Triple-negative breast cancer: current treatment and future perspectives

G. El Hachem, MD[1,2*], Y. Jounblat, MD[1*], A. Awada, MD, PhD[1], A. Gombos, MD[1]

SUMMARY

Triple-negative breast cancer is a heterogeneous subtype of breast carcinoma lacking the expression of oestrogen, progesterone and human epidermal growth factor 2 receptors. For many decades, cytotoxic chemotherapy has been the standard of care offering only a short-living disease control. Knowing its poor outcome and aggressive behaviour, researchers are trying to find new therapeutic options hoping to improve the survival of this population. Many cytotoxic and targeted therapies were tested without major benefit. However, in the era of molecular and mutational classification of tumours, as well as the immune mediated mechanisms of proliferation and progression, the trials are currently oriented towards the identification of potential targets in the tumoral heterogenic environment. Here, we present a review of literature concerning the potential anti-neoplastic options and novel therapies for metastatic triple-negative breast cancers: new cytotoxic agents, new targeted therapies, anti-angiogenic agents, antibody-drug conjugates, poly-ADP ribose transferase inhibitors and immunotherapy. Many agents are promising, yet not powerful enough to get approvals for use into clinical practice.

(BELG J MED ONCOL 2019;13(3):84-92)

INTRODUCTION

Breast cancer is the most common cancer in women worldwide and remains an important global health issue.[1] Triple-negative breast cancer (TNBC), which lacks expression of the oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2 (HER2), accounts for approximately 15% of breast cancer cases.[2-6]

Over the last decade, gene expression profiling has been used to classify invasive breast cancers into biologically and clinically distinct subtypes. The majority of TNBC cases are of the basal-like subtype, and they are characterised by a high histologic grade, high mitotic index, early disease recurrence and poor outcomes.[7-10]

Furthermore, data highlights that TNBC is a heterogeneous disease that encompasses distinct intrinsic molecular subtypes. Lehmann *et al.* were one of the first groups to use gene expression profiling to sub-classify TNBC. Initially, they identified six distinct subtypes that were refined into four tumour-specific subtypes: (1) basal-like 1; (2) basal-like 2; (3) mesenchymal; and (4) luminal androgen receptor (LAR).[11,12]

Owing to the absence of approved targeted therapies, cytotoxic chemotherapy remains the mainstay of medical treatment for advanced TNBC. The outcomes are poor compared to other subtypes, the median survival of patients diagnosed with this stage of disease being no longer than 13 months.[13,14] Thus, the improvement of therapeutic strategies is urgently required.

[1]Oncology Medicine Department, Institut Jules Bordet, Université Libre de Bruxelles, [2]Medical Oncology Department, Hôpital Erasme, Université Libre de Bruxelles, *G. El Hachem and Y. Jounblat contributed equally to this work.

Please send all correspondence to: A. Gombos, MD, Institut Jules Bordet, 121 Boulevard de Waterloo, 1000 Brussels, tel: 0032 25413111, email: andrea.gombos@bordet.be.

Conflict of interest: The authors have nothing to disclose and indicate no conflict of interest.

Keywords: heterogenic disease, immunotherapy, targeted therapy, triple-negative breast cancer.

The purpose of this review is to discuss the different therapeutic options to treat TNBC including old and new cytotoxic chemotherapies, molecular-targeted therapies which are currently in late clinical development.

CYTOTOXIC CHEMOTHERAPY

Despite all the research that has been performed in the field of advanced TNBC and the promising results obtained with some targeted drugs, cytotoxic chemotherapy remains an essential part of the treatment. Here, we summarise selected cytotoxic options with proven efficacy in treating metastatic TNBC. It is important to remember that anthracyclines, taxanes and antimetabolites remain the main agents in metastatic TNBC with overall response rates (ORRs) ranging from 15-40 %.[15,16] There is no reason to deny in this setting these important agents in the management of metastatic breast cancer (MBC).

ERIBULIN

Derived from a synthetic analogue of the marine sponge halichondrin B, eribulin is a mechanistically unique inhibitor of microtubule dynamics. The results of EMBRACE (the Eisai Metastatic Breast Cancer Study Assessing Physician's Choice (TPC: treatment of physician's choice) versus E7389), a multicentre, randomised phase III trial, definitely confirm the place of this agent in the treatment of advanced breast cancer. It recruited 762 patients, including 19% triple-negative tumours that progressed after treatment with anthracyclines and taxanes. A group of patients also received capecitabine. The overall survival (OS) in the eribulin-treated patients (1.4 mg/m^2 administered intravenously on days 1 and 8 of a 21-day cycle) was significantly improved: 13.1 months compared to 10.6 months in the TPC treated group (p=0.041, hazard ratio [HR] 0.81 [95% CI: 0.66-0.99]). However, median progression-free survival (PFS) was not significantly longer (3.7 months *vs* 2.2 months, p=0.137, HR 0.87 [95% CI: 0.71-1.05]). Grade 3/4 adverse events, which occurred more frequently with eribulin than with TPC, were neutropenia (45% *vs* 21%), leukopenia (14% *vs* 6%) and peripheral neuropathy (9% *vs* 2%).[17]

Another randomised phase III study compared eribulin (given in the same schedule as in the above mentioned trial) with standard doses of capecitabine in patients who had previously received treatment with anthracyclines and taxanes. The median OS for eribulin (n=554 including 150 patients with TNBC) and capecitabine (n=548 including 134 patients with TNBC) was similar (15.9 *vs* 14.5 months, HR 0.88 [95% CI: 0.77-1.00]; p=0.056). The median PFS for eribulin and capecitabine was 4.1 and 4.2 months, respectively (HR 1.08 [95% CI: 0.93-1.25]; p=0.30). Quality of life was similar in both arms. Safety profiles were concordant with what was previously noticed with these drugs.[18]

A pooled analysis from two phase III studies aimed to analyse the efficacy of eribulin in different subgroups of MBC including patients with TNBC, clearly showing a benefit in this patient population. A total of 1644 patients, who had previously received at least one prior chemotherapy regimen for advanced disease, was included (eribulin: 946; control 698). In the 352 TNBC patients included in this analysis, the OS was significantly higher with eribulin (12.4 months *vs* 8.1 months, p<0.01, HR 0.72).[19]

DNA-DAMAGING CHEMOTHERAPY AGENTS: PLATINUM COMPOUNDS

Platinum salts exert their therapeutic efficacy through production of direct DNA damage. Cancer cells with a *BRCA1* mutation have a defect in the homologous recombination-based repair of double-strand DNA breaks and are sensitive to inter-strand cross-linking agents. *BRCA* germline mutation or epigenetic abnormalities are present in TNBC patients.[20-22]

Platinum-based regimens are regularly used in patients with metastatic TNBC even though there is a lack of prospective trials demonstrating a survival advantage.[23] This practice pattern is based on the extrapolated data from the neo-adjuvant trials (and little data from the metastatic setting), where platinum-based chemotherapy combinations were shown to be associated with a higher rate of pathologic complete response, albeit with more myelosuppression compared to non-platinum regimens.[24,25]

The most relevant data in metastatic setting that confirms a clear benefit of carboplatin alone in a first-line setting is coming from a randomised phase III trial comparing carboplatin with the standard docetaxel in patients diagnosed with advanced TNBC, including *BRCA1/2* mutation carriers. Among the 43 *BRCA*-mutated patients, the ORR was 68% with carboplatin and 33% with docetaxel, meaning a 34.7% absolute difference (p=0.03). In contrast, for the 273 *BRCA*-negative patients, response rates (RRs) were not significantly different (28.1% *vs* 34.5%, p=0.16). The median PFS with carboplatin was 6.8 months in *BRCA*-mutated patients and 3.1 months in non-*BRCA* carriers. No differences were seen with docetaxel. The homologous recombination deficiency (HRD; Myriad Genetics) score was available for 195 patients: 81 patients were classified as HRD 'high' (≥42) and 114 as HRD 'low' (<42). The efficacy of the tested regimens was the same in HRD high, with a RR of 38.2% with carboplatin and 42.6% with docetaxel (p=0.82). The same results were seen in HRD 'low' patients: RR was 29.2% with carboplatin and

TABLE 1. Phase III trials investigating bevacizumab in metastatic breast cancer.

Study	US Study[31]	AVADO[32]	RIBBON-1[33]	RIBBON-2[34]
Treatment	First-line PTX + BVZ vs PTX	First-line DTX + BVZ 15mg/kg* vs DTX + BVZ 7.5mg/kg# vs DTX + PL	First-line CT (CAPE or TAX or ATC) + PL vs CT + BVZ	Second-line CT (CAPE or TAX or GEM or NVB) + PL vs CT + BVZ
N (n)	722 (233)	736 (167)	1237 (279)	684 (159)
mPFS (mo)	11.8 vs 5.9 (HR 0.6 [CI: 0.51-0.70)]; p<0.001)	*10 vs 8.1 (HR 0.67 [CI: 0.54-0.83]; p<0.001) #9 vs 8.1 (HR 0.8 [CI: 0.65-1.00)]; p=0.045)	CAPE cohort: 8.0 vs 9.2 (HR 0.64 [CI: 0.52-0.80]; p<0.001) TAX/ATC cohort: 5.7 vs 8.6 (HR 0.69 [CI: 0.56-0.84]; p<0.001)	5.1 vs 7.2 (HR 0.78 [CI: 0.64-0.93]; p=0.0072)
mOS (mo)	26.7 vs 25.2 (HR 0.88; p=0.16)	*30.2 vs 31 (HR 1.03 [CI: 0.70-1.33]; p=0.85) #30.8 vs 31.9; (HR 1.05 [CI: 0.81-1.36]; p=0.72)	No statistical significance	16.4 vs 18.0 (HR 0.90 [CI: 0.71-1.14]; p=0.3741)
Subgroups analysis in TNBC (mPFS-mo)	8.8 vs 4.6 (HR 0.53 [CI: 0.4-0.7])	NA	CAPE cohort: 4.2 vs 6.1 (HR 0.72 [CI: 0.49-1.06]) TAX/ATC cohort: 6.2 vs 6.5 (HR 0.78 [CI: 0.53-1.15])	2.7 vs 6.0 (HR 0.49 [CI: 0.33-0.74])

N: total number of patients included in the trial, n: number of triple negative breast cancer patients, mo: months, mOS: median overall survival, mPFS: median progression-free survival, vs: versus, HR: hazard ratio, CI: confidence interval, PTX: paclitaxel, BVZ: bevacizumab, PL: placebo, DTX: docetaxel, CT: chemotherapy, CAPE: capecitabine, TAX: taxanes, ATC: anthracyclines, GEM: gemcitabine, NVB: navelbine, NA: not applicable.

34.7% with docetaxel (p=0.55). According to these results, the '*BRCA*ness' status as defined by the HRD score is not predictive of benefit from platinum-based chemotherapy.[26-28]

On the other side, a platinum-based combination with gemcitabine showed some efficacy (RR: 26%, PFS: 3.8 months in heavily pre-treated patients, 4.2 months in minimally pre-treated patients) in a small phase II trial.[29]

These results showed a clear benefit among patients harbouring germline *BRCA* mutation early after the diagnosis of MBC. In every other case, platinum-based regimens can be considered later on during disease evolution.

LURBINECTEDIN

Lurbinectedin (PM01183) is a DNA minor groove binding agent, which seems to be active in diverse tumour types, even in those that are resistant to platinum-based chemotherapy. Early signs of efficacy of this drug were seen in a small series of MBC patients (n=54) harbouring a *BRCA* mutation. The ORR was 40.7% (95% CI: 27-55) with a median duration of response (DOR) of 6.7 months (95% CI: 3.0-11.3) and PFS of 4.1 months (95% CI: 2.8-5.9). Platinum pre-treated patients showed a promising ORR of 26% (95% CI: 11-26).[30] These early results have to be confirmed in a larger trial.

TARGETED THERAPIES IN THE TREATMENT OF ADVANCED TNBC

ANGIOGENESIS INHIBITORS - BEVACIZUMAB

Bevacizumab is a monoclonal antibody against circulating vascular endothelial growth factor (VEGF), thereby interfering with the process of tumour angiogenesis. Several phase III studies have been conducted to evaluate the efficacy of using bevacizumab in MBC patients with corresponding results listed in *Table 1.*

One trial investigated the role of maintenance bevacizumab in association with capecitabine *versus* bevacizumab alone after a first-line docetaxel + bevacizumab combination (IMELDA) in HER2-negative MBC patients showing a significantly longer PFS (11.9 months *vs* 4.3 months p<0.0001) and a significant improvement of OS in the combination group (39.0 months *vs* 23.7, p=0.0003) with the price of higher toxicity. This benefit was not significant in the TNBC subgroup in terms of PFS (7.6 months *vs* 3.3 months, HR: 0.57, p=0.46) and OS (1 year OS 90% *vs* 62%, HR: 0.44, p= 0.88).[35]

Overall, these results suggest a clearly higher RR and PFS with the addition of bevacizumab to different chemotherapy regimens. However, no benefit in OS and quality of life was noticed, this is why the Food and Drug Administration

decided to withdraw approval for bevacizumab use in breast cancer. According to the available data, it is difficult to clearly define which clinical situation indicates the use of this targeted drug. Probably the most appropriate setting is first line in association with taxanes in patients with bulky disease where a quick response is needed.

TARGETING THE ANDROGEN RECEPTOR IN ADVANCED TRIPLE-NEGATIVE BREAST CANCER

Androgen receptor (AR) expression in TNBC varies widely depending on the assay used and cut-off for positivity. According to current evidence, low-grade tumours are more often AR positive.[36,37] However, the functional role of the AR pathway in TNBC remains uncertain.[38-40] AR is expressed in 70-90% of primary breast cancers.[41-42] Significant variability exists in metastatic TNBC, mainly due to a non-standardisation of the assessment – cut-off used for AR positivity (≥1% or >10%).

The first trial, showing preliminary activity of an AR antagonist (bicalutamide) in heavily pre-treated ER-negative breast cancer, demonstrated no objective response, a clinical benefit rate (CBR) at 24 weeks of 19% and a PFS of only 12 weeks. However, this trial was the first proof of principle of the use of a minimally toxic androgen blockade in advanced AR-positive TNBC.[42]

Enzalutamide is a novel targeted AR inhibitor that competitively binds to the ligand-binding domain of AR and inhibits AR translocation to the nucleus, recruitment of AR co-factors and AR binding to DNA.[43] Traina *et al.* evaluated the efficacy of this potent anti-androgen in a single-arm, phase II clinical trial in advanced AR-positive TNBC.[44] AR positivity was defined as an expression of greater than 0% by immunohistochemistry. More than 50% of the patients received enzalutamide as their first or second line. This study showed a promising CBR of 25% at 16 weeks and 20% at 24 weeks. In 75 patients with tumours having AR positivity of at least 10%, the CBRs were further improved to 35% at 16 weeks and 29% at 24 weeks. Notably, two patients had complete responses and five partial responses. The median PFS in patients with tumours having AR positivity of at least 10% was 14.7 weeks, *versus* 12.6 weeks in patients with tumours having AR positivity of greater than 0%. A predictive assay, called Predict-AR, was even more able to differentiate responsive patients: 36% CBR at 24 weeks in Predict-AR positive patients, compared to 6% in those whose tumours were Predict-AR negative. The PFS in patients with Predict-AR positive TNBC was 16 weeks, compared to 8 weeks in Predict-AR negative patients. The OS was not reached in the genomic test positive cohort.[45] Unfortunately, the phase III development of the drug was halted for unknown reasons.

Several novel anti-androgenic agents are currently under investigation in AR-positive TNBC tumours, targeting 17,20-lyase (CY17 or CYP17), which is a key enzyme in the androgen biosynthesis pathway. Orteronel (TAK-700) and VT-464 are currently in phase I/II development in AR-positive TNBC.

ANTIBODY-DRUG CONJUGATES

Sacituzumab govitecan

Sacituzumab govitecan is an antibody-drug conjugate (ADC) made from a humanised anti-Trop-2 monoclonal antibody (hRS7) conjugated with the active metabolite of irinotecan, SN-38.

Sacituzumab govitecan was evaluated in a single arm trial, including 69 TNBC patients who received a median of five prior therapies. The objective RR was as high as 30%, the median response duration was 8.9 months. Median PFS was 6.0 months and median OS 16.6 months. Grade ≥3 adverse events included neutropenia (39%), leukopenia (16%), anaemia (14%) and diarrhoea (13%); the incidence of febrile neutropenia was 7%.[46] These promising results conducted to the design of a phase III trial (ASCENT), which will recruit 328 patients that had received at least two prior lines of chemotherapy for metastatic TNBC. Patients will be randomised with 1:1 ratio to receive either sacituzumab govitecan or TPC (NCT02574455).

Glembatumumab vedotin

Glycoprotein NMB (gpNMB) is overexpressed in multiple tumours and known as a negative prognostic marker. EMERGE is a phase II study (n=124, TNBC n=39) that compared glembatumumab vedotin, a gpNMB-specific ADC, to investigator's choice chemotherapy. Both arms were similar with a less toxicity profile for the investigational drug. In patients with TNBC, the ORR was 18%. Tumours expressing gpNMB on >25% of tumour cells (40% of TNBC samples) showed a better response.[47] A phase III study (METRIC) randomised metastatic gpNMB over-expressing TNBC patients to glembatumumab vedotin *versus* capecitabine; this trial completed accrual (NCT01997333).

PARP INHIBITORS

PARP inhibitors are a group of pharmacological inhibitors of the enzyme poly ADP ribose polymerase (PARP). *BRCA*1, *BRCA*2 and PALB2 are proteins that are important for the repair of double-strand DNA breaks by the error-free homologous recombination repair pathway. Tumours deficient in repairing double-strand DNA breaks by homologous recombination, such as those with defects in *BRCA*1 and *BRCA*2,

TABLE 2. Results of the two studies OlympiAD and EMBRACA.

Study	OlympiAD[52]	EMBRACA[53]
Population	gBRCAm HER2-negative BC olaparib (N=205) vs chemotherapy (N=97)	gBRCAm HER2-negative BC talazoparib (N=287) vs chemotherapy (N=144)
ORR	59.9% vs 28.8%	62.2% vs 27.2%
mPFS	7 mo vs 4.2 mo (HR 0.58 [95% CI: 0.43-0.80]; p<0.001)	8.6 mo vs 5.6 mo (HR 0.54 [95% CI: 0.41-0.71]; p<0.0001)
OS	No difference (HR 0.90 [95% CI: 0.63-1.29]; p=0.57)	22.3 mo vs 19.5 mo (HR 0.76 [95% CI: 0.55-1.06]; p=0.11)
Common AE (>10%)	G1/2: anaemia, nausea, vomiting, fatigue, headache, cough G3/4: anaemia	G1/2: anaemia, fatigue, neutropenia, nausea, headache, thrombocytopenia G3/4: anaemia, neutropenia, thrombocytopenia

ORR: overall response rate, mPFS: median progression-free survival, OS: overall survival, AE: adverse events, mo: months, N: number of patients, CI: confidence interval, gBRCAm: germline BRCA mutation, BC: breast cancer, G: grade, HR: hazard ratio.

are highly sensitive to the blockage of single-strand DNA repair mechanisms. This effect is called 'synthetic lethality'.[48] Thus, there is a strong biological rational to use PARP inhibitors as single agent in patients with germline *BRCA1* or *BRCA2* mutations. A second role for PARP inhibitors might be in the sensitisation to the effect of chemotherapy or ionising radiation.[49,50]

Olaparib, a PARP inhibitor, firstly tested in TNBC patients in a proof of concept trial showing an ORR of 41% in the cohort assigned to 400 mg twice daily and 22% in the cohort assigned to 100 mg twice daily.[51] Subsequently, a randomised, open-label, phase III trial, OlympiAD, randomised 302 patients with HER2-negative MBC (TNBC n=150) with no more than two prior treatment lines for metastatic disease who received either olaparib 300 mg twice daily (n=205) or standard therapy, that didn't contain platinum-based agents (capecitabine, eribulin, or vinorelbine; n=97).[52] Talazoparib, another PARP inhibitor, was evaluated in a phase III trial, EMBRACA, and compared with TPC (capecitabine, eribulin, gemcitabine or vinorelbine) in patients with locally advanced or MBC. The study included 430 patients (TNBC n=190).[53] The results of the two studies, OlympiAD and EMBRACA, are summarised in the *Table 2*.

In conclusion, PARP inhibitors can now be considered as an option for the treatment of MBC patients harbouring a germline *BRCA* mutation. However, their role compared to and following platinum salts still needs to be defined.

IMMUNOTHERAPY

In recent years, overwhelming data have revealed the prognostic value of tumour-infiltrating lymphocytes (TILs) in early breast cancer.[54] Compared with ER-positive breast cancers, ER-negative disease was shown to have a higher TIL infiltration, increased mutational load and thus potentially higher immunogenicity.[55,56] Therefore, the use of immunotherapeutic strategies seems to be a promising approach in TNBC.

Most advanced immunotherapy trials in TNBC are those investigating checkpoint inhibitors alone or in combination with chemotherapy (pembrolizumab, atezolizumab and avelumab). Overall, these trials identified few patients who have a durable benefit of PD-1/PD-L1 blockade. Among the recently presented results of immune checkpoint inhibitors (CPi), pembrolizumab monotherapy was evaluated in two studies (one phase I and one phase II); avelumab was evaluated as single agent in one phase I trial; and the atezolizumab in two phase I trials.[57-61] When the CPi were used earlier in the advanced disease setting (first line) and cohorts were enriched with PD-L1-positive metastatic TNBC patients, the ORRs were higher: 18.5% in Keynote 012 and 23% in cohort B of Keynote 086 *versus* 5% in cohort A of Keynote 086 where patients were unselected for PD-L1 overexpression.[57,58] In the same manner, atezolizumab monotherapy was associated with an ORR of 10% when patients were not selected for PD-L1.[61] However, the ORR increased to 24% when patients were selected for PD-L1-positive metastatic TNBC.[60] Furthermore, the ORR in the overall metastatic TNBC population was 5.4% for patients treated with avelumab monotherapy in the JAVELIN study: a trend towards a higher ORR was seen in patients with PD-L1-posi-

TABLE 3. Selected published and ongoing trials with checkpoint inhibitors in triple-negative breast cancer.

Checkpoint inhibitors	N	PD-L1 status	Results
Pembrolizumab monotherapy[57] (keynote 012) Phase Ib Patients were heavily pre-treated	32	Recurrent or mTNBC, PD-L1-positive (>1% of tumour cells)	ORR: 18.5% Median response duration not reached (range 15 to >47 weeks) and 3 responders remaining on treatment for at least 12 months
Pembrolizumab monotherapy[58] (keynote 086) Phase II – cohort B First-line treatment	52	Recurrent or mTNBC, PD-L1-positive (>1% of tumour cells)	ORR: 23% mPFS: 2.1 mo (95% CI: 2.0-3.9); estimated 6-mo PFS rate was 29%
Avelumab monotherapy (phase Ib JAVELIN study) in mTNBC who received 0-3 prior lines[59]	58	PD-L1-positive and -negative tumours PD-L1 expression by immune cells within the tumour was associated with response to avelumab	ORR of 22.2% in the PD-L1-positive mTNBC, compared to 2.6% for TNBC and PD-L1-negative tumours
Atezolizumab monotherapy (majority of patients pre-treated)[60]	21	PD-L1-positive (≥5% of infiltrating immune cells)	ORR: 24%
Atezolizumab monotherapy (first line or pre-treated)[61]	116	Independent of PD-L1 status	ORR: 10% (when used as first line, ORR: 24% and as second line, ORR: 6%)
Pembrolizumab + eribulin Phase Ib/II in mTNBC patients who received 0-2 lines of chemotherapy[62]	89	Independent of PD-L1 status	ORR: 34.4% 7.7% of patients achieved durable stable disease
Atezolizumab + nab-paclitaxel Phase Ib in mTNBC patients who received 0-2 lines of chemotherapy[63]	24	mTNBC with PD-L1-positive (>5% of tumour cells) and PD-L1-negative status Responses were seen in both groups	ORR: 42% in all patients

N: number of patients, mTNBC: metastatic triple-negative breast cancer, PD-L1: Programmed-death ligand 1, ORR: overall response rate, CBR: clinical benefit rate, PR: partial response, CI: confidence interval, mPFS: median progression-free survival, mo: months.

tive *versus* PD-L1-negative tumour-associated immune cells in the TNBC subgroup (22.2% *vs* 2.6%).[59]

Because of the modest responses observed with monotherapy, combinations of CPi and chemotherapy were evaluated. Tolaney *et al.* conducted a phase Ib/II study to evaluate the safety and efficacy of eribulin combined with pembrolizumab in metastatic TNBC.[62] Moreover, Adams *et al.* conducted a phase Ib study combining atezolizumab with nab-paclitaxel in metastatic TNBC (*Table 3*).[63] The results of a phase III trial assessing this combination will be published soon.

The efficacy of pembrolizumab combined with chemotherapy (nab-paclitaxel, paclitaxel or gemcitabine + carboplatin) has been further investigated in a large phase III trial (KEYNOTE-355; NCT02819518).[64] This trial has completed accrual. The patients recruited in these phase III trials were unselected but stratified for PD-L1 positivity.

Relevant data is listed in *Table 3*.

CONCLUSION

The treatment of TNBC remains a challenge in medical practice and a continuously unmet clinical need. Clinicians are often facing a highly heterogeneous disease clinically and at the molecular level, implying that not all patients will benefit from the given therapeutic strategy. The mainstay of treatment remains the classical sequencing of chemotherapy regimens, including platinum-based chemotherapy in patients harbouring germline *BRCA* mutations. The only targeted drugs that seem to ameliorate the outcome of TNBC patients are PARP inhibitors, with two trials showing PFS benefit in *BRCA* mutant patients. The optimal sequencing of these agents with platinum-based chemotherapy is not clear. Checkpoint inhibitors showed promising results in early clinical trials with few long-lasting responses. The anti-tumour activity was mainly seen in the first-line setting, especially in patients over-expressing PD-L1 or those who had stromal im-

KEY MESSAGES FOR CLINICAL PRACTICE

1. Triple-negative breast cancer is an aggressive subtype characterised by an early relapse and dismal outcome despite its high sensitivity to chemotherapy.
2. Triple-negative breast cancer is a heterogeneous disease with no targetable molecular abnormalities in the majority of patients.
3. Cytotoxic chemotherapy remains the mainstay of treatment. Poly (ADP-ribose) polymerase (PARP) inhibitors showed positive results in phase III trials in patients with germline BRCA mutations.
4. Antibody-drug conjugates and immunotherapy are promising strategies, currently in advanced stage development.
5. Triple-negative breast cancer treatment is still an unmet need, and novel strategies are awaited.

mune cell infiltrations. This needs to be confirmed with larger trials, and the optimal combination strategy is still to be defined, given the low benefit with the single agent approach.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-E386.
2. Hudis CA, Gianni L. Triple-negative breast cancer: an unmet medical need. Oncologist. 2011;16(suppl 1):1-11.
3. Boyle P. Triple-negative breast cancer: epidemiological considerations and recommendations. Ann Oncol. 2012;23(suppl 6):vi7-vi12.
4. Bauer KR, Brown M, Cress RD, et al. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2- negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007;109(9):1721-8.
5. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006;295(21):2492-2502.
6. Lara-Medina F, Pérez-Sánchez V, Saavedra-Pérez D, et al. Triple-negative breast cancer in Hispanic patients: high prevalence, poor prognosis, and association with menopausal status, body mass index, and parity. Cancer. 2011;117(16):3658-69.
7. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747-52.
8. Livasy CA, Karaca G, Nanda R, et al. Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. Mod Pathol. 2006;19(2):264-71.
9. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A. 2003;100(14):8418-23.
10. Nielsen TO, Hsu FD, Jensen K, et al. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. Clin Cancer Res. 2004;10(16):5367-74.
11. Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011;121(7):2750-67.
12. Lehmann BD, Jovanović B, Chen X, et al. Refinement of triple-negative breast cancer molecular subtypes: Implications for neoadjuvant chemotherapy selection. PLoS ONE 2016;11(6):e0157368.
13. Gelmon K, Dent R, Mackey JR, et al. Targeting triple-negative breast cancer: optimising therapeutic outcomes. Ann Oncol. 2012;23(9):2223-34.
14. Kassam F, Enright K, Dent R, et al. Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. Clin Breast Cancer. 2009;9(1):29.
15. Piccart-Gebhart MJ, Burzykowski T, Buyse M, et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. J Clin Oncol. 2008;26(12):1980.
16. Rugo HS, Roche H, Thomas E, et al. Ixabepilone plus capecitabine vs capecitabine in patients with triple negative tumors: a pooled analysis of patients from two large phase III clinical studies. San Antonio, TX. 2008; Abstract 3057.
17. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377(9769):914-23.
18. Kaufman PA, Awada A, Twelves C, et al. A phase III, open-label, randomized, multi-center study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. Cancer Res. 2012;72(24 Suppl):Abstr S66.
19. Pivot X, Marmé F, Koenigsberg R, et al. Pooled analyses of eribulin in metastatic breast cancer patients with at least one prior chemotherapy. Ann Oncol. 2016;27(8):1525-31.
20. Tentori L, Graziani G. Chemopotentiation by PARP inhibitors in cancer therapy. Pharmacol Res. 2005;52(1):25.
21. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature.2005;434(7035):913.
22. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434(7035):917.
23. Carrick S, Ghersi D, Wilcken N, et al. Platinum containing regimens for met-

astatic breast cancer. Cochrane Database Syst Rev. 2004;2:CD003374.

24. Sikov WM, Berry DA, Perou DM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol. 2015;33(1):13-21.

25. Von Minckwitz G, Schneeweiss A, Loibel S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol. 2014;15(7):747-56.

26. Tutt A, Ellis P, Kilburn L, et al. The TNT Trial: A randomized phase III trial of carboplatin compared with docetaxel for patients with metastatic or recurrent locally advanced triple-negative or BRCA1/2 breast cancer. Cancer Res. 2015;75(9): Abstract S3-01.

27. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer. 2004;4(10):814-9.

28. Lord CJ, Ashworth A. BRCAness revisited. Nat Rev Cancer. 2016;16(2):110-20.

29. Chew HK, Doroshow JH, Frankel P, et al. Phase II studies of gemcitabine and cisplatin in heavily and minimally pretreated metastatic breast cancer. J Clin Oncol. 2009;27(13):2163-9.

30. Balmaña J, Cruz C, Arun BK, et al. Anti-tumor activity of PM01183 (lurbinectedin) in BRCA1/2-associated metastatic breast cancer patients: Results of a single-agent phase II trial. Ann Oncol. 2016;27(suppl 6):2230.

31. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007;357(26):2666-76.

32. Miles D, Chan A, Dirix L, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol. 2010;28(20):3239-47.

33. Robert NJ, Diéras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol. 2011;29(10):1252-60.

34. Brufsky AM, Hurvitz S, Perez E, et al. RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol. 2011;29(32):4286-93.

35. Gligorov J, Doval D, Bines J, et al. Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(12):1351-60.

36. Wilson JD, Griffin JE, Leshin M, et al. Role of gonadal hormones in development of the sexual phenotypes. Hum Genet. 1981;58(1):78-84.

37. Zhu X, Li H, Funder JW, et al. Androgen stimulates mitogen-activated protein kinase in human breast cancer cells. Mol Cell Endocrinol. 1999;152(1-2):199-206.

38. Peters AA, Buchanan G, Ricciardelli C, et al. Androgen receptor inhibits estrogen receptor-alpha activity and is prognostic in breast cancer. Cancer Res. 2009;69(15):6131-40.

39. Safarpour D, Pakneshan S, Tavassoli FA. Androgen receptor (AR) expression in 400 breast carcinomas: is routine AR assessment justified? Am J Cancer Res. 2014;4(4):353-68.

40. Vera-Badillo FE, Templeton AJ, De Gouveia P, et al. Androgen receptor expression and outcomes in early breast cancer: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(1):djt319.

41. Gucalp A, Tolaney S, Isakoff SJ, et al. Translational Breast Cancer Research Consortium (TBCRC 011). Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic breast cancer. Clin Cancer Res. 2013;19(19):5505-12.

42. Zhao TP, He GF. A phase II clinical trial of flutamide in the treatment of advanced breast cancer. Tumori. 1988;74(1):53-6.

43. Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science. 2009;324(5928):787-90.

44. Traina TA, Miller K, Yardley DA, et al. Results from a phase 2 study of enzalutamide (enza), an androgen receptor (AR) inhibitor, in advanced AR+ triple-negative breast cancer [ASCO abstract 1003]. J Clin Oncol. 2015;33(15):1003.

45. Parker JS, Peterson A, Tudor JC, et al. A novel biomarker to predict sensitivity to enzalutamide in TNBC [ASCO abstract 1083]. J Clin Oncol. 2015;33(15):1083.

46. Bardia A, Mayer I, Diamond J, et al. Efficacy and safety of anti-Trop-2 antibody drug conjugate sacituzumab govitecan (IMMU-132) in heavily pretreated patients with metastatic triple-negative breast cancer. J Clin Oncol 2017;35(19):2141-8.

47. Yardley D, Weaver R, Melisko M, et al. EMERGE: A randomized phase II study of the antibody-drug conjugate glembatumumab vedotin in advanced glycoprotein NMB-expressing breast cancer. J Clin Oncol. 2015;33(14):1609-19.

48. Ashworth A. A synthetic lethal therapeutic approach: Poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. J Clin Oncol. 2008;26(22):3785-90.

49. Gonzalez-Angulo AM, Timms KM, Liu S, et al. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res. 2011;17(5):1082-9.

50. Couch FJ, Hart SN, Sharma P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol. 2015;33(4):304-11.

51. Tutt A, Robson M, Garber JE, et al. 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;376(9737):235-44.

52. Robson M, Im S, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med. 2017;377(17):523-33.

53. Litton J, Rugo HS, Ettl J, et al. EMBRACA: A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced breast cancer and a germline *BRCA* mutation. Cancer Res 2018;78(4): Abstract GS6-07.

54. Fridman WH, Dieu-Nosjean MC, Pages F, et al. The immune microenvironment of human tumors: General significance and clinical Impact. Cancer Microenviron. 2013;6(2):117-22.

55. Loi S, Michiels S, Salgado R, et al. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. Ann Oncol. 2014;25(8):1544-50.

56. Wang Y, Waters J, Leung ML, et al. Clonal evolution in breast cancer re-

vealed by single nucleus genome sequencing. Nature. 2014;512(7513):155-60.
57. Nanda R, Chow L, Dees E, et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib Keynote-012 Study. J Clin Oncol. 2016;34(21): 2460-7.
58. Adams S, Loi S, Toppmeyer D, et al. Phase 2 study of pembrolizumab as first-line therapy for PD-L1–positive metastatic triple-negative breast cancer (mTNBC): Preliminary data from KEYNOTE-086 cohort B. J Clin Oncol. 2017;35(15):1088.
59. Dirix LY, Takacs I, Jerusalem G, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. Breast Cancer Res Treat. 2018;167(3):671-86.
60. Emens LA, Braiteh FS, Cassier P, et al. Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer. Cancer Res. 2015;75(9): Abstract PD1-6.
61. Schmid P, Cruz C, Braiteh FS, et al. Atezolizumab in metastatic TNBC: Long-term clinical outcomes and biomarker analysis. Cancer Res. 2017;77(13 Suppl):Abstract 2986.
62. Tolaney S, Savulsky C, Aktan G, et al. Phase 1b/2 study to evaluate eribulin mesylate in combination with pembrolizumab in patients with metastatic triple-negative breast cancer [Abstract P5-15-02]. EJC. 2017;72(Suppl 1):S16.
63. Adams S, Diamond JR, Hamilton EP, et al. Phase Ib trial of atezolizumab in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer. J Clin Oncol. 2016;34(15):1009.
64. Cortés J, Guo Z, Karantza V, et al. KEYNOTE-355: Randomized, double-blind, phase III study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy for previously untreated, locally recurrent, inoperable or metastatic triple-negative breast cancer (mTNBC). J Clin Oncol 2018;36(5_suppl):Abstract CT069.