CURRENT ONCOLOGY
A Canadian Cancer Research Journal

REVIEW ARTICLE

Advances in the systemic treatment of triple-negative breast cancer

J.M. Lebert MD MSc,* R. Lester MD,* E. Powell MD,* M. Seal MD,* and J. McCarthy MD*

ABSTRACT

Triple-negative breast cancer constitutes a heterogeneous group of malignancies that are often aggressive and associated with a poor prognosis. Molecular characterization, while not a standard of care, can further subtype triple-negative breast cancer and provide insight into prognostication and behaviour. Optimal chemotherapy regimens have yet to be established; however, there have been advances in the systemic treatment of triple-negative breast cancer in the neoadjuvant, adjuvant, and metastatic settings. In this review, we discuss evidence for the potential benefit of neoadjuvant platinum-based chemotherapy, adjuvant combination chemotherapy with weekly paclitaxel, and *BRCA* mutation–directed therapy in the metastatic setting. The role for adjuvant capecitabine in patients who do not achieve a pathologic complete response with neoadjuvant chemotherapy is reviewed. Future directions and data concerning novel targeted agents are reviewed, including the most recent data on PARP [poly (ADP-ribose) polymerase] inhibitors, antiandrogen agents, and immunotherapy.

Key Words Breast cancer, triple-negative breast cancer

Curr Oncol. 2018 Jun;25(S1):S142-S150 www.current-oncology.com

INTRODUCTION

Breast cancer continues to be the most common solid tumour affecting women, and it is the second leading cause of cancer-related death in women[1]. In triple-negative breast cancer (TNBC), which accounts for approximately 10%–15% of diagnosed breast cancers[2], expression of the estrogen and progesterone receptors is lacking, and the tumour is also negative for overexpression of HER2 (human epidermal growth factor receptor 2)[3,4].

Compared with the hormone receptor–positive breast cancers, TNBC has a worse prognosis, with an aggressive natural history[2], and it is more commonly seen in younger and obese women, the average age of onset being 53 years. The prevalence of TNBC is higher in premenopausal African American women[5–9]. Importantly, TNBC has a strong correlation with *BRCA1/2* mutation status, and up to 20% of TNBC patients will be carriers of a mutation[10]. Guidelines suggest screening for *BRCA* status in women with TNBC diagnosed at 60 years of age or younger (Table I).

Approximately 70% of TNBCs fall into the basal-like subtype, and most basal-like cancers are triple-negative; however, those characteristics are not mutually exclusive[19]. In a recent genomic analysis of TNBC, four subtypes were described: luminal androgen receptor, mesenchymal, basal-like immunosuppressed, and basal-like immunoactivated[20]. Of those subtypes, basal-like immunoactivated is associated with the best prognosis[20], which is in keeping with prior research showing that prognosis is better for TNBC tumours with lymphocytic infiltration[21]. The *BRCA*-mutated cancers tend to be triple-negative and generally fall into the basal subtype[22]. Tumours that do not have germline mutations in *BRCA1/2*, but that display the characteristics of *BRCA* pathway deficiency are described as having "*BRCA*ness"[23]. Those tumours are proposed to behave potentially more similarly to *BRCA*-mutated cancers in terms of natural history and response to systemic therapy. Molecular characterization of TNBC is an area of active research, but the application and relevance of that research to clinical practice has yet to be established.

At diagnosis, TNBC tumours are more likely to be T2 or T3, to be positive for lymphovascular invasion, and to have already metastasized to lymph nodes[5]. The pattern of spread is distinct from that for hormone receptor–positive tumours: TNBC has a greater propensity for brain and lung metastases, and a lower prevalence of bone metastases[8]. In a large observational prospective study of women with stages I–III breast cancer, women with TNBC were found to have worse overall survival (OS) compared with those having hormone receptor–positive, HER2-negative tumours [hazard ratio (HR): 2.72; $p < 0.0001$][8]. The difference was most pronounced in the first 2 years, the HR for OS being 8.30[8].

Correspondence to: Joy McCarthy, Dr. H. Bliss Murphy Cancer Centre, 300 Prince Philip Drive, St. John's, Newfoundland and Labrador A1B 3V6.
E-mail: joy.mccarthy@easternhealth.ca ■ **DOI:** https://doi.org/10.3747/co.25.3954

SYSTEMIC TREATMENT FOR TNBC

Neoadjuvant Setting

Neoadjuvant chemotherapy is used in the treatment of localized early-stage breast cancer with a goal of breast-conserving surgery, or for patients for whom surgery is temporarily contraindicated[13,24]. The use of chemotherapy in the neoadjuvant setting allows for a direct assessment of the *in vivo* response by clinical examination or imaging evaluation.

TABLE I Excerpts from current guidelines by major organizations for the management of triple-negative breast cancer (BCa)[11–18]

Management option	Organization	Recommendation	Level of evidence[a]
Screening and supportive care			
	ASCO	In patients with triple-negative or luminal metastatic BCa, genetic counselling and possibly *BRCA* testing should be discussed with the patient, if the results can affect the treatment decision or clinical trial entry (or both).	Expert opinion
		Risk evaluation and genetic counselling: genetic counselling should be offered if hereditary risk factors are suspected [for example, women with a strong family history of cancer (breast, colon, endometrial) or for those 60 years of age or younger with triple-negative BCa.	II, A
	NCCN	In an individual with triple-negative BCa diagnosed at 60 years of age or younger, consider referral to cancer genetics professional.	II, A
Neoadjuvant treatment			
	ESMO	The addition of a platinum compound (carboplatin) to neoadjuvant chemotherapy allows for an increase in the pCR rate in triple-negative tumours, particular those carrying deleterious *BRCA1/2* or *RAD51* mutations or those occurring in patients with a family history of breast or ovarian cancer. But the effect of those compounds on long-term outcomes is unknown.	I, B
	NCCN	The NCCN panel does not recommend the addition of carboplatin to neoadjuvant standard chemotherapy for patients with triple-negative BCa outside a clinical trial setting.	
Adjuvant treatment			
	ESMO	Triple-negative tumours benefit from adjuvant chemotherapy with the possible exception of low-risk "special histologic subtypes" such as secretory juvenile, apocrine, or adenoid cystic carcinomas.	I, A
	ASCO/CCO	When considering lymph node–negative tumours with T > 5 mm, these features should be considered high-risk (and thus the patient should be considered a candidate or chemotherapy): ■ Grade 3 ■ Triple-negative ■ Lymphovascular invasion–positive ■ An Oncotype DX recurrence score that is associated with an estimated relapse risk of 15% or more at 10 years ■ HER2 positivity In patients who can tolerate it, use of an anthracycline–taxane regimen is considered the optimal strategy for adjuvant chemotherapy, particularly in patients deemed to be high risk.	
Advanced or metastatic disease			
	ESMO	For triple-negative locally advanced BCa, anthracycline–taxane chemotherapy is recommended as initial treatment.	I, A
		In triple-negative advanced BCa patients (regardless of *BRCA* status) previously treated with an anthracycline with or without a taxane in the neoadjuvant or adjuvant setting, carboplatin (compared with docetaxel) demonstrated comparable efficacy and a more favourable toxicity profile. It is therefore an important treatment option.	I, A
		In patients with *BRCA*-associated triple-negative or endocrine-resistant metastatic BCa previously treated with an anthracycline with or without a taxane (in the adjuvant or metastatic setting, or both), a platinum regimen, if not previously administered, is the preferred option when no suitable clinical trial is available.	I, A
	ASCO	Tumour type should not be used to dictate the choice of first-line treatment. That choice should be based on efficacy, prior treatment, risk of life-threatening disease, relative toxicities, performance statue, comorbid conditions, and patient choice.	

[a] Refer to the original guidelines for their definitions of level of evidence.

ASCO = American Society of Clinical Oncology; NCCN = U.S. National Comprehensive Cancer Network; ESMO = European Society for Medical Oncology; pCR = pathologic complete response; CCO = Cancer Care Ontario.

Neoadjuvant chemotherapy results in higher rates of pathologic complete response (pCR) in TNBC than in hormone receptor–positive, HER2-negative disease (28%–30% vs. 6.7%)[25]. The rate of pCR varies according to the subtype of TNBC, with the basal-like 1 subtype having the highest frequency of pCR (52%) and the basal-like 2 and luminal androgen receptor subtypes having the lowest frequency[26]. In a prospective database analysis, response to neoadjuvant therapy and long-term survival were compared in patients with TNBC and non-TNBC[27]. In that study, the rate of pCR was found to be higher in TNBC than in non-TNBC (22% vs. 11%, $p = 0.34$); however, TNBC was associated with a decreased 3-year progression-free survival (PFS) and a decreased 3-year OS[27]. Patients who achieved a pCR showed the strongest association with positive long-term outcomes[25,27,28].

The optimal chemotherapy regimen for the neoadjuvant treatment of TNBC has not been established. Platinum-based regimens have been suggested to possibly be more active in TNBC[29]. In the Cancer and Leukemia Group B 40603 (Alliance) study, the rate of pCR was compared in patients receiving carboplatin or bevacizumab (or both) in addition to weekly paclitaxel, followed by dose-dense doxorubicin and cyclophosphamide[30]. Rates of pCR were significantly improved with the addition of either carboplatin or bevacizumab in breast-confined disease (60% vs. 44%, $p = 0.0018$, and 59% vs. 48%, $p = 0.0089$, respectively). In locally advanced disease involving both breast and axilla, only carboplatin resulted in improved rates of pCR (54% vs. 41%, $p = 0.0029$).

In the GeparSixto GBG 66 study, patients with stages II–III TNBC or HER2-positive breast cancer were treated with neoadjuvant weekly paclitaxel and non-pegylated liposomal doxorubicin, and either bevacizumab for TNBC or trastuzumab every 3 weeks for HER2-positive breast cancer, with or without the addition of weekly carboplatin (area under the curve 1.5)[31]. The study found that pCR was observed more frequently in patients with TNBC who received additional carboplatin (53.2% vs. 36.9%, $p = 0.005$); however, that result came at the expense of greater toxicities.

As did the Cancer and Leukemia Group B 40603 study, the GeoarSixto GBG 66 study reported rates of pCR and did not assess disease-free survival (DFS) and OS. However, pCR was associated with improved long-term outcomes[25,27]. Thus, although DFS and OS were not studied, some experts believe that, given the increased rates of pCR, an OS benefit can be predicted. However, controversy surrounds that assumption. As investigated in a meta-analysis by Cortazar *et al.*[28], using pCR as a surrogate endpoint for event-free survival or OS could not be validated.

Adjuvant Setting

As of February 2018, European Society for Medical Oncology guidelines do not recommend further adjuvant systemic treatment if residual disease is present after completion of neoadjuvant chemotherapy[13]. However, that principle has recently been challenged in the CREATE-X trial[32]. In that study, patients with HER2-negative disease who did not achieve a pCR with neoadjuvant chemotherapy were randomized to receive either standard of care, which included hormonal therapy or radiation therapy if indicated (or both), or the addition of oral capecitabine (1250 mg/m^2 twice daily for 14 of 21 days) for 6–8 cycles. The study included patients with both hormone receptor–positive and –negative tumours.

The primary endpoint of the study was DFS, and the secondary endpoint was OS. Collectively, statistically significant improvements in DFS and OS were observed (74.1% vs. 67.6%, $p = 0.01$, and 89.2% vs. 83.5%, $p = 0.01$, respectively). A HR of 0.59 (95% CI: 0.39 to 0.90; $p = 0.01$) was reported for OS. On subgroup analysis, the greatest benefit was observed in patients with TNBC, with the DFS rate being 69.8% in the capecitabine group compared with 56.1% in the standard-treatment group. Similarly, OS was greater for patients with TNBC in the capecitabine arm (78.8% vs. 70.3%; HR: 0.52; 95% CI: 0.30 to 0.90). Adverse events were frequent in patients taking capecitabine, with 73.4% reporting hand–foot syndrome. Dose reductions were required in 23.9% and 36.7% of the patients assigned to 6 and 8 cycles of capecitabine respectively. In contrast to the European Society for Medical Oncology guidelines, the U.S. National Comprehensive Cancer Network guidelines were updated in February 2018 and incorporate the consideration of using capecitabine in this setting[14].

A number of studies have examined the potential benefit of adjuvant treatment after neoadjuvant chemotherapy. They include a phase III study examining the use of avelumab, a monoclonal antibody inhibitor of PD-L1, in the adjuvant or post-neoadjuvant setting in high-risk patients (see NCT02926196 at http://ClinicalTrials.gov) and another phase III trial assessing pembrolizumab in patients with TNBC who have residual disease after neoadjuvant chemotherapy (see NCT02954874). Table II presents studies for TNBC patients that are currently recruiting in Canada.

For patients who do not receive neoadjuvant chemotherapy (with the possible exception of those having rare histologic subtypes), the European Society for Medical Oncology guidelines suggest treatment with adjuvant chemotherapy (Table I)[13]. Some controversy surrounds the choice of systemic chemotherapy for small tumours (≤0.5 cm) that are node-negative, and that decision must therefore be individualized[13–16]. The optimal adjuvant regimen for TNBC has not been established, but current guidelines support the use of regimens that contain an anthracycline and a taxane, if feasible (Table I)[13,16].

The GEICAM 9906 trial compared adjuvant fluorouracil–epirubicin–cyclophosphamide (FEC) with FEC-P (FEC followed by weekly paclitaxel) in lymph node–positive breast cancer[33]. That study found a 23% reduction in the risk of relapse and a 22% reduction in the risk of death with the addition of paclitaxel. On subgroup analysis, patients with TNBC were found to experience improved DFS when treated with FEC plus weekly paclitaxel compared with FEC alone (76% vs. 62%, $p = 0.0254$)[34].

The role of weekly paclitaxel was also studied in the E1199 phase III trial[35]. In that study, women with stages II–III breast cancer were treated with 4 cycles of doxorubicin–cyclophosphamide followed by paclitaxel or docetaxel every 3 weeks for 4 doses or weekly for 12 doses in a 2×2 design[35]. At the 10-year follow-up, significant improvement in DFS and OS was observed for the TNBC subgroup treated with weekly paclitaxel compared with paclitaxel every 3 weeks (HR: 0.69; $p = 0.01$) or with docetaxel in either

TABLE II Clinical trials in triple-negative breast cancer (TNBC) currently recruiting in Canada

Title	ClinicalTrials.gov identifier	Phase or study type	Intervention
A Study to Evaluate the Safety, Pharmacokinetics and Clinical Activity of RO6870810 and Atezolizumab (PD-L1 Antibody) in Participants with Advanced Ovarian Cancer or Triple Negative Breast Cancer			
	NCT03292172	Phase I	Atezolizumab
			RO6870810
A Study of Atezolizumab and Paclitaxel Versus Placebo and Paclitaxel in Participants with Previously Untreated Locally Advanced or Metastatic Triple Negative Breast Cancer (TNBC)			
	NCT03125902	Phase III	Atezolizumab (MPDL3280A), an engineered anti–PD-L1 antibody
			Atezolizumab placebo
			Paclitaxel
A Study to Investigate Atezolizumab and Chemotherapy Compared with Placebo and Chemotherapy in the Neoadjuvant Setting in Participants with Early Stage Triple Negative Breast Cancer			
	NCT03197935	Phase III	Atezolizumab (MPDL3280A), an engineered anti–PD-L1 antibody
			Placebo
			Nab-paclitaxel
			Doxorubicin
			Cyclophosphamide
			Filgrastim
			Pegfilgrastim
Study of Pembrolizumab (MK-3475) Plus Chemotherapy vs. Placebo Plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer (MK-3475-355/KEYNOTE-355)			
	NCT02819518	Phase III	Pembrolizumab
			Nab-paclitaxel
			Paclitaxel
			Gemcitabine
			Carboplatin
Study of Pembrolizumab (MK-3475) Plus Chemotherapy vs Placebo Plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs Placebo as Adjuvant Therapy in Participants with Triple Negative Breast Cancer (TNBC) (MK-3475-522/KEYNOTE-522)			
	NCT03036488	Phase III	Pembrolizumab
			Carboplatin
			Paclitaxel
			Doxorubicin
			Epirubicin
			Cyclophosphamide
			Placebo
A Study of Ipatasertib in Combination with Paclitaxel as a Treatment for Participants with PIK3CA/AKT1/PTEN-Altered, Locally Advanced or Metastatic, Triple-Negative Breast Cancer or Hormone Receptor–Positive, HER2-Negative Breast Cancer			
	NCT03337724	Phase II	Ipatasertib
		Phase III	Paclitaxel
			Placebo
Doxorubicin Hydrochloride and Cyclophosphamide Followed by Paclitaxel With or Without Carboplatin in Treating Patients With Triple-Negative Breast Cancer			
	NCT02488967	Phase III	Carboplatin
			Cyclophosphamide
			Doxorubicin Hydrochloride
			Paclitaxel
			Laboratory Biomarker Analysis

TABLE II Continued

Title	ClinicalTrials.gov identifier	Phase or study type	Intervention
A Study of PDR001 in Combination with CJM112, EGF816, Ilarisa (Canakinumab) or Mekinistb (Trametinib)			
	NCT02900664	Phase I	PDR001
			ACZ885
			CJM112
			TMT212
			EGF816
A Study to Test the Safety and Effectiveness of Nivolumab Combined with Daratumumab in Patients with Pancreatic, Non–Small Cell Lung or Triple Negative Breast Cancers, That Have Advanced or Have Spread			
	NCT03098550	Phase I	Nivolumab
		Phase II	Daratumumab
AZD8186 First Time in Patient Ascending Dose Study			
	NCT01884285	Phase I	Part A: AZD8186 monotherapy
			Part B: AZD8186 monotherapy
			Part C1: Abiraterone acetate combination with AZD8186
			Part D1: AZD2014 combination with AZD8186
			Part D2: AZD2014 combination with AZD8186
			Part C2: Abiraterone acetate combination with AZD8186
A Study of FAZ053 Single Agent and in Combination with PDR001 in Patients with Advanced Malignancies			
	NCT02936102	Phase I	FAZ053
			PDR001
Study of the Effects of Pembrolizumab in Patients with Advanced Solid Tumors (INSPIRE)			
	NCT02644369	Phase II	Pembrolizumab
Phase I/II Study of PDR001 in Patients with Advanced Malignancies			
	NCT02404441	Phase I	PDR001
		Phase II	
A Dose Escalation and Cohort Expansion Study of CD122-Biased Cytokine (NKTR-214) in Combination with Anti–PD-1 Antibody (Nivolumab) in Patients with Select Advanced or Metastatic Solid Tumors			
	NCT02983045	Phase I	Combination of NKTR-214 and nivolumab
		Phase II	
Phase 1/1b Study to Evaluate the Safety and Tolerability of CPI-444 Alone and in Combination with Atezolizumab in Advanced Cancers			
	NCT02655822	Phase I	CPI-444
			CPI-444 plus atezolizumab
A Phase 2 Study of Cediranib in Combination with Olaparib in Advanced Solid Tumors			
	NCT02498613	Phase II	Cediranib maleate
			Olaparib
A Study of RO7198457 (Personalized Cancer Vaccine [PVC]) as a Single Agent and in Combination with Atezolizumab in Participations with Locally Advanced or Metastatic Tumors			
	NCT03289962	Phase Ia/Ib	RO7198457
			Atezolizumab
Olaparib as Adjuvant Treatment in Patients with Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer (OlympiA)			
	NCT02032823	Phase III	Olaparib
			Placebo

[a] Novartis, Basel, Switzerland.
[b] GlaxoSmithKline, Brentford, U.K.

schedule (HR: 0.69; $p = 0.019$). Those findings suggest that a benefit might accrue to the addition of weekly paclitaxel to adjuvant chemotherapy in TNBC; however, that regimen was not the primary objective of the study, and thus it is difficult to base recommendations on the subgroup analysis alone.

The addition of bevacizumab to chemotherapy was studied in the adjuvant setting in the BEATRICE study[36]. No invasive DFS or OS benefit was demonstrated in that setting.

Although studies supporting the role of neoadjuvant and palliative platinum-based chemotherapy in TNBC have been published, no data in the adjuvant setting are currently available. Clinical trials investigating the role of platinum-based adjuvant chemotherapy are ongoing (for example, see NCT02488967 at http://ClinicalTrials.gov; Table II).

Metastatic Setting

Triple-negative breast cancer is associated with a high risk of distant recurrence, predominantly in the first 2 years after diagnosis[5,8]. When metastases occur, biopsy of the site of distant disease should be attempted to assess for discordance in hormone receptor and HER2 status[37]. A retrospective analysis found that 8% of tumours that were initially estrogen receptor–negative had converted to estrogen receptor–positivity when the metastatic tumour deposit was assessed for hormone receptor status[38]. No statistical discordance in HER2 receptor status was observed.

The choice of initial systemic chemotherapy should be individualized based on a number of factors, including tumour burden, rate of disease progression, performance status, previous chemotherapy exposure, and patient preferences[17,18]. With respect to agent selection, Table I describes several guideline recommendations. Although combination chemotherapy is generally avoided in the palliative setting, TNBC often results in visceral involvement and a more aggressive course, making combination chemotherapy a more frequent choice in this population[39].

Platinum-based chemotherapy has been suggested to potentially be more effective than non-platinum-based chemotherapy in metastatic TNBC. In a retrospective cohort study, longer PFS was observed in patients receiving platinum-based chemotherapy compared with non-platinum-based therapy in the first line (7.8 months vs. 4.9 months, $p < 0.001$)[40]. However, no difference in OS was observed. No improvement in PFS or OS was shown in the preliminary results of the prospective TNT study, which compared carboplatin with docetaxel in metastatic or recurrent locally advanced TNBC[41]. The TNT study randomized 376 patients with metastatic TNBC or with known *BRCA1/2* mutation to either carboplatin (area under the curve 6 every 3 weeks) or docetaxel (100 mg/m^2 every 3 weeks) for 6–8 cycles or until progression. The initial results, presented at the 2014 San Antonio Breast Cancer Symposium, showed no statistical difference in PFS or OS for the TNBC group (3.1 months vs. 4.5 months and 12.4 months vs. 12.3 months respectively). However, on subgroup analysis of *BRCA1/2* carriers, PFS was improved in those receiving carboplatin (6.8 months vs. 3.1 months). The objective response rate was also significantly higher (68.0% vs. 33.3%, $p = 0.03$). Interestingly, on subgroup analysis of basal-like malignancies by immunohistochemistry, no statistical difference in the overall response rate was evident between the two treatment arms. That finding suggests that "*BRCA*ness" might not be a reliable means of predicting the clinical response of TNBCs to certain chemotherapy agents.

BRCA Carriers and TNBC

The treatment of *BRCA* mutation–associated breast cancer and the use of directed agents for that patient subset is an active area of research. Because the *BRCA1* and *BRCA2* genes code for proteins involved in double-stranded DNA break repair, it is hypothesized that *BRCA* mutation–associated cancers might be more sensitive to chemotherapy agents that cause DNA damage, such as the platinums. Sensitivity of that kind has been shown *in vitro*[42]; however, its translation into clinical application has yet to be established. A small phase II study of cisplatin chemotherapy in *BRCA1* mutation carriers, not selected for hormone receptor status, demonstrated high efficacy for cisplatin, with an overall response rate of 80% and 9 of 20 patients achieving a complete response[43]. However, the study lacked a control group. Further research into the role of cisplatin in the treatment of metastatic TNBC and *BRCA* mutation–associated breast cancer is ongoing (NCT02595905 at http://ClinicalTrials.gov).

The impaired DNA repair pathway in *BRCA1/2* carriers can also be targeted with PARP [poly (ADP-ribose) polymerase] inhibitors, which interfere with the repair of single-stranded DNA breaks and, when combined with an already weakened repair process, can result in synthetic lethality[44]. That activity has been confirmed by *in vitro* studies, showing that tumours in carriers are in fact sensitive to PARP inhibitors[45,46]. Recently, the PARP inhibitor olaparib was studied in the setting of metastatic breast cancer in the olympiAD trial[47]. That study included 302 patients with metastatic breast cancer who had known *BRCA* mutations, who were negative for HER2 overexpression, and who had received up to 2 prior lines of chemotherapy. The patients were randomized to single-agent chemotherapy (capecitabine, eribulin, or vinorelbine every 3 weeks) or to olaparib (300 mg twice daily). The response rate was 59.9% in the olaparib group compared with 28.8% in the chemotherapy group. Furthermore, PFS was improved in the olaparib group (7.0 months vs. 4.2 months; HR: 0.58; 95% CI: 0.43 to 0.80; $p < 0.001$). Olaparib was approved in January 2018 by the U.S. Food and Drug Administration for use in *BRCA*-mutated metastatic breast cancer. In Canada, olaparib is currently approved for use only in *BRCA*-mutated ovarian, fallopian tube, or primary peritoneal cancers. A phase III Canadian Cancer Trials Group study, currently open to accrual, is examining the role of olaparib in the adjuvant setting for carriers of *BRCA1/2* mutations (see NCT02032823 at http://ClinicalTrials.gov). Other PARP inhibitors are also actively being investigated in the metastatic setting, including veliparib and niraparib (for example, NCT02595905, NCT01905592)[48]. Whether tumours that are *BRCA*-proficient or that have *BRCA* pathway impairment (*BRCA*ness) will respond to these targeted therapies is currently unknown.

The angiogenesis inhibitor bevacizumab has been examined in combination with chemotherapy agents in

the treatment of metastatic breast cancer[49,50]. Although the relevant studies demonstrated benefit in PFS, no improvement in OS was observed. Miles *et al.*[51] reported a pooled subgroup analysis of bevacizumab use in poor-prognosis groups. In the TNBC subgroup, median PFS was significantly improved with the use of bevacizumab (HR: 0.63; 95% CI: 0.53 to 0.76)[51]; however, that improvement did not translate into an OS benefit. Thus, no role for bevacizumab is accepted at this time.

FUTURE DIRECTIONS: IMMUNOTHERAPY AND TARGETED THERAPY

The role of immunotherapy in the treatment of TNBC is currently under investigation in several trials recruiting in Canada (Table II). In TNBC, strong lymphocytic infiltration or immune response has been associated with improved prognosis[52]. That observation suggests that harnessing the immune system against this disease might be beneficial. Pembrolizumab is a PD-1 inhibitor that has been shown to be effective in the treatment of several other cancers, including lung, melanoma, and bladder malignancies[53–55]. In a phase IB study of pembrolizumab in patients with advanced TNBC, only 18.5% of patients experienced a complete or partial response[56], with the duration of response varying from 15 to more than 47.3 weeks. A phase III trial of pembrolizumab in the treatment of metastatic or locally recurrent inoperable TNBC is ongoing (see NCT02819518 at http://ClinicalTrials.gov)[57]. The anti–PD-L1 antibody atezolizumab is also actively being investigated in the neoadjuvant and metastatic settings (see NCT03197935 and NCT03125902). Immunotherapy has shown great potential in a number of other disease sites, and thus the results of the foregoing trials are highly anticipated.

In a subgroup of TNBC, expression of the androgen receptor (AR) is increased[20]. The clinical relevance of AR status has yet to be established in breast cancer; however, several recent phase II studies have examined the use of anti-androgen agents in this setting. In one study, tumours from 242 patients with breast cancer negative for the estrogen and progesterone receptors were tested for AR expression[58]. Of those tumours, only 12% were found to be AR-positive. Patients whose tumours tested positive received bicalutamide 150 mg daily. The clinical benefit rate, defined as complete response, partial response, or stable disease for more than 6 months, was 19%, and the median PFS was 12 weeks (95% CI: 11 weeks to 22 weeks)[58]. A phase III evaluation of bicalutamide is still pending.

Enzalutamide is an AR signalling inhibitor that is used in the treatment of metastatic castration-resistant prostate cancer. The effect of enzalutamide has also been studied in AR-positive TNBC in a phase II trial[59]. In that trial, androgen positivity was defined as any level exceeding 0% by immunohistochemistry, and patients were further assessed for an androgen-driven gene signature by gene profiling. The clinical benefit rate was greater in patients with a positive gene signature (39% vs. 11%). Additionally, median PFS was 32 weeks compared with 9 weeks for patients testing negative. Research into the role of enzalutamide in the treatment of AR-positive TNBC is being conducted in the United States (see NCT02750358 at http://ClinicalTrials.gov).

SUMMARY

Triple-negative breast cancer constitutes a heterogeneous group of malignancies that differ in natural history and response to treatment. The mainstay of treatment continues to be chemotherapy; however, optimal chemotherapy regimens for TNBC have yet to be established.

In this article, we have reviewed the current evidence for systemic treatment for TNBC in the neoadjuvant, adjuvant, and metastatic settings. In the neoadjuvant setting, the use of platinum agents has been associated with improved rates of PCR, but OS was not reported in the associated studies[30,31]. In the recently published CREATE-X trial, an OS benefit was shown for adjuvant capecitabine in patients who do not achieve a PCR with neoadjuvant chemotherapy[32]. However, that approach has not been widely adopted in clinical practice, perhaps because of the associated toxicity. For adjuvant treatment of TNBC, two trials that added weekly paclitaxel to combination chemotherapy showed improvements in DFS[33–35]. In metastatic TNBC, preliminary results show that the response rate might be higher with platinum than with docetaxel in *BRCA* mutation–associated malignancies[40]; however, research to guide the optimal choice of systemic treatment for metastatic disease is limited. Olaparib, a PARP inhibitor, has recently been approved by the U.S. Food and Drug Administration for use in germline *BRCA*-mutated metastatic breast cancer, based on the olympiAD trial[47].

As molecular research advances an understanding of the driver mutations in this disease, more targeted treatments could become available. A number of investigational therapies hold promise, including PARP inhibitors, AR pathway inhibitors, and immunotherapy. Given those new developments, the hope is that more effective treatments and better outcomes will be achieved for patients with TNBC.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: RL has received education funding from Amgen and Eisai and fees as an advisory board member for AstraZeneca, Novartis, and Pfizer. EP has received travel funding from Roche and fees as an advisory board member for Amgen, Genomic Health, Novartis, and Pfizer. MS has received conference funding from Amgen and fees as an advisory board member for Pfizer and Shire. JM has received conference travel funding from AstraZeneca and Roche and fees as an advisory board member from Novartis and Pfizer.

AUTHOR AFFILIATIONS

*Memorial University of Newfoundland, Saint John's, NL.

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