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 predominantly 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

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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 170,000 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 synonymous\(^1\)\(^2\). In one study, 70% of TNBC belonged to the basal subtype and 76% of basal-type tumours would be classified as TNBC\(^1\). A small proportion of basal-like tumours express ER or express HER2\(^2\).\(^3\).

Importantly, basal-like tumours express cytokeratins such as CK5/6, cadherin as well as epidermal like growth factor (EGFR)\(^4\). 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\(^5\).\(^6\).

Mutations in BRCA1/BRCA2 are commonly associated with the basal-like subtype of breast cancer on a genomic level\(^7\).\(^8\). Of course, BRCA1/BRCA2 is associated with a high lifetime incidence of all breast cancers\(^9\). 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\(^10\). 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\(^10\). 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\(^10\).

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’\(^11\). ‘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)\(^11\). 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\(^11\). 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\(^11\).\(^12\). 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\(^13\).\(^14\). Additionally, there is a high level of expression of TILs in patients with TNBC\(^15\).\(^16\). These have been shown to be a useful prognostic indicator across malignancies\(^17\). 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\(^18\). Ibrahim et al\(^19\) found that patients with lymphocyte-predominant breast cancer had a 40% pathological complete response rate compared to 7% of those patients without\(^19\). 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\(^20\).\(^21\).\(^22\). 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\(^23\). PD-L1 has an important role in regulating our immune system, preventing overactivation of T cells and promoting the differentiation of regulatory T cells\(^24\). 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. On average, TNBCs carry 1.68 somatic mutations per Mb of coding regions (approximately 60 somatic mutations in each tumour). 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. 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. 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.

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. 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. 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. 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. Platinum-based regimens have demonstrated significant efficacy for patients with BRCA1/BRCA2 mutant TNBC and other deficiencies in homologous recombination. The TNT study directly studied platinum therapy responses in comparison to standard of care in advanced unselected TNBC. 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. 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. 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+            | 27.0-60.0 | 2.9-7.0  | 8.1-16.5|

1 L-3 Lines. 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 | 9.6 vs 10.6  |                    |                         |                         | Verret et al[87], 2019 |
| chemo                        |     |                  |              |                    |                         |                         |                       |

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

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%)[30].

**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[32]. 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 in the nab-paclitaxel arm (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 reason 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[31]. 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 pembrolizumab/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 | mOS 1st line | mOS 2nd line | ORR ≥ 2 line | Ref. |
|-------|---|------|--------------|--------------|-------------|-------------|-----|
| NCT01633970 Phase Ib | 33 | Atezolizumab + nab-paclitaxel | 53.8% | 30 | 42.2 | 12.4 | Adams et al [55], 2019 |
| KEYNOTE-150 Phase Ib/II | 82 | Pembrolizumab + Eribulin | 25% | 26.5 | 17.7 | NE | Tolaney et al [57], 2018 |
| Pilot and phase II. 1-2L | 29 | Pembrolizumab + capecitabine or paclitaxel | 43% pembro + cap. 23% pembro + paclitaxel | 13.8 pembro + cap 7.9 pembro + pac | | Page et al [90], 2019 |

1One 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

| Drugs | IMpassion130 (PD-L1 inhibitor) vs placebo/nab-paclitaxel | Keynote-355 (PD1 inhibitor) vs chemotherapy (nab-paclitaxel or paclitaxel or gemcitabine/carboplatin vs placebo + chemo) | IMpassion131 (PD-L1 inhibitor) 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%)] |
| Primary endpoints | PD-L1 IHC 22C3 pharmDx kit | PD-L1 IHC 22C3 pharmDx kit | PD-L1 antibody ventana platform |
| 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.

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/CP ≥ 10) and the ITT population. In this trial, a hierarchial statistical testing method involved statistical testing of OS and PFS in the CP > 10 group initially, followed by CP > 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 CPS 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\(^\text{65}\).

Kaufman et al\(^\text{66}\) investigated olaparib further in a large phase 2 basket trial with 298 patients in a single-arm study\(^\text{67}\). 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 gBRCA 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\(^\text{68}\).

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\(^\text{69}\). 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\(^\text{70}\). Half of patients had ER/PR-positive breast cancer with the remainder having TNBC. The cohort was heterogeneous 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\(^\text{71}\). 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 \((19.3 mo vs 19.5 mo)\). 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\(^\text{72}\). 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
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-

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**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 | Median PFS (mo) ≥ 1 line | Median OS (mo) 1st line | Median 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.
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 govitcan-hziy**

Sacituzumab govitcan (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\(^7\). 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\(^8\). 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 govitcan (\( n = 267 \)) vs treatment of physician’s choice (\( n = 262 \)) in patients (pts) with previously treated metastatic TNBC\(^9\). 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\(^9\). 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 deruxtecan**

Trastuzumab deruxtecan (DS-8201) is an ADC with an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor\(^9\). It has shown promising activity in HER2 + metastatic breast cancer and is part of the treatment
| 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 vedotin     | 54%          | -            |              |              |              | Han et al[63], 2020      |
| NCT029380341 phase I/II     | 21  | US-1402                                   | 33%          | -            |              |              |              | Kim et al[82], 2019      |
| NCT03279257 phase I/II      | 40  | Alpelisib                                 | 57%          | 7            |              |              |              | Sharma et al[83], 2018   |
| LOTUS phase II              | 124 | Ipatasertib                               | 40%          | 6.2          |              |              |              | Kim et al[84], 2017      |
| NCT02978716 phase II        | 102 | Trilaciclib                               | 43%          | 20.6/17.6    |              |              |              | Tan et al[85], 2019      |
| ASCENT phase III            | 529 | Sacituzumab Govitecan                     | 35%          | 5.6          | 12.1         |              |              | Bardia et al[86], 2020   |

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

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

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[83].

**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 I 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 immunohistochemistry), 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 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) gemcitabine/carboplatin (D2/D9) and Trilaciclib (D1/2/8/9). Approximately 2/3rd 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 demonstrated 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 combination 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.
REFERENCES

1. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lonning PE, Børresen-Dale AL, Brown PO, Botstein D. Molecular portraits of human breast tumours. Nature 2000; 406: 747-752 [PMID: 10963602 DOI: 10.1038/35021093

2. Costa RB, Gradishar WJ. Triple-Negative Breast Cancer: Current Practice and Future Directions. J Oncol Pract 2017; 13: 301-303 [PMID: 28489982 DOI: 10.1200/JOP.2017.023333

3. Nielsen TO, Hsu FD, Jensen K, Cheang M, Karaca G, Hu Z, Hernandez-Bousard T, Livasy C, Cowan D, Dressler L, Akslen LA, Ragaz J, Gown AM, Gilks CB, van de Rijn, Perou CM. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. Clin Cancer Res 2004; 10: 5367-5374 [PMID: 15328174 DOI: 10.1186/1078-0432.CCR-04-0220

4. Liu Y, Xin T, Huang DY, Shen WX, Li L, Ly YJ, Jin YH, Song XW, Teng C, Jiang QY. Prognosis in very young women with triple-negative breast cancer: retrospective study of 216 cases. Med Oncol 2014; 31: 222 [PMID: 25391919 DOI: 10.1007/s12032-014-0222-2

5. Stead LA, Lash TL, Sobieraj JE, Chi DI, Westrup JL, Charlton M, Blanchard RA, Lee JC, King TC, Rosenberg CL. Triple-negative breast cancers are increased in black women regardless of age or body mass index. Breast Cancer Res 2009; 11: R18 [PMID: 19320967 DOI: 10.1186/bcr2242

6. Sorlie T, Wang Y, Xiao C, Johnsen H, Naume B, Samaha RR, Børresen-Dale AL. Distinct molecular mechanisms underlying clinically relevant subtypes of breast cancer: gene expression analyses across three different platforms. Breast Cancer Res Genomics 2006; 7: 127 [PMID: 16729877 DOI: 10.1186/1471-2164-7-127

7. Howlader N, Cronin KA, Kurian AW, Andridge R. Differences in Breast Cancer Survival by Molecular Subtypes in the United States. Cancer Epidemiol Biomarkers Prev 2018; 27: 619-626 [PMID: 29929110 DOI: 10.1158/1055-9965.EPI-17-0627

8. Yao Y, Chu Y, Xu B, Hu Q, Song Q. Risk factors for distant metastasis of patients with primary triple-negative breast cancer. Bioess Rep 2019; 39: BSR20190288 [PMID: 31113872 DOI: 10.1042/BSR20190288

9. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, Lickley LA, Rawlinson E, Sun P, Narod SA. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007; 13: 4429-4434 [PMID: 17671126 DOI: 10.1186/1055-9965.EPI-17-0627

10. Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Meija JA, Symmans WF, Gonzalez-Angulo AM, Hennessy B, Green M, Cristofanilli M, Hortobagyi GN, Pusztai L. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008; 26: 1275-1281 [PMID: 18250347 DOI: 10.1200/JCO.2007.14.4147

11. Jin J, Gao Y, Zhang J, Wang L, Wang B, Cao J, Shao Z, Wang Z. Incidence, pattern and prognosis of brain metastases in patients with metastatic triple negative breast cancer. BMC Cancer 2018; 18: 446 [PMID: 29673325 DOI: 10.1042/BSR20190288

12. Fan C, Oh DS, Wessels L, Weigelt B, Nuyten DS, Nobel AB, van't Veer LJ, Perou CM. Concordance among gene-expression-based predictors for breast cancer. N Engl J Med 2006; 355: 560-569 [PMID: 16899776 DOI: 10.1056/NEJMoa052933

13. Bertucci F, Finetti P, Cervora N, Esterni B, Hermite F, Viens P, Birnbaum D. How basal are triple-negative breast cancers? Int J Cancer 2008; 123: 236-240 [PMID: 18398844 DOI: 10.1002/ijc.23518

14. Rakha EA, Reis-Filho JS, Ellis IO. Basal-like breast cancer: a critical review. J Clin Oncol 2008; 26: 2568-2581 [PMID: 18487574 DOI: 10.1200/JCO.2007.13.1748

15. Reis-Filho JS, Tutt AN. Triple negative tumours: a critical review. Histopathology 2008; 52: 108-118 [PMID: 18171422 DOI: 10.1111/j.1365-2559.2007.02889.x

16. Foukles WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N Engl J Med 2010; 363: 1938-1948 [PMID: 21067385 DOI: 10.1056/NEJMoa1001389

17. Lim E, Vaillant F, Wu D, Forrest NC, Pal B, Hart AH, Asselin-Labat ML, Grykoi DE, Ward T, Partanen A, Feleppa F, Huschtscha LJ, Thomte HJ; kConFab, Fox SB, Yan M, French JD, Brown MA, Smyth GK, Visvader JE, Lindeman GJ. Aberrant luminal progenitors as the candidate target population for basin tumour development in BRCA1 mutation carriers. Nat Med 2009; 15: 907-913 [PMID: 19648928 DOI: 10.1038/nm.2000

18. Foukles WD, Stefansson IM, Chappuis PO, Bègin LR, Goffin JR, Wong N, Trudel M, Akslen LA. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. J Natl Cancer Inst 2003; 95: 1482-1485 [PMID: 14519755 DOI: 10.1093/jnci/djg050

19. Lakhani SR, Reis-Filho JS, Fulford L, Pelant-Llorea F, van der Vijver M, Parry S, Bishop T, Benitez J, Rivas C, Bignon YJ, Chang-Claude J, Hamann U, Cornelisse CJ, Devilee P, Beckmann MW, Nestle-Kraümling C, Daly PA, Haines N, Varley J, Laloo F, Evans G, Maugard C, Meijers-Heijboer H, Klijn JG, Oehl E, Gusterson BA, Pilotti S, Radice P, Schernthaner G, Sobol H, Jacquemier J, Wagner T, Peto J, Stratton MR, McGuffog L, Easton DF. Breast Cancer Linkage Consortium. Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. Clin Cancer Res 2005; 11: 5175-5180 [PMID: 16033833 DOI: 10.1186/1078-0432.CCR-04-0424

20. Peshkin BN, Alabek ML, Isaacs C. BRCA1/2 mutations and triple negative breast cancers. Breast Dis 2010; 32: 25-33 [PMID: 21778580 DOI: 10.3233/BD-2010-0306

21. Byrum AK, Vindigni A, Mosammaparast N. Defining and Modulating 'BRCAness'. Trends Cell Biol
O'Reilly D et al. Advances in TNBC 2019; 29: 740-751 [PMID: 31362850 DOI: 10.1016/j.chb.2019.06.005]

Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 2004; 4: 814-819 [PMID: 15510162 DOI: 10.1038/nrc1457]

Keung MYT, Wu Y, Vagdama JV. PARP Inhibitors as a Therapeutic Agent for Homologous Recombination Deficiency in Breast Cancers. J Clin Med 2019; 8 [PMID: 30934991 DOI: 10.3390/jcm8040435]

Yu T, Di G. Role of tumor microenvironment in triple-negative breast cancer and its prognostic significance. Chin J Cancer Res 2017; 29: 237-252 [PMID: 28729775 DOI: 10.21147/j.issn.1000-9604.2017.03.10]

Nagarajan D, McArdle SEB. Immune Landscape of Breast Cancers. Biomedicines 2018; 6 [PMID: 29439457 DOI: 10.3390/biomedicines6010020]

García-Tejido P, Cabal ML, Fernández IP, Pérez YF. Tumor-Infiltrating Lymphocytes in Triple Negative Breast Cancer: The Future of Immune Targeting. Clin Med Insights Oncol 2016; 10: 31-39 [PMID: 27081325 DOI: 10.4137/CMO.S34540]

Loi S, Drubay D, Adams S, Pruner G, Francis PA, Lacroix-Triki M, Joensuu H, Dieci MV, Badve S, Demaria S, Gray R, Munzene E, Lemonnier J, Sotiriou C, Piccart MJ, Kolokoumpu-Lehtinen PL, Vinjani A, Gray K, Andre F, Denkert C, Salgado R, Michiels S. Tumor-Infiltrating Lymphocytes and Prognosis: A Pooled Individual Patient Analysis of Early-Stage Triple-Negative Breast Cancers. J Clin Oncol 2019; 37: 559-569 [PMID: 30650045 DOI: 10.1200/JCO.2018.01010]

Zhang L, Wang XL, Ding J, Sun Q, Zhang S. The predictive and prognostic value of Foxp3+/CD25+ regulatory T cells and PD-L1 expression in triple negative breast cancer. Ann Diag Pathol 2019; 40: 143-151 [PMID: 31906176 DOI: 10.1016/j.anndiagpath.2019.04.004]

Ibrahim EM, Al-Foheidi ME, Al-Mansour MM, Kazkaz GA. The predictive value of tumor-infiltrating lymphocytes in triple-negative breast cancer: a meta-analysis. Breast Cancer Res Treat 2014; 148: 467-476 [PMID: 25361613 DOI: 10.1007/s10549-014-3185-2]

Pagis F, Galon J, Dieu-Noüjean MC, Tartour E, Sautès-Fridman C, Fridman WH. Immune infiltration in human tumors: a prognostic factor that should not be ignored. Oncogene 2010; 29: 1093-1102 [PMID: 19946335 DOI: 10.1038/ooe.2009.416]

Salgado R, Denkert C, Demaria S, Sirtaine N, Klauschen F, Pruner G, Wienert S, Van den Eynden G, Baechner FL, Renault-Llorca F, Perez EA, Thompson EA, Symmans WF, Richardson AL, Brock J, Criscitelli C, Bailey H, Ignatiadis M, Fliss C, Sartoretti F, Jiao J, Keros N, Nielsen T, Rimm DL, Allison KH, Reis-Filho JS, Loibl S, Sotiriou C, Viale G, Badve S, Adams S, Willard-Gallo K, Loi S, International TILs Working Group 2014. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann Oncol 2015; 26: 259-271 [PMID: 25214542 DOI: 10.1093/annonc/mdu450]

Denkert C, Wienert S, Poterie A, Loibl S, Budczies J, Badve S, Bago-Horvath Z, Bane A, Bedri S, Brock J, Chmieliak E, Christgen M, Colpaert C, Demaria S, Van den Eynden G, Fliss C, Fox SB, Gao D, Ingold Heppner B, Kon M, Sartoretti F, Jiao J, Keros N, Nielsen T, Rimm DL, Allison KH, Reis-Filho JS, Loibl S, Sotiriou C, Viale G, Badve S, Adams S, Willard-Gallo K, Loi S, International TILs Working Group 2014. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: results of the ring studies of the international immunology-oncology biomarker working group. Mod Pathol 2016; 29: 1155-1164 [PMID: 27363491 DOI: 10.1038/modpathol.2016.109]

Mittendorf EA, Phillips AV, Meric-Bernstam F, Qiao N, Wu Y, Harrington S, Su X, Wang Y, Gonzalez-Angulo AM, Akakonat A, Chawla A, Curran M, Hwu P, Sharma P, Litton JK, Middlere JJ, Alatras G. PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res 2014; 2: 361-370 [PMID: 24746583 DOI: 10.1158/2326-6066.CIR-13-0127]

Narang P, Chen M, Sharma AA, Anderson KS, Wilson MA. The neoptoepe landscape of breast cancer: implications for immunotherapy. BMC Cancer 2019; 19: 200 [PMID: 30832597 DOI: 10.1186/s12885-019-5402-1]

Sabatier R, Finetti P, Manessiere E, Adeleja D, Chaffanet M, Ali HR, Viens P, Caldas C, Birmbaum D, Bertucci F. Prognostic and predictive value of PDL1 expression in breast cancer. Oncotarget 2015; 6: 5449-5464 [PMID: 25669979 DOI: 10.18632/oncotarget.3216]

Salmanninejad A, Valioli SF, Shabgah AG, Aslani S, Alimardani M, Pasdar A, Sehebkar A. PD-L1/PD-L2 pathway: Basic biology and role in cancer immunotherapy. J Cell Physiol 2019; 234: 16824-16833 [PMID: 30784085 DOI: 10.1002/jcp.28358]

Barroso-Sousa R, Keenan TE, Pernas S, Exmon P, Jain E, Garrido-Castro AC, Hughes M, Bichkovsky B, Umeton R, Files J, Lindeman NI, MacConaill LE, Hodis H, Krop IE, Dillon D, Winer EP, Wagle N, Lin NU, Mittendorf EA, Van Allen EM, Tolnay SM. Tumor Mutational Burden and PTEN Alterations as Molecular Correlates of Response to PD-L1/L2 Blockade in Metastatic Triple-Negative Breast Cancer. Clin Cancer Res 2020; 26: 2565-2572 [PMID: 32019858 DOI: 10.1158/1078-0432.CCR-19-3507]

Goodman AM, Kato S, Bazhenova L, Patel SP, Frampston GM, Miller V, Stephens PJ, Daniels GA, Kurzrock R. Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. Mol Cancer Ther 2017; 16: 2598-2608 [PMID: 28835386 DOI: 10.1158/1535-7163.MCT-17-0386]

Chan TA, Yarcham M, Jaffee E, Swanton C, Quezada SA, Stenzinger A, Peters S. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. Ann Oncol 2019; 30: 44-56 [PMID: 30395155 DOI: 10.1093/annonc/mdy495]
Yonenori K, Masuda N, Takahashi S, Kogawa T, Iwata, H. Single agent activity of U3-1402, a HER3-targeting antibody–drug conjugate, in HER3-overexpressing metastatic breast cancer: updated results from a phase I/II trial. *Ann Oncol* 2019; 30 [DOI: 10.1093/annonc/mdz100.002]

Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, Collichio F, Olivda DW, Sartor CI, Graham ML, Perez CM. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. *Clin Cancer Res* 2007; 13: 2329-2334 [PMID: 17438091 DOI: 10.1158/1078-0432.CCR-06-1109]

Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, Harbeck N, Aguilar Lopez B, Barrios CH, Bergh J, Biganzoli L, Boers-Doets CB, Cardoso MJ, Carey LA, Cortés J, Curigliano G, Diéses V, El Saghir NS, Éniu A, Fallowfield L, Francis PA, Gelmon K, Johnston SRD, Kaufman B, Koppikar S, Krop IE, Mayer M, Nakigudde G, Offerzen BV, Ohno S, Panagio M, Paluch-Shimon S, Pauwels-Llorca F, Prat A, Rustin H, Sledge GW, Spence D, Thomssen C, Vorobiof DA, Xu B, Norton L, Winer EP. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). *Ann Oncol* 2018; 29: 1634-1657 [PMID: 30032243 DOI: 10.1093/annonc/mdy192]

Smith KL, Smith M Lou, Burns J. Breast Cancer. NCCN Guidelines. 2020

Sparano JA, Makkosh AN, Semiglazov VF, Tjulandin SA, Balashova OI, Bondarenko IN, Bogdanova NV, Manikhas GM, Oliyivenchenko GP, Chatikhine VA, Zhuang SX, Xiu L, Yuan Z, Rackoff WR. Pegylated liposomal doxorubicin plus docetaxel significantly improves time to progression without additive cardiotoxicity compared with docetaxel monotherapy in patients with advanced breast cancer previously treated with neoadjuvant-adjuvant anthracycline therapy: results from a randomized phase III study. *J Clin Oncol* 2009; 27: 4522-4529 [PMID: 19687336 DOI: 10.1200/JCO.2008.20.5013]

Cardoso F, Bedral PL, Winer EP, Pagani O, Senkus-Konefka E, Fallowfield LJ, Kyriakides S, Costa A, Cufer T, Albin K; ECOG-ACRIN Cancer Research Group. International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. *J Natl Cancer Inst* 2009; 101: 1174-1181 [PMID: 19657108 DOI: 10.1093/jnci/djp235]

Isakoff SJ, Mayer EL, He L, Traina TA, Carey LA, Krag KJ, Rugo HS, Liu MC, Stearns V, Come SE, Timms KM, Hartmann AR, Borger DR, Finkelstein DM, Garber JE, Ryan PD, Winer EP, Goss PE, Ellison LW. TBRC-C009: A Multicenter Phase II Clinical Trial of Platinum Monotherapy With Biomarker Assessment in Metastatic Triple-Negative Breast Cancer. *J Clin Oncol* 2015; 33: 1902-1909 [PMID: 25847936 DOI: 10.1200/JCO.2014.57.6660]

Telli ML, Timms KM, Reid J, Hennessy B, Mills GB, Jensen KC, Szallasi Z, Barry WT, Winer EP, Tung NM, Isakoff SJ, Ryan PD, Greene-ColoZZi A, Gutin A, Sangale Z, Ilyev N, Nett C, Abkevich V, Jones JT, Lanchbury JS, Hartman AR, Garber JE, Ford JD, Silver DP, Richardson AL. Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer. *Clin Cancer Res* 2016; 22: 3764-3773 [PMID: 26957554 DOI: 10.1158/1078-0432.CCR-15-2477]

Tutt A, Tovey H, Chiang MCU, Kerkavanah S, Kilburn L, Gazinska P, Owen J, Abraham J, Barrett S, Barrett-Lee P, Brown R, Chan S, Dowsett M, Flanagan JM, Fox L, Grigoriadis A, Gutin A, Harper-Tutt A, Koppikar S, Krop IE, Mayer M, Nakigudde G, Offenzen BV, O'Shaughnessy J, Petrakova K, Chollet P, Manikas A, Rackoff WR. Pegylated liposomal doxorubicin plus docetaxel significantly improves time to progression without additive cardiotoxicity compared with docetaxel monotherapy in patients with advanced breast cancer previously treated with neoadjuvant-adjuvant anthracycline therapy: results from a randomized phase III study. *J Clin Oncol* 2009; 27: 4522-4529 [PMID: 19687336 DOI: 10.1200/JCO.2008.20.5013]

Dirix LY, Takacs I, Jerusalem G, Nikolina G, Arkenau HT, Forero-Torres A, Boccia R, Lippmann ME, Somer R, Tovey H, Cheang MCU, Kernaghan S, Kilburn L, Gazinska P, Owen J, Abraham J, Barrett S, Brown R, Chan S, Dowsett M, Flanagan JM, Fox L, Grigoriadis A, Gutin A, Harper-Tutt A, Koppikar S, Krop IE, Mayer M, Nakigudde G, Offenzen BV, O'Shaughnessy J, Petrakova K, Chollet P, Manikas A, Rackoff WR. Pegylated liposomal doxorubicin plus docetaxel significantly improves time to progression without additive cardiotoxicity compared with docetaxel monotherapy in patients with advanced breast cancer previously treated with neoadjuvant-adjuvant anthracycline therapy: results from a randomized phase III study. *J Clin Oncol* 2009; 27: 4522-4529 [PMID: 19687336 DOI: 10.1200/JCO.2008.20.5013]

O'Reilly D et al. Advances in TNBC.
pembrolizumab (pembro) vs single-agent chemotherapy (chemo) for metastatic triple negative breast cancer (mTNBC). Ann Oncol 2019; 30: v859-v860 [DOI: 10.1093/annonc/mdz394.010]

55 Adams S, Diamond JR, Hamilton E, Pohlmann PR, Tolaney SM, Chang CW, Zhang W, Iizuka K, Foster PG, Molinero L, Funke R, Powderly J. Atezolizumab Plus nab-Paclitaxel in the Treatment of Metastatic Triple-Negative Breast Cancer With 2-Year Survival Follow-up: A Phase 1b Clinical Trial. JAMA Oncol 2019; 5: 334-342 [PMID: 30347025 DOI: 10.1001/jamaoncol.2018.5152]

56 Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, Didras V, Hegg R, Im SA, Shaw Wright G, Henschel V, Molinero L, Chui SY, Funke R, Hussain A, Winer EP, Loi S, Emens LA; IMpassion130 Trial Investigators. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med 2018; 379: 2108-2121 [PMID: 30345906 DOI: 10.1056/NEJMoa1806159]

57 Tolaney SM, Kalinsky K, Kaklamanis V, Savulsky C, Diab S. Abstract PD6-13: Phase 1b/2 study to evaluate eribulin mesylate in combination with pembrolizumab in patients with metastatic triple-negative breast cancer. Cancer Res 2018; 78: PD6-13 [DOI: 10.1185/1538-7445.SABCS17-PD6-13]

58 Castan JC, Guo Z, Karantza V, Aktan G. Keynote-355: randomized, double-blind, phase iii study of pembrolizumab (pembro) + chemotherapy (chemo) vs placebo (pbo) + chemo for previously untreated, locally recurrent, inoperable or metastatic triple-negative breast cancer (mtnbc) - sciencedirect. Ann Oncol 2017; 28: x25 [DOI: 10.1093/annonc/mdx656]

59 Rugo HS, Loi S, Adams S, Schmid P, Schneeweiss A, Barrios CH, Iwata H, Dieras VC, Winer EP, Koekk M, Peeters D, Chui SY, Lin JC, Nguyen Duc A, Viale G, Molinero L, Emens LA. LA20 - Performance of PD-L1 immunohistochemistry (IHC) assays in unresectable locally advanced or metastatic triple negative breast cancer (mTNBC): Post-hoc analysis of IMpassion130. Ann Oncol 2019; 30: v858-v859 [DOI: 10.1093/annonc/mdz394.009]

60 Kulangara K, Zhang N, Corigliano E, Guerrero L, Waldrup S, Saiswal D, Mi MJ, Shah S, Hanks D, Wang J, Lunceford J, Savage MJ, Juco J, Emancipator K. Clinical Utility of the Combined Positive Score for Programmed Death Ligand-1 Expression and the Approval of Pembrolizumab for Treatment of Gastric Cancer. Arch Pathol Lab Med 2019; 143: 330-337 [PMID: 30028179 DOI: 10.5855/arpa.2018-0043-OA]

61 Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Fouldakis T, Fasching BA, Cardoso F, Untch M, Jia L, Karantza V, Zhao J, Aktan G, Dent R, O'Shaughnessy J. KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med 2020; 382: 810-821 [PMID: 32101663 DOI: 10.1056/NEJMoa1915049]

62 Fuentes-Antrás J, Guevara-Hoyer K, Balu-Iqiqué M, García-Sáenz JA, Pérez-Segura P, Pandiella A, Ocaña A. Adoptive Cell Therapy in Breast Cancer: A Current Perspective of Next-Generation Medicine. Front Oncol 2020; 10: 650633 [PMID: 33194771 DOI: 10.3389/fonc.2020.650633]

63 Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel NJ, Friedlander ML, Arun B, Loman N, Schmutzler RK, Wardley A, Mitchell G, Earl H, Wickens M, Carmichael J. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010; 375: 235-244 [PMID: 20609467 DOI: 10.1016/S0140-6736(10)60892-6]

64 Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander ML, Balmàña J, Mitchell G, Fried G, Stemmer SM, Hubert A, Rosengarten O, Steiner M, Loman N, Bowen K, Fielding A, Domchek SM. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015; 33: 244-250 [PMID: 25366685 DOI: 10.1200/JCO.2014.56.2728]

65 Turner NC, Telli ML, Rugo HS, Maillois R, Robson ME. Final results of a phase 2 study of talazoparib (TALA) following platinum or multiple cytotoxic regimens in advanced breast cancer patients (pts) with germline BRCA1/2 mutations (ABRAZO). J Clin Oncol 2017; 35: 1007 [PMID: 10.1200/JCO.2017.35.15_suppl.1007]

66 Han HS, Didras V, Robson M, Palacová M, Marcon PK, Jager A, Bondarenko I, Citrin D, Campone M, Telli ML, Domchek SM, Friedlander M, Kaufman B, Garber JE, Shappik Y, Chmielowska E, Jakobsen EH, Kaklamanis V, Gradishar W, Ratjakczak CK, Nickner C, Qin Q, Qian J, Shepherd SP, Isakov SJ, Pahalla S, Velivaliap R with temozolomide or carboplatin/paclitaxel versus placebo with carboplatin/paclitaxel in patients with BRCA1/2 locally recurrent/metastatic breast cancer: randomized phase II study. Ann Oncol 2018; 29: 154-161 [PMID: 29045554 DOI: 10.1093/annonc/mdx565]

67 Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, Delaloge S, Li W, Tung N, Armstrong A, Wu W, Goessl C, Runswick S, Conte P. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med 2017; 377: 523-533 [PMID: 28578601 DOI: 10.1056/NEJMoa1706450]

68 Llütton JK, Rugo HS, Etll J, Hurvitz SA, Gonçalves A, Lee KH, Fehrenbacher L, Yerushalmi R, Mina LA, Martin J, Roché H, Im YH, Quek RGW, Markova D, Tudor IC, Hannah AL, Eiermann W, Blum JL. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med 2018; 379: 753-763 [PMID: 31015079 DOI: 10.1056/NEJMoa1802905]

69 Llütton JK, Hurvitz SA, Mina LA, Rugo HS, Lee KH, Gonçalves A, Diab S, Woodward N, Goodwin A, Yerushalmi R, Roché H, Im YH, Eiermann W, Quek RGW, Usari T, Lanzalone S, Cizbère A, Blum JL, Martin J, Etll J. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol 2020; 31: 1526-1535 [PMID: 32828825 DOI: 10.1016/j.annonc.2020.08.2098]
70 Díeras VC, Han HS, Kaufman B, Wildiers H, Arun BK. LBA9 - Phase III trial of veliparib with carboplatin and paclitaxel in HER2-negative advanced/metastatic gBRCA-associated breast cancer. Ann Oncol 2019; 30: v857-v858 [DOI: 10.1093/annonc/mdz394.008]

71 Han HS, Arun B, Kaufman B, Wildiers H, Arun BK. Veliparib (V) monotherapy (monoTX) following combination therapy with V + carboplatin/paclitaxel (CP) in patients with gBRCA-associated advanced breast cancer: Exploratory results from BROCADE3. J Clin Oncol 2020; 38: 1091 [DOI: 10.1200/JCO.2020.38.15_suppl.1091]

72 Tung NM, Robson ME, Venta S, Santa-Maria CA, Garber JE. TBCRC 048: A Phase II study of olaparib monotherapy in metastatic breast cancer patients with germline or somatic mutations in DNA damage response (DDR) pathway genes (Olaparib Expanded). J Clin Oncol 2020; 38: 1002 [DOI: 10.1200/JCO.2020.38.15_suppl.1002]

73 Sharma P, Rodler E, Barlow WE, Gralow J, Hortobagyi GN. Results of a Phase II randomized trial of cisplatin +/- veliparib in metastatic triple-negative breast cancer (TNBC) and/or germline BRCA-associated breast cancer (SWOG S1416). J Clin Oncol 2020; 38: 1001 [DOI: 10.1200/JCO.2020.38.15_suppl.1001]

74 Takaya H, Nakai H, Takamatsu S, Mandai M, Matsumura N. Homologous recombination deficiency status-based classification of high-grade serous ovarian carcinoma. Sci Rep 2020; 10: 2757 [PMID: 32066851] [DOI: 10.1038/s41598-020-9678-3]

75 Starodub AN, Ocean AJ, Shah MA, Guarino MJ, Picozzi VJ Jr, Vahdat LT, Thomas SS, Govindan SV, Malakal PP, Wegener WA, Hamburger SA, Sharkey RM, Goldenberg DM. First-In-Human Trial of a Novel Anti-Trop-2 Antibody-SN-38 Conjugate, Sacituzumab Govitecan, for the Treatment of Diverse Metastatic Solid Tumors. Clin Cancer Res 2015; 21: 3870-3878 [PMID: 25944802] [DOI: 10.1158/1078-0432.CCR-14-3321]

76 Bardia A, Mayer JA, Vahdat LT, Tolaney SM, Isakoff SJ, Diamond JR, O'Shaughnessy J, Morooco RL, Santin AD, Abramson VG, Shah NC, Rugo HS, Goldenberg DM, Sweidan AM, Iannone R, Washkowitz S, Sharkey RM, Wegener WA, Kalinsky K. Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer. N Engl J Med 2019; 380: 741-751 [PMID: 30786188] [DOI: 10.1056/NEJMoa1814213]

77 Bardia A, Tolaney SM, Loirat D, Punie K, Oliveira M, Rugo HS, Brufsky A, Kalinsky K, Cortés J, O’Shaughnessy J, Dieras VC, Carey LA, Gianni L, Piccart M, Loibl S, Goldenberg DM, Sweidan AM, Iannone R, Washkowitz S, Sharkey RM, Wegener WA, Kalinsky K. Homologous recombination deficiency status-based classification of high-grade serous ovarian carcinoma. Sci Rep 2018; 8: 1512-1522 [PMID: 29037983] [DOI: 10.1038/s41598-020-59671-3]

78 Han H, Diab S, Alemany C. Abstract PD1-06: Open label phase 1b/2 study of ladiratumab vedotin in combination with pembrolizumab for first-line treatment of patients with unresectable locally-advanced or metastatic triple-negative breast cancer. Cancer Res 2020; 80: PD1-06 LP [DOI: 10.1158/1358-7455.SABCS19-PD1-06]

79 Doi T, Shiitara K, Naito Y, Shimomura A, Fujiwara Y, Yonemori K, Shimizu C, Shimoi T, Kuboki Y, Matsubara N, Kitano A, Jikoh T, Lee C, Fujisaki Y, Ogitani Y, Yver A, Tamura K. Safety, pharmacokinetics, and antitumor activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study. Lancet Oncol 2017; 18: 1512-1522 [PMID: 29037983] [DOI: 10.1016/S1470-2045(17)30604-6]

80 Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, Andre F, Iwata H, Ito Y, Tsuturani J, Sohn J, Denduluri N, Perrin C, Aogi K, Tokunaga E, Im SA, Lee KS, Hurvitz SA, Cortes J, Lee C, Chen S, Zhang L, Shahidi J, Yver A, Kroop I; DESTINY-Breast01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med 2020; 382: 610-621 [PMID: 31825192] [DOI: 10.1056/NEJMoa1914519]

81 Modi S, Park H, Murthy RK, Iwata H, Tamura K, Tsuturani J, Moreno-Aspitia A, Doi T, Sagara Y, Redfern C, Kroop I, Lee C, Fujisaki Y, Sugihara M, Zhang L, Shahidi J, Takahashi S. Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients With HER2-Low-Expressing Advanced Breast Cancer: Results From a Phase Ib Study. J Clin Oncol 2020; 38: 1887-1896 [PMID: 32058843] [DOI: 10.1200/JCO.19.02318]

82 Kim SB, Meric-Bernstam F, Kalyan A, Babich A, Berlin J. First-in-human phase i study of aprutumab ixadotin, a fibroblast growth factor receptor 2 antibody-drug conjugate (bay 1187982) in patients with advanced cancer. Target Oncol 2019; 14: 591-601 [PMID: 31502117] [DOI: 10.1007/s11523-019-00670-4]

83 Verrett B, Cortes J, Bachelor T, Andre F, Arnedos M. Efficacy of PI3K inhibitors in advanced breast cancer. Ann Oncol 2019; 30: x12-x20 [PMID: 31928690] [DOI: 10.1093/annonc/mdz381]

84 Sharma P, Abramson VG, O’Dea A, Pathak HB, Godwin AK. Clinical and biomarker results from phase I/II study of PI3K inhibitor BYL 719 (alpelisib) plus nab-paclitaxel in HER2-negative metastatic breast cancer. J Clin Oncol 2018; 36: 1018 [DOI: 10.1200/JCO.2018.36.15_suppl.1018]

85 A First-in-Human Phase I Study of the ATP-Competitive AKT Inhibitor Ipatasertib Demonstrates Robust and Safe Targeting of AKT in Patients with Solid Tumors. Cancer Discov 2018; 8: 1490 [PMID: 30355525] [DOI: 10.1158/2159-8290.CD-18-1114]

86 Kim SB, Dent R, Im SA, Espié M, Blau S, Tan AR, Isakoff SJ, Oliveira M, Saura C, Wongchenko MJ, Kapp AV,Chan WY, Singel SM, Misdary DI, Baselga J. LOTUS investigators. Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast
cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 2017; 18: 1360-1372 [PMID: 28800861 DOI: 10.1016/S1470-2045(17)30450-3]

87 He S, Roberts PJ, Sorrentino JA, Bisi JE, Storrie-White H, Tiessen RG, Makhuli KM, Wargin WA, Tadema H, van Hoogdalem EJ, Strum JC, Malik R, Sharpless NE. Transient CDK4/6 inhibition protects hematopoietic stem cells from chemotherapy-induced exhaustion. *Sci Transl Med* 2017; 9 [PMID: 28446688 DOI: 10.1126/scitranslmed.aal3986]

88 Tan AR, Wright GS, Thummala AR, Danso MA, Popovic L, Pluard TJ, Han HS, Vojnović Ž, Vasev N, Ma L, Richards DA, Wilks ST, Milenković D, Yang Z, Antal JM, Morris SR, O’Shaughnessy J. Trilaciclib plus chemotherapy versus chemotherapy alone in patients with metastatic triple-negative breast cancer: a multicentre, randomised, open-label, phase 2 trial. *Lancet Oncol* 2019; 20: 1587-1601 [PMID: 31575503 DOI: 10.1016/S1470-2045(19)30616-3]

89 Li CH, Karantza V, Aktań G, Lala M. Current treatment landscape for patients with locally recurrent inoperable or metastatic triple-negative breast cancer: a systematic literature review. *Breast Cancer Res* 2019; 21: 143 [PMID: 31842957 DOI: 10.1186/s13058-019-1210-4]

90 Page DB, Chun B, Pucilowska J, Kim I, McArthur HL. Pembrolizumab (pembro) with paclitaxel (taxol) or capecitabine (cape) as early treatment of metastatic triple-negative breast cancer (mTNBC). *J Clin Oncol* 15: 1015-1015 [DOI: 10.1200/JCO.2019.37.15_suppl.1015]
