) patients showed that these patients were much more likely to develop distant recurrence (HR = 2.6, $P < 0.0001$) or death (HR 3.2, $P < 0.00001$) compared to other breast cancer subtypes. The risk of distant recurrence peaked at three years and declined rapidly thereafter[9]. A large cohort study from MD Anderson Cancer Centre identified similar patterns of distant recurrence and death[10].

TNBC is most commonly associated with visceral metastases including lung, liver and brain. Jin *et al*[11] identified 433 women with metastatic TNBC and found that 29% of them had 1 or greater brain metastases[11]. Median survival from time of diagnosis of brain metastases in this study was just 7.3 mo highlighting the significant mortality associated with intracranial disease.

THE BIOLOGY OF TNBC

Genomic features of TNBC

Triple negative breast cancer is characterised by the absence of expression of ER/PR/HER2. Almost 20 years ago breast cancer was classified using gene expression profiling into four main subtypes; Luminal A (ER+/PR+ with a low proliferation index), Luminal B (ER+/PR + with a high proliferation index), HER2-overexpressing (HER2+ disease) and basal-like. Although basal-like broadly corresponds to TNBC, the terms are not synomonous[1,3,12]. In one study, 70% of TNBC belonged to the basal subtype and 76% of basal-type tumours would be classified as TNBC[13]. A small proportion of basal-like tumours express ER or express HER2[14,15].

Importantly, basal-like tumours express cytokeratins such as CK5/6, cadherin as well as epidermal like growth factor (EGFR)[3]. Contrary to previous doctrine, it appears that basal-like tumours do not arise from normal breast tissue (basal cells) but instead arise from luminal progenitor cells[16,17].

Mutations in *BRCA1/BRCA2* are commonly associated with the basal-like subtype of breast cancer on a genomic level[18,19]. Of course, *BRCA1/BRCA2* is associated with a high lifetime incidence of all breast cancers[20]. However, the highest incidence of *BRCA1/BRCA2* is found within the triple negative subgroup. It is estimated that approximately 20% of patients with TNBC may harbour a germline defect in *BRCA1/BRCA2*[20]. As a consequence, it is now recommended that all patients with TNBC should have *BRCA1/BRCA2* testing particularly if they are under 50 years old[21]. It is hypothesised that *BRCA1/BRCA2* results in the suppression of basal-like genes thus a pathogenic mutation acts as an oncogene specifically within the basal subtype[20].

Conversely, basal-like breast cancers may be a surrogate for cancers which behave biologically similar to *BRCA1/BRCA2*-mutated disease. These cancers are considered under the term 'BRCAness'[20]. 'BRCAness' refers to cancers without *BRCA1/BRCA2* mutations but have other causes of homologous recombination deficiency (HRD) rendering susceptibility to poly adenosine diphosphate (ADP) ribose polymerase inhibitors (PARPi)[21]. Basal-like tumours associated with a *BRCAness* phenotype are characterized by high tumour grade, lymphocytic infiltrate, pushing margins, ER and HER2-negativity, an association with TP53 mutations, c-myc amplification, and multiple chromosome abnormalities[22]. Candidate genes which may result in a *BRCA-like* phenotype include *ATM, CDK1/2, PALB2* and many others. However, the clinical significance of these and their sensitivity to PARPi has generally been significantly less compared to patients with *BRCA1/BRCA2* mutations[23]. The American Society of Clinical Oncology (ASCO) Annual Meeting in June 2020 included presentations which showed objective responses similar to those seen in germline *BRCA*-mutation associated breast cancer in patients with somatic *BRCA* gene mutations and with *PALB2* mutations which are discussed later in this article.

Immunogenic potential of TNBC

The tumour microenvironment (TME) plays an important role in defining the interaction of our immune system with tumours. In TNBC, the TME is characterized by higher levels of vascular endothelial like growth factor (VEGF), tumour infiltrating lymphocytes (TILs) and tumour associated macrophages in contrast to other types of breast cancer[24]. Additionally, there is a high level of expression of TILs in patients with TNBC[24-29]. These have been shown to be a useful prognostic indicator across malignancies[30]. TNBC has been shown to have consistently elevated TILs in contrast to other subtypes and TILs have been shown to be associated with improved survival[29]. Ibrahim *et al*[29] found that patients with lymphocyte-predominant breast cancer had a 40% pathological complete response rate compared to 7% of those patients without[29]. High TILS are more frequent in TNBC (30%) compared to HER2-positive (19%) and luminal tumours (13%) and are associated with improved disease free survival and OS in early stage breast cancer[27,31,32]. This is consistent with findings in other malignancies demonstrating the important role of the immune system in cancer biology and prognostication. All of these features demonstrate that the TME of TNBC is highly immunogenic.

It is recognised that TNBC typically has higher levels of programmed cell death ligand [programmed death-ligand 1 (PD-L1)] expression in contrast to other subtypes of breast cancer[33-35]. PD-L1 has an important role in regulating our immune system, preventing overactivation of T cells and promoting the differentiation of regulatory T cells[36]. PD-L1 is the most agnostic and clinically utilised biomarker of response to checkpoint inhibition in patients with advanced malignancies. However, it's

sensitivity and specificity as an immunotherapy (IO) biomarker is variable across malignancies. There are several different antibodies used to detect it and there are also different staining algorithms adopted to measure it. This will be discussed in greater detail below (See PD-L1 assays).

TNBC has a relatively high tumour mutational burden (TMB) in contrast to other histological subtypes of breast cancer[37]. On average, TNBCs carry 1.68 somatic mutations per Mb of coding regions (approximately 60 somatic mutations in each tumour)[34]. The mutation burden is not uniform across TNBC, and some tumours have a high mutation burden (more than 4.68 somatic mutations per Mb) and a frequent occurrence of multiple copy-number aberrations involving genes that lead to multiple pathway alterations. TMB has been identified as a potential biomarker of IO response across malignancies[38]. There is a strong biological rationale for the use of TMB. Higher levels of TMB results in greater neoantigen expression and presentation to our immune cells enhancing our immune response. However, the clinical utility of TMB has not been fully demonstrated and it has failed to enter routine practice in most disease subtypes[39]. The Food and Drug Administration (FDA) has recently licensed pembrolizumab for the treatment of high TMB tumours (> 10 mutations/Megabase) with the FoundationCDx assay as a companion diagnostic[40].

THERAPIES IN METASTATIC TNBC

Chemotherapy

Chemotherapy remains the cornerstone of therapy in the treatment of metastatic TNBC (Table 1). It is well recognised that TNBC is intrinsically chemo-sensitive but unfortunately prone to rapid relapse and resistance, this is referred to as the triple negative paradox[41]. Most guidelines recommend a first-line anthracycline or taxane-based regimen for *BRCA1/BRCA2* wild-type patients who have not received these agents in the neoadjuvant or adjuvant settings[42,43]. There is evidence that patients may respond to re-challenge with these agents however most physician's would favour avoiding this in the case of anthracyclines due to the cumulative cardiac toxicity[44]. Much debate over the years has focused on the benefits of single-agent *vs* combination regimens. Combination regimens are now generally reserved for patients who are at-risk of or in visceral crisis[45]. Platinum-based regimens have demonstrated significant efficacy for patients with *BRCA1/BRCA2* mutant TNBC and other deficiencies in homologous recombination[46-48]. The TNT study directly studied platinum therapy responses in comparison to standard of care in advanced unselected TNBC[48]. The study, which randomised 376 patients to docetaxel *vs* carboplatin, found no evidence of a difference between carboplatin and docetaxel in objective response rate, progression free- or OS in the overall population. However, a prespecified subgroup analyses of patients with germline *BRCA1/BRCA2* mutations demonstrated improved Overall response rate (ORR) (68% *vs* 33%) and progression free survival (PFS) (6.8 mo *vs* 4.4 mo) but there was no OS advantage observed. The interpretation of OS is complex by the protocol specified planned cross over at progression.

Finally, a variety of other cytotoxic can be used in later lines of treatments including gemcitabine, capecitabine and the more recent addition-eribulin[49]. However, 30 years of experimentation with a variety of chemotherapeutics has yielded overall disappointing results. There is a significant unmet clinical need for newer more effective treatments which results in durable remissions for this patient population.

Targeted agents such as PARPi, drugs targeting the phosphoinositide 3-kinase (PI3K) pathway, immunotherapy and antibody drug conjugates are being incorporated alone or in combination with chemotherapy in treatment approaches.

IMMUNOTHERAPY IN METASTATIC TNBC

Monotherapy trials

In the Phase 1b KEYNOTE- 012 trial, published in 2016, patients with pre-treated TNBC were treated with pembrolizumab (Table 2) TNBC population as part of a larger basket trial[50]. A modest response rate of 18% (5/27) was seen with a further 25.9% of patients having stable disease. There was a suggestion of increased likelihood of response for patients with a higher PD-L1 score (*P* = 0.028).

In the JAVELIN Phase 1b trial, authors' investigated the use of avelumab in patients with metastatic, heavily pre-treated breast cancer with 58 patients in the group having

Table 1 Historical outcomes in metastatic triple negative breast cancer

	ORR (%)	PFS (mo)	OS (mo)
Single agent chemotherapy			
1L	10.0-28.0	3.5-5.4	9.9-17.5
2L	6.0-18.0	2.7-3.4	9.2-15.2
Combination chemotherapy			
1L	14.8-64.3	4.8-9.0	13.9-24.2
2L+	27.0[1]-60.0	2.9-7.0	8.1-16.5

[1]1-3Lines. Adapted from: Li *et al*[89]. ORR: Overall response rate; PFS: Progression free survival; OS: Overall survival.

Table 2 Immunotherapy as a monotherapy in metastatic triple negative breast cancer

Trial	n	Drug	ORR 1st line	ORR ≥ 1 prior line	Median OS (mo) 1st line	Median OS (mo) ≥ 1 line	Ref.
NCT01375842 Phase Ia	116	Atezolizumab	24%	6%	17.6	7.3	Emens *et al*[52], 2019
KEYNOTE-012 Phase Ib	32	Pembrolizumab		18.5		11.2	Nanda *et al*[50], 2016
JAVELIN/Phase Ib	58	Avelumab		5.2		9.2	Dirix *et al*[51], 2018
KEYNOTE-086 Phase II	170	Pembrolizumab	23.1%	5.3	18.0	9.0	Adams *et al*[53], 2019
KEYNOTE-119/Phase III	622	Pembrolizumab *vs* chemo		9.6 *vs* 10.6		CPS ≥ 1; 10.7 *vs* 10.2. CPS ≥10; 12.7 *vs* 11.6. CPS ≥ 20; 14.9 *vs* 12	Verret *et al*[83], 2019

ORR: Overall response rate; OS: Overall survival; CPS: Combined positive score.

TNBC[51]. The response rate within the TNBC cohort was disappointing at 5.2% with stable disease in a further 25.9% of patients. The combined positive score (CPS) was associated with higher likelihood of response (22.2% *vs* 2.2% within the TNBC population).

In a Phase 1a trial of atezolizumab in TNBC, authors' investigated the use of atezolizumab in TNBC in both the first line and second line setting[52]. Overall response rates were significantly higher in the first-line setting in contrast to the second-line setting (24% *vs* 6%) with a median duration of response of 21 mo. Patients with a higher immune cell (IC) PD-L1 score had improved clinical outcomes in contrast to patients with a negative PD-L1 IC.

In the KEYNOTE-086 study, authors' investigated pembrolizumab monotherapy in patients with heavily pretreated TNBC[53]. They included 170 patients in a single-arm phase 2 study. The majority of patients (61.8%) had PD-L1 positive tumours. Almost half of patients received 3 or more prior lines of therapy. Median PFS was modest at 2 mo with a 6 mo and 12 mo PFS of 14.9% and 6.2% respectively.

These early phase studies culminated in the phase III KEYNOTE-119 study which investigated pembrolizumab *vs* chemotherapy in patients who had received 1-2 prior lines of systemic therapy for patients with TNBC[54]. Patients had received at least one anthracycline or taxane based treatment and were randomised to either pembrolizumab or physician's choice of gemcitabine/eribulin/capecitabine. This study was powered for OS in the intention-to-treat (ITT) population. The PD-L1 immunohistochemistry (IHC) 22C3 pharmDX assay was used to determine the CPS on a specimen from a site of metastatic disease. Patients were randomised in a 1:1 manner between pembrolizumab and physician's choice of chemotherapy (*n* = 611). The majority of patients (61 %) had a CPS > 1. Pembrolizumab did not improve OS in patients with a CPS > 10 or CPS > 1 with a median OS of 9.6 mo for pembrolizumab and 10.6 mo for chemotherapy in the overall population. In an exploratory analysis, they did find that patients with a CPS > 20 had an improved OS with pembrolizumab (14.9 mo compared to 12.5 mo, HR 0.58). Grade 3-5 adverse events were significantly

higher in the chemotherapy group compared to the pembrolizumab arm (49% *vs* 34.9%). Although results only showed modest activity, it did suggest a relationship between efficacy and PD-L1 expression.

Combination studies-immunotherapy and chemotherapy

The early phase studies in metastatic TNBC indicated that treating patients with IO at earlier time points in their disease before exposure to multiple lines of treatment is associated with improved response (Table 2).

There was subsequently a shift of focus to combination chemotherapy and IO in TNBC (Table 3 and 4). In the phase 1a trial of atezolizumab and nab-paclitaxel, 33 patients were treated with the combination approach. The response rate was 39.1 % with a median duration of response of 9.1 mo. PD-L1 status did not stratify for responders. However, patients in the first-line setting had significantly higher response rates than those in the second-line setting or later (53.8% *vs* 30.0%)[55].

Phase III IMpassion 130 trial

This led to the pivotal IMpassion-130 study which was a phase 3, first-line study investigating atezolizumab + nab-paclitaxel *vs* nab-paclitaxel/placebo in 902 patients with advanced TNBC[56]. The trial was initially due to enroll 300 patients but the primary endpoint was expanded to include OS. The PD-L1 SP142 assay was used for PD-L1 assessment. Patients were excluded if they had completed treatment with curative intent < 12 mo before registration or if they had untreated or symptomatic brain metastases. The median PFS in the ITT population favoured the group receiving atezolizumab with a PFS of 7.2 mo *vs* 5.5 mo (HR = 0.80; 9, *P* = 0.002). However, within the PD-L1 positive subgroup (PD-L1 > 1%) the median PFS benefit was greater favouring the atezolizumab group with a PFS of 7.5 mo *vs* 5 mo (HR 0.62; *P* < 0.001). Final OS was presented at the European Society of Medical Oncology (ESMO) congress in 2020. In the ITT population, the median OS was 21 mo in the atezolizumab/nab-paclitaxel arm and 18.7 mo in the nab-paclitaxel arm (HR = 0.87; *P* = 0.07). The median OS in the PD-L1 positive group reached 25.4 mo in the atezolizumab arm *vs* 17.9 mo (HR 0.67; 95%CI: 0.53-0.86). However, this benefit was not statistically significant as the prespecified statistical hierarchical testing required a benefit to be seen in the ITT population to allow formal statistical analysis of the PD-L1 positive subgroup. No new safety signals emerged. Toxicity with combination approaches appears to be representative of the toxicity of each individual drug without evidence of synergistic effects thus far. The incidence of grade 3/grade 4 adverse events was higher in the atezolizumab arm (42% *vs* 32%). However, there was similar numbers of serious adverse events in each group (24% in the atezolizumab arm *vs* 19% in the placebo arm).

Phase III IMpassion 131

The IMpassion-131 study investigated if nab-paclitaxel could be replaced with paclitaxel in combination with atezolizumab in the first-line setting of advanced TNBC. Inclusion criteria were identical to the IMpassion130 trial, but the primary endpoint pertained to investigator-assessed PFS/OS tested first in the PD-L1 positive population. Patients were randomised in a 2:1 ratio to atezolizumab/paclitaxel *vs* placebo/paclitaxel (*n* = 651). In the PD-L1 positive population, there was no significant improvement in the atezolizumab arm with a PFS of 6 mo compared to 5.7 in the placebo arm (HR 0.82, 95%CI: 0.6-1.12). There were also no significant differences in PFS in the overall population (5.7 mo *vs* 5.6 mo). In an interim OS analysis, there was no significant differences in OS in the PD-L1 population (28.3 mo with placebo *vs* 22.1 mo with atezolizumab, HR 1.12, 95%CI: 0.76-1.65) or the ITT population (22.8 mo *vs* 19.2 mo, HR 1.11, 95%CI: 0.87-1.42). The trend towards an improvement in OS was somewhat of a concern for investigators and the medical oncology community. Further analysis demonstrated that patients in both arm had an equivalent exposure to paclitaxel. The reasons for this trend however remain unclear. Speculation includes the potential immune mitigating effects of dexamethasone usage for paclitaxel treatment. This trial resulted in an FDA alert warning against the use of paclitaxel in combination with atezolizumab in TNBC. No new safety signals emerged.

Pembrolizumab and eribulin were studied in a phase 1b study which enrolled 81 patients who had 0-2 Lines of previous treatment with advanced TNBC[57]. Overall response rate was disappointing-25.6%. Median PFS was again disappointing at 4.1 mo.

Another phase 1b study investigated (Table 3) the combination of pembro-lizumab/capecitabine *vs* pembrolizumab/paclitaxel in the first-line setting in TNBC (*n*

Table 3 Early studies of Immunotherapy and chemotherapy in metastatic triple negative breast cancer

Trial	n	Drug	ORR 1st line	ORR ≥ 2 line	mOS 1st line	mOS 2nd line	Ref.
NCT01633970 Phase Ib	33	Atezolizumab + nab-paclitaxel	53.8%	30	24.2	12.4	Adams *et al* [55], 2019
KEYNOTE-150 Phase 1b/II	82	Pembrolizumab + Eribulin	25%	26.5	17.7	NE	Tolaney *et al*[57], 2018
Pilot and phase II. 1-2L[1]	29	Pembrolizumab + capecitabine or paclitaxel	43% pembro + cap. 23% pembro + paclitaxel		13.8 pembro + cap 7.9 pembro + pac		Page *et al*[90], 2019

[1]One to two lines of prior treatment. Pembro: Pembrolizumab; Cap: Capecitabine; Pac: Paclitaxel; ORR: Overall response rate; OS: Overall survival.

Table 4 Phase III first line metastatic immunotherapy + chemotherapy

	IMpassion130 (PD-L1 inhibitor)	Keynote-355 (PD1 inhibitor)	IMpassion131 (PD-L1 inhibitor)
Drugs	Atezolizumab/nab-paclitaxel *vs* placebo/nab-paclitaxel	Pembrolizumab + chemotherapy (nab-paclitaxel or paclitaxel or gemcitabine/carboplatin *vs* placebo + chemo	Atezolizumab/paclitaxel *vs* placebo/paclitaxel
ITT (N)	451 *vs* 451 (1:1 randomisation)	566 *vs* 281 (2:1 randomisation)	430 *vs* 221 (2:1 randomisation)
Inclusion	≥ 1 yr DFI	≥ 6 mo DFI	≥ 1 yr DFI
PD-L1 status	IC [positive (≥ 1%) *vs* negative (< 1%)]	CPS [positive (≥ 1%) *vs* negative (< 1%)]	IC [positive (≥ 1%) *vs* negative (< 1%)]
	SP142 antibody ventana platform	PD-L1 IHC 22C3 pharmDx kit	SP142 antibody ventana platform
Primary endpoints	PFS and OS in ITT population	PFS and OS by PD-L1 status (CPS ≥ 10 and ≥ 1) in ITT	PFS and OS in PD-L1 positive cohort
Median FU	18.0 mo (ASCO 2019)	25.9 mo and 26.3 mo (ASCO 2020)	8.6 and 9 mo (ESMO 2020)
PFS in PD-L1 +	7.5 mo *vs* 5 mo	9.6 mo *vs* 5.6 mo	5.7 mo *vs* 5.6 mo
OS in PD-L1 +	25.4 mo *vs* 17.9 mo	Awaited	22.1 mo *vs* 28.3 mo

PD-1: Programmed death 1; PD-L1: Programmed death-ligand 1; ITT: Intention-to-treat; DFI: Disease Free Interval; IHC: Immunohistochemistry; OS: Overall survival; ASCO: American Society of Clinical Oncology; ESMO: European Society of Medical Oncology; PFS: Progression free survival; CPS: Combined positive score.

= 28). Response rates were higher in the capecitabine cohort (ORR = 43%) compared to the paclitaxel cohort (ORR = 25%). Overall response rates were higher in those treated greater than > 12 mo from primary treatment (ORR 45% *vs* 27%).

Phase III KEYNOTE 355 trial

The much anticipated KEYNOTE-355 trial was presented at the inaugural virtual ASCO annual meeting in June 2020. This trial investigated pembrolizumab/chemo *vs* chemo (taxane *vs* gemcitabine/carboplatin) in patients with treatment-naïve, metastatic TNBC[58]. Patients were excluded if they had active brain metastases or recurrence of disease < 6 mo prior to primary treatment. PD-L1 was assessed with the IHC 22C3 pharmDx CPS assay in a central laboratory. The primary outcome measure was pre-defined as OS and PFS in the PD-L1 positive population (CPS > 1/CPS > 10) and the ITT population. In this trial, a hierarchial statistical testing method involved statistical testing of OS and PFS in the CPS > 10 group initially, followed by CPS > 1 and then the ITT population. The trial included 566 patients in the chemotherapy/IO arm *vs* 281 in the chemotherapy arm. In patients with a CPS score of 10 or greater, the median PFS favoured pembrolizumab with a PFS of 9.6 mo *vs* 5.6 mo (P = 0.0012, HR = 0.65). In patients with a CPS score of 1 or greater, the median PFS favoured the pembrolizumab arm with a PFS of 7.6 mo *vs* 5.6 mo (P = 0.0014, HR = 0.74). This was not statistically significant. This was similar to the ITT population where the PFS was 7.5 mo in the pembrolizumab arm and 5.6 mo in the placebo arm (HR = 0.82). OS data is awaited. This progression free survival improvement led to accelerated FDA approval for pembrolizumab in combination with chemotherapy in the first-line setting in November of 2020.

PD-L1 assays

A major challenge in IO trials is defining appropriate biomarkers to aid patient selection. However even within PD-L1, not all assays are equal[59]. The CPS utilises staining of both tumour and immune cells to reach a combined score which is thought to be enhance clinical utility of PD-L1[60]. Rugo *et al*[59] performed a post-hoc analysis of the IMpassion130 study investigating three PD-L1 assays; SP142, VENTANA SP263 IHC assay (IC ≥ 1%) and Dako 22C3A assay (CPS ≥ 1, 22C3+)[59]. They found that the clinical benefit seen in patients with positive PD-L1 scores using the Dako 22C3A and SP263 subgroups was driven by the SP142 PD-L1 subgroup. This study demonstrates that greater collaboration is needed to harmonise the assays utilised for PD-L1 scoring in clinical trials and clinical practice. The FDA appropriately has linked licensing approval of regimens with biomarker assays but this practice has not yet occurred in Europe.

In KEYNOTE-522, patients were randomised to receive chemotherapy + pembrolizumab *vs* chemotherapy + placebo[61]. Patients with PD-L1 positive and negative TNBC had an improvement in pathological complete response (pCR) with the addition of pembrolizumab. This is in contrast to the metastatic setting (in IMpassion130 and KEYNOTE-355), patients with high PD-L1 expression derived the benefit from the addition of IO. This would indicate that in the metastatic setting PD-L1 expression is required for response[56,58].

Adoptive immunotherapy approaches

Much of our focus in clinical practice involves utilising checkpoint inhibitors to enhance our immune response to malignancies. Adoptive immunotherapy involves infusing or adopting T cells or other immune cells in order to enhance the host *vs* malignancy response. Such approaches have been demonstrated to be effective in specific clinical circumstances. For example, tumor infiltrating lymphocytes have been used in melanoma and chimeric antigen receptor T cell therapies have demonstrated efficacy in leukaemia. There has been limited application of these treatments to TNBC thus far. Studies are limited to small numbers (< 10) of patients with limited evidence of activity. However, these treatments do offer a compelling rationale for harnessing the power of our immune system and it is likely they will be part of the treatment paradigm in years to come[62].

Take home message

Targeting PD-L1 in first-line, treatment naïve metastatic TNBC has resulted in the demonstration of clinical activity. The combination of atezolizumab and nab-paclitaxel has demonstrated an impressive 6 mo' OS advantage in the PD-L1 positive subgroup, however due to the hierarchial testing model, formal significance testing was not conducted. The phase III trial KEYNOTE-355 also demonstrated an improvement in PFS in patients with a CPS > 10 but OS data is awaited. The recently presented IMpassion-131 did not demonstrate any improvement in PFS and has led to an FDA alert cautioning against the use of this combination due to lack of efficacy and potentially increased toxicity. Further results will be needed to confirm the activity of IO in this setting.

It is important to note that all of these trials excluded patients that relapsed within either 6 or 12 mo of primary treatment. It is important that we do not extrapolate these clinical trial outcomes to our entire TNBC population.

Targeting homologous recombination deficiency in TNBC

PARPi offer a biologically appealing treatment for patients with intrinsic HRD. HRD renders cells vulnerable to neoplastic transformation. However, this vulnerability to neoplastic changes also renders tumour cells vulnerable to genotoxic cell death *via* PARP inhibition as cells are reliant on base excision repair by PARP so it represents an 'Achilles Heel'. By inhibiting two pathways of DNA repair, the tumour cells have impaired DNA replication. The combination of PARP inhibition and *BRCA1/BRCA2* mutations is termed synthetic lethality.

GERMLINE *BRCA1/BRCA2* MUTATIONS

Early stage clinical trials

In a proof of concept study published in the Lancet, authors' investigated olaparib in patients with advanced metastatic breast cancer (MBC) with germline *BRCA1/BRCA2*

(gBRCA) mutations. They investigated two doses of olaparib at 400 mg BD and 100 mg BD. Approximately half of patients in this study (26 of 51 patients) had TNBC with the remainder having other histological subtypes. Patients were heavily pretreated with a median of 3 prior chemotherapy regimens and platinum sensitivity was not needed for trial enrolment. Overall response rates were impressive in this heavily pre-treated population at 41% in the group receiving the higher dose and 22% in the group receiving the lower dose[63].

Kaufman *et al*[64] investigated olaparib further in a large phase 2 basket trial with 298 patients in a single-arm study[64]. Patients with any advanced solid-organ malignancy were included if they harboured a gBRCA mutation. In the breast cohort, patients may have received multiple lines of treatment and there was no requirement for platinum sensitivity. Response rates were modest with only 8 of 62 (12.9%) patients responding in this unselected population.

In the ABRAZO trial, investigators studied talazoparib in patients with MBC with g BRCA mutations in two cohorts (*n* = 84). In cohort 1, patients had responded to platinum based chemotherapy. In cohort 2, they had progressed through multiple lines of non-platinum based regimens and had gBRCA mutations. In cohort 1, 60% of patients had TNBC. Response rates in TNBC were modest at 26% (including both cohorts). There was a subset of patients with durable responses with 11% having prolonged response at the time of data cutoff[65].

In the phase II BROCADE trial, investigators studied the addition of veliparib in a randomised (1:1:1) trial with three arms with intermittent Veliparib/Carboplatin/Paclitaxel (VCP), Placebo/Carboplatin/Paclitaxel or Veliparib/Temozolomide[66]. Investigators identified a non-significant PFS benefit of 1.8 mo with the addition of veliparib to carboplatin/paclitaxel (14.1 mo *vs* 12.3 mo, HR = 0.79, *P* = 0.22) There was also no significant OS difference between these arms (28.3 mo *vs* 25.9 mo). The temozolomide/veliparib arm was significantly inferior with a median PFS of 7.4 mo and OS of 19.1 mo.

Phase III OLYMPIAD trial

In the phase 3 study, OLYMPIAD investigators (Table 5) studied olaparib in patients with MBC and gBRCA[67]. Half of patients had ER/PR-positive breast cancer with the remainder having TNBC. The cohort was heterogenous with 71.2% of patients having received any lines of treatments previously and 29.3% of patients having had prior exposure to platinum-based chemotherapy. Patients were randomised in a 2:1 manner (201:95) to receive olaparib *vs* standard therapy (capecitabine/eribulin/vinorelbine). Median PFS was significantly longer in the olaparib group in contrast to the chemotherapy group (7 mo *vs* 4.2 mo). In a subgroup analysis, the HR of benefit was significantly elevated in the TNBC group (0.43 *vs* 0.82 in the HR positive group). The response rate was 59.9% in the olaparib group *vs* 28.8% in the standard group. However, OS did not significantly differ between groups-19.3 mo in the olaparib group and 17.1 mo in the control group.

Phase III EMBRCA trial

In the pivotal phase 3 study EMBRCA, author's investigated talazoparib in 431 patients with gBRCA mutations and MBC[68]. Approximately half of patients had TNBC with the remainder having ER/PR-positive breast cancer. Patients had a median of 2 prior lines of chemotherapy and were randomised in a 2:1 manner to receive talazoparib *vs* physician's choice (eribulin/capecitabine/gemcitabine/vinorelbine). Median PFS was greater in the talazoparib group compared to the control group-8.6 mo *vs* 5.6 mo with an objective response rate of 62.6% *vs* 27.2%. Benefit within the TNBC and HR positive subgroups was equivalent. Crucially however, median OS was not significantly greater in the talazoparib group compared to the placebo group (19.3 mo *vs* 19.5 mo)[69]. Patients in the talazoparib group did however have improved health related quality of life outcomes. More than a quarter (25.5%) of patients suffered from a grade 3 or grade 4 adverse event in the talazoparib group which was similar to the control group (25.4%). Notably, one patient suffered from the rare but well described PARPi toxicity of acute myeloid leukaemia.

Phase III BROCADE3 trial

In the phase III study presented at ESMO in 2019, the BROCADE3 investigators compared VCP compared to carboplatin/paclitaxel in patients with MBC and a gBRCA mutation[70]. Patients were randomised in a 2:1 manner, with 337 patients in the veliparib group and 172 patients in the control group. Once again, half of patients had TNBC (52%). Only 19% of patients had previously received any line of treatment for

Table 5 Pivotal Phase III studies of poly adenosine diphosphate ribose polymerase inhibitors in patients with germline *BRCA1/BRCA2* mutations

Trial	*n*	Drug	Median PFS (mo) 1st line	Media PFS (mo) ≥ 1 line	Media OS (mo) 1st line	Media OS (mo) ≥ 1 line	Ref.
OLYMPIAD	296	Olaparib		7.3		19.3	Robson *et al*[67], 2017
EMBRCA	431	Talazoparib		8.6		19.6	Litton *et al*[69], 2020
BROCADE3 (1st line)	337	Veliparib	14.5		33.5		Bardia *et al*[77], 2020

PFS: Progression free survival; OS: Overall survival.

MBC. Patients had an improved PFS with veliparib compared to placebo (14.5 mo *vs* 12.6 mo, HR = 0.70). PFS in the ER/PR-positive group and TNBC groups were equivalent. However, OS was not significantly different between groups at an interim analysis (33.5 mo *vs* 28.2 mo, HR 0.95). The addition of veliparib did cause increased toxicities including any adverse event leading to discontinuation (15.6% *vs* 10.8%), anaemia (81.1% *vs* 69.1%), thrombocytopenia (79.6% *vs* 70.5%) and diarrhoea (48% *vs* 38.1%). At ASCO 2020, further analysis was presented which investigated patients who transitioned to monotherapy prior to progression in patients in either arm of the study[71]. In the VCP arm, 136 patients crossed over to veliparib monotherapy and 58 patients in the carboplatin/paclitaxel crossed over to monotherapy. The analysis suggests that the PFS benefit seen in the overall population is at least partially contributed to by those patients receiving veliparib monotherapy and the trial suggests significant antitumour activity with veliparib monotherapy. It remains unclear if a carboplatin induction regimen with PARPi maintenance may result in similar efficacy outcomes while sparing patients of some of the toxicity of combination approaches.

Beyond BRCA
The antitumor activity of PARP inhibitors has been established in *BRCA1/BRCA2* germline mutation carriers however whether they have a role in patients with somatic mutations in *BRCA1/BRCA2* or in germline mutations in DNA damage response genes other that *BRCA1/BRCA2* remains unclear. Recent studies have tried to provide data to answer the question.

In the TBCRC 048 study presented at ASCO in 2020, investigators studied the antitumour activity of olaparib in a basket study. Cohort 1 included patients with germline mutations in HRD excluding *BRCA1/BRCA2* and Cohort 2 included somatic mutations in these genes or *BRCA1/BRCA2*[72]. 27 patients were enrolled in cohort 1 and 26 patients in cohort 2. Most notably, only 19% of patients had TNBC with the majority of the remainder diagnosed with ER/PR-positive tumours. The most common mutations included *BRCA1* (6), *BRCA2* (9), *ATM* (10), *CHEK2* (8), *PALB2* (13). In the germline cohort, the overall response rate was 33% however all responses were in the *PALB2* cohort with an 82% response within that group. The median duration of response was 9 mo. For the somatic cohort, the overall response rate was 31% however all responses were in the *BRCA1/BRCA2* cohort with a 50% response within that group. The study met its primary endpoint of greater than 20% overall response rate in the cohort.

The SWOG S1416 study, presented at ASCO in 2020, investigated the combination of veliparib and cisplatin in patients with metastatic TNBC whom were mostly (70%) chemotherapy naïve[73]. Patients were enrolled and treated up-front with the combination approach. During their treatment, blood and tissue samples were analysed for g BRCA mutations, HRD score, germline non-*BRCA1/BRCA2* HRD associated mutations and *BRCA1* associated methylation mutations. The HRD score utilises loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions to develop a score which identifies tumours with a *BRCA-like* phenotype[74]. 37 patients with gBRCA mutations were identified, 101 patients with *BRCA1/BRCA2*-like phenotype (most identified *via* HRD score) and 110 non-*BRCA1/BRCA2* like patients. The gBRCA group was underpowered. Within the *BRCA1/BRCA2*-like group, PFS was significantly greater within the veliparib group in contrast to the placebo arm (5.7 mo *vs* 4.3 mo, *P* = 0.02). Within this same cohort, there was a numerical but non-

significant improvement in OS in patients in the veliparib group in contrast to the placebo group (13.7 mo *vs* 12.1 mo, *P* = 0.14). There was no improvement in PFS in the non-HRD group. No new safety signals emerged.

Take home message

In patients with gBRCA mutations, three phase III studies have demonstrated efficacy in terms of improvements in PFS and quality of life compared to chemotherapy. No study has demonstrated an OS advantage however cross over to a PARPi at progression complicates the analysis of this endpoint. These trials identified a subset of patients with long and durable responses however the majority of patients become resistant to these drugs (median PFS of 7 and 8.6 mo in the OLYMPIAD and EMBRCA study). Clinical trials in progress are examining PARPi in combination with immunotherapy and other combinations which may prevent the development of resistance to therapy.

Antibody drug conjugates

Antibody drug conjugates (ADC) offer the potential to deliver highly potent cytotoxic chemotherapy to tumour cells with reduced systemic toxicity (Table 6).

Sacituzumab govitecan-hziy

Sacituzumab govitecan (SG)-hziy is an ADC in which a topoisomerase I inhibitor, is coupled to the humanized antitrophoblast cell-surface antigen 2 (Trop-2) monoclonal antibody hRS7 IgG1κ through the cleavable CL2A linker. SN-38, a derivative of irinotecan, is subsequently delivered into the cells both intracellularly and into the tumour microenvironment and has demonstrated potent antitumour activity[75]. SG-hziy has been investigated in multiple epithelial tumours including TNBC. In a phase 2 single arm study, SG-Hziy demonstrated impressive response rates in a heavily pre-treated TNBC population[76]. 108 patients with metastatic TNBC were enrolled in the trial whom had multiple previous lines of treatment with a median of 3 prior treatments received. Overall response rate was 33% with 3 complete responses. The median duration of response was 7.7 mo with a median PFS of 5.5 mo. Notably, patients were able to remain on treatment longer than they had on prior therapies, suggesting a lack of cross resistance. The safety profile was acceptable with only 2.8% of patients discontinuing due to an adverse event. Grade 3 events included neutropenia (26%), anaemia (11%), fatigue and asthenia (11%). Grade 4 neutropenia was reported in 16% of patients.

At the ESMO congress in 2020, authors presented results from the ASCENT study, a randomized phase 3 study of sacituzumab govitecan (*n* = 267) *vs* treatment of physician's choice (*n* = 262) in patients (pts) with previously treated metastatic TNBC[77]. Patients had received at least 2 prior lines of treatment prior to enrolment. The primary outcome was investigator assessed PFS in the brain metastases free population. Progression free survival was significantly prolonged in the investigation arm with a PFS (5.6 mo *vs* 1.7 mo, HR 0.41, *P* < 0.0001). Median OS was significantly prolonged with SG (12.1 mo *vs* 6.7 mo, HR 0.48, *P* < 0.0001). The most common grade 3 or 4 adverse events with SG were diarrhoea (10%), anaemia (8%) and leukopenia (10%). Only 4.7% of patients discontinued the drug due to toxicity and there was no treatment related deaths.

Ladiratuzumab vedotin

Ladiratuzumab vedotin (LV) targets LIV-1, a transmembrane cell adhesion molecule highly overexpressed in TNBC. The drug's payload is the microtubule disrupting agent-monomethyl auristatin E. A Phase 1b/2 trial of LV in combination with pembrolizumab was investigated in a treatment naïve population with metastatic TNBC[78]. The trial was based on the biological rationale for a synergistic effect of the addition of two immune modulating agents in the first-line setting. 19 patients were included in the dose finding cohort with a further 32 in the dose expansion cohort. Patients were not pre-selected for LIV1 or PD-L1 expression. Response rates were encouraging at 54% in 26 evaluable patients regardless of their PD-L1 expression. Further work will be needed to clarify where LV may fit into the treatment paradigm for TNBC in the crowded field of the first-line setting.

Trastuzumab detuxtecan

Trastuzumab deruxtecan (DS-8201) is an ADC with an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor[79]. It has shown promising activity in HER2 + metastatic breast cancer and is part of the treatment

Table 6 Key phase I/II/III involving antibody drug conjugates and targeted therapies

Trial	*n*	Drug	ORR 1st line	ORR ≥ 2 line	mPFS ≥ 2 line	mOS 1st line	mOS ≥ 2 line	Ref.
NCT01631552 phase II	108	Sacituzumab govitecan		33%	5.5		12.4	Schmid *et al*[61], 2020
NCT03310957 phase I/II	51	Pembrolizumab + ladiratuzumab vedoitin	54%		-			Han *et al*[78], 2020
NCT029380341 phase Ib/II	21	US-1402		33%	-			Kim *et al*[82], 2019
NCT03279257 phase 1b/II	40	Alpelisib		57%	7			Sharma *et al*[84], 2018
LOTUS phase II	124	Ipatasertib		40%	6.2			Kim *et al*[86], 2017
NCT02978716 phase II	102	Trilaciclib	43%			20.6/17.6		Tan *et al*[88], 2019
ASCENT phase III	529	Sacituzumab Govitecan		35%	5.6		12.1	Bardia *et al*[77], 2020

ORR: Overall response rate; PFS: Progression free survival; OS: Overall survival.

paradigm post trastuzumab emtansine (TDM1) for HER2 + MBC[80]. However, there has been interest in the drug in patients with HER2 low tumours (IHC1 +/IHC2 + and FISH -) tumours. A phase 1b study investigated its utility in this subgroup with safety evaluated in 53 patients[81]. A total of 54 patients were included with a median of 7.5 treatments previously received. The objective response rates were encouraging at 37% and a median duration of response of 10.4 mo. However, the majority of patients had ER/PR-positive tumours with only 7 TNBC patients included. There was one of 7 patients who responded within the TNBC subgroup. Notably, 3 patients developed fatal drug induced interstitial lung disease.

US-1402

U3-1402 is a novel HER3-targeted antibody-drug conjugate designed with a peptide-based cleavable linker and a topoisomerase I inhibitor exatecan derivative (DXd) payload. It has a high drug-to-antibody ratio (approximately 8:1), and the stable linker is selectively cleaved by lysosomal enzymes upregulated in tumour cells[82]. It also exhibits bystander effect onto neighbouring tumour cells with antigen heterogeneity. A phase 1/2 multicentre, open label trial evaluated the safety and efficacy of the U3-1402 in HER2 negative, (including ER/PR-positive and TNBC) HER3 expressing advanced breast cancer. Among the 21 patients that received U3-1402, the ORR was 33% and disease-control rate (including complete response, partial response and stable disease) was 95%. Grade 3 or 4 toxicities included thrombocytopenia and increased liver enzymes[40].

TARGETED THERAPIES

Alpelisib

The PI3K pathway has been a focus of research in solid organ tumours due to its role in cell growth, deregulated apoptosis and association with both taxane and endocrine resistance[83]. Alpelisib is a potent, oral, class 1 inhibitor of the PI3K alpha isoform. A Phase I/II study investigated alpelisib plus nab-paclitaxel in HER2-negative MBC[84]. Patients were enrolled into the phase I dose expansion cohort (*n* = 10) or the efficacy phase II (*n* = 30) component. Among the cohort, 30% had TNBC and 74% of patients had received prior chemotherapy. Overall response rate was encouraging at 57% with a median PFS of 7 mo. However, within the PI3K mutated cohort, response rate was 65% with a median PFS of 13 mo. Results are encouraging that targeting the PI3K pathway may have clinical utility in TNBC.

Ipatasertib

The protein kinase B (AKT) pathway is commonly mutated in solid organ tumours playing a crucial role in cell survival and growth. AKT activation commonly occurs

through phosphate and tensin homolog (PTEN) loss or PIK3CA mutations. However, targeting the AKT pathway has proven to be challenging due to the associated toxicities. Ipatasertib is a potent AKT pathway signalling inhibitor which has demonstrated tolerability and antitumour activity in early clinical studies[85]. The LOTUS trial investigated ipatasertib in 124 patients in a randomised phase 2 study of ipatasertib/paclitaxel *vs* placebo/paclitaxel as first-line therapy for TNBC[86]. In the overall population, the median PFS was enhanced with ipatasertib (6.2 mo *vs* 4.9 mo, HR =0.6, *P* = 0.037). In patients with PTEN-low tumours (identified *via* immuno-histochemistry), median PFS was 6.2 mo with ipatasertib *vs* 3.7 mo with placebo. However, within the PIK3CA/AKT1/PTEN-altered tumours, PFS was 9 mo *vs* 4.9 mo (HR 0.44, *P* = 0.041). The most common toxicity was diarrhoea in 23 % of patients in the ipatasertib arm leading to discontinuation in 3% of patients.

Trilaciclib

Trilaciclib is a potent, intravenous cyclin dependent kinase 4/6 (CDK4/6) inhibitor which is thought to acutely protect from cytotoxic associated myelosuppression and may promote immunogenic tumour cell death[87]. A phase II study of trilaciclib in TNBC in combination with the doublet of gemcitabine/carboplatin was designed to identify a reduction in myelosuppression associated with chemotherapy[88]. Patients (*n* = 102) were assigned in a 1:1:1 fashion to (Cohort 1) gemcitabine/carboplatin alone *vs* (Cohort 2) gemcitabine/carboplatin/trilaciclib (D1/D8) *vs* (Cohort 3) gemci-tabine/carboplatin (D2/D9) and Trilaciclib (D1/2/8/9). Approximately 2/3rds of patients were treatment naïve (in the metastatic setting). There was no significant difference in myelosuppression between the groups, however there was a significant OS benefit in the trilaciclib arms. Patients in Cohort 1 had a median OS of 12.6 mo *vs* 20.6 mo in Cohort 2 and 17.6 mo in Cohort 3.

CONCLUSION

Despite recent advances, metastatic TNBC remains an aggressive disease which predominantly affects younger patients. Recent advances in pre-clinical science have demonstrated an impressive rationale for the use of IO and PARPi.

There is evidence of activity for the use PD-L1 or PD-1 inhibitors in the first-line setting of TNBC. However, this has not yet resulted in statistically significant improvements in OS. Additionally, it remains unclear why findings with the combination of nab-paclitaxel and atezolizumab were not reproducible when atezolizumab was combined with paclitaxel. OS analysis from the KEYNOTE-355 study may assist us in reaching final conclusions for the up-front combination of IO and chemotherapy. However, these conflicting results suggest that the addition of IO into routine practice should be done so with caution.

Patients with g BRCA mutations have a consistent but modest PFS benefit of 1-3 mo across multiple phase I/II/III studies. However, these have unfortunately not translated into an OS benefit. While PARPi may have a future role in the treatment paradigm for TNBC, the OS benefits for patients remains unclear.

Encouragingly, antibody-drug conjugates and targeted therapies have demon-strated impressive response rates and PFS benefits in the monotherapy or combination settings in patients with TNBC. Most recently, SG has demonstrated an impressive 6 mo' OS benefit in a heavily pre-treated population. It is likely that SG will have a significant role to play in the future of TNBC in the monotherapy or combi-nation setting.

It is likely that the future of metastatic TNBC will involve treatment algorithms with combination approaches using chemotherapy, immunotherapy, PARPi, ADC and targeted therapies. Hopefully, the combination of the old and new will ensure that clinical outcomes continue to improve for our patients.

Clinical practice points

(1) Despite recent drug developments, chemotherapy remains integral to the management of advanced TNBC; (2) Immunotherapy and PARPi have shown much promise but have yet to demonstrate a proven OS benefit in this disease; and (3) Antibody drug conjugates and other targeted therapies may ultimately prove to be the next frontier in treating this illness.

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