Emerging trends in the treatment of triple-negative breast cancer in Canada: a survey

S. Verma MD MSEd,[*] L. Provencher MD MA,[†] and R. Dent MD MSc[*]

ABSTRACT

Triple-negative breast cancer (TNBC) has a poor prognosis compared to other subtypes and lacks common therapeutic targets, including HER2 and the estrogen and progesterone receptors. The clinicopathological heterogeneity of the disease and limited treatment options make clinical management particularly challenging. Here we present the results of a survey of Canadian clinical oncologists regarding treatment of TNBC, and review recent and ongoing clinical research in this area. Our survey results show that the majority of respondents use a combination of anthracyclines-taxanes as adjuvant therapy for early TNBC. For the first-line treatment of metastatic TNBC, most clinicians recommend taxanes, while single agent capecitabine and platinum-based therapies are more common for subsequent lines of therapy. Despite the ongoing development of novel targeted therapies, chemotherapy remains the mainstay of treatment for TNBC.

KEY WORDS

Triple-negative, basal-like, breast neoplasms, cancer treatment, clinical opinion, clinical research, chemotherapy, targeted therapy

1. INTRODUCTION

Triple-negative (TN) breast cancers are heterogeneous, with significant variability in morphological and pathological features. These tumors lack the most significant therapeutic markers that guide clinical management of breast cancer: human epidermal growth factor receptor 2 (HER2), estrogen receptor-alpha (ER), and progesterone receptor (PR)[1]. TN disease accounts for 12% to 17% of all breast cancers[1-3], and epidemiologic studies indicate a higher prevalence of TN tumors among younger women and those of African descent[4-6]. Clinicopathologic features of TN breast cancers (TNBCs) include young age at onset, large mean tumor size, high grade and higher incidence of node positivity at presentation compared to what is expected based on tumor size. TN status remains an independent risk factor for distant relapse and survival, with a rapid rise in distant relapse in the first three years after diagnosis[2,7]. Additionally, patients with TN breast tumors have an increased propensity for lung and brain metastases, making these tumors especially challenging to treat.

Molecular classification of breast cancer has further improved our understanding of the biology of this disease. Five intrinsic molecular subgroups of breast cancer have been described, including luminal A, luminal B, HER2-enriched, normal-like, and basal-like breast cancer (BLBC)[8]. Compared to the highly estrogen-sensitive luminal A subgroup, BLBC has significantly worse clinical outcomes with decreased recurrence free and overall survival[8]. BLBC and TNBC share many pathological, molecular, and clinical features, but they are not equivalent. Studies have demonstrated that not all TNBCs are basal-like[9,10] and not all BLBCs have a TN profile[10]. A study analyzing molecular markers differentiating TN tumor subtypes indicated that only 71% of TN tumors (n = 172) had a basal phenotype[9]. Research has also suggested that non-basal TNBC may have a more favorable prognosis[8,10,11].

A "five marker" method has been proposed, combining the absence of ER, PR and HER2 with the expression of either epidermal growth factor receptor (EGFR) or cytokeratin (CK) 5/6, to differentiate BLBC from TNBC. While this method has demonstrated specificity for basal-like cancers, the definition has not been uniformly accepted. In the absence of a consensus regarding the optimal method of defining the basal-like subgroup of patients, TN status remains a clinical surrogate.

Unlike patients with ER/PR-positive or HER2-overexpressing subtypes, systemic treatment options for patients with TNBC are limited to cytotoxic chemotherapy due to a lack of clinically-validated molecular treatment targets[12]. Standards have not

yet been developed to guide clinical decisions on the types of chemotherapy and targeted agents that should be used to treat TNBC, as trials have been conducted predominantly in unselected patient populations. However, there is emerging evidence indicating that patients with TNBC are sensitive to chemotherapy, and that some therapies directed at molecular targets frequently associated with TNBC may be effective.

The disease severity of TNBC, coupled with the lack of guidelines related to treatment, has lead us to conduct a survey of Canadian physicians to assess their approach to the diagnosis and clinical management of this breast cancer subtype. This review will discuss survey findings within the context of emerging evidence on therapeutic strategies for TNBC, and provide clinical opinions based on the authors' interpretation of the survey results.

2. METHODS

A total of 350 Canadian medical oncologists, of whom 120 specialize in the treatment of breast cancer, received 2 separate mailings of a 20-question survey addressing the clinical management of TNBC. Recipients were requested to complete and return the survey, with no incentives to encourage response. The overall survey response rate was 13% (n = 46), with the greatest proportion of respondents located in Ontario (52%, n = 24), followed by the western provinces (24%; n = 11) and Quebec (22%; n = 10). The Maritimes were minimally represented (2%; n = 1).

The first series of survey questions addressed issues related to diagnosis and incidence of TNBC. Although TNBC is universally accepted as a molecularly distinct disease, controversy remains regarding the exact definition of ER or PR negativity. Recent guidelines proposed by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) indicate ER or PR positivity if ≥ 1% of tumor cell nuclei are immunoreactive[13]. This very low threshold appropriately ensures that the greatest number of patients are offered hormone therapy. However, in the context of TNBC, a low threshold for hormone receptor (HR)-positivity may be overly limiting, preventing some TNBC patients from receiving appropriately aggressive early treatment. The most commonly used HR-negative definition in studies reviewed by Badve and colleagues in the context of TNBC[14], as well as in ongoing adjuvant TNBC trials[15], is an ER and PR protein expression level of ≤ 10% in cells. Although the more stringent ASCO/CAP guidelines for HR-negativity are acknowledged, there are still no precise surrogate markers to indicate a true basal-like phenotype[16]. Therefore, it may be necessary to consider those with ≤ 10% ER/PR expression as candidates for TN-directed treatment, to ensure that all patients with the potential to benefit are considered for more aggressive treatment and relevant targeted therapies as they evolve.

Understandably, there was considerable variability in the definition of HR-negativity among survey respondents. The majority of participants (66%) defined HR-negativity as 0% protein expression, while 23% considered ≤ 5% expression to be negative and 11% considered ≤ 10% ER/PR to be negative (Table I).

Our survey findings reflect published TNBC rates[2,3], with the majority of respondents reporting that between 10% and 20% of patients in their practices had TNBC regardless of setting. There was some variability in response, with 33% and 26% of respondents reporting fewer than 10% TNBC patients in the early and metastatic settings, respectively. Additionally, 4% and 19% of respondents reported that 21% to 30% of their patients had TNBC, in the early and metastatic settings, respectively.

Clinical Opinion: Despite variations among respondents, the definitions and rates of TNBC described are in line with those reported in the literature. ASCO/CAP guidelines consider a very low threshold of HR protein expression to indicate HR-negativity (< 1%)[13], while large clinical trials define HR-negativity as ≤ 10% cell staining[14,15]. The more stringent definition helps clinicians determine which patients may benefit from hormone therapy, but broader TNBC-specific guidelines may also be required to identify patients for clinical trial recruitment as well as TNBC-directed therapy.

3. RESULTS

3.1 Adjuvant Therapy for TNBC

Despite the poor prognosis of TNBC, studies have demonstrated that TNBC is more responsive to chemotherapy than other molecular subtypes[10,17,18]. Since common treatments for hormone receptor-positive and/or HER2-positive breast cancers are ineffective in TN disease, both National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend the use of third-generation chemotherapy, similar to that offered to other high-risk patients[12,19]. Studies have demonstrated that TNBC patients are more likely to respond to anthracycline-based[17,20] or anthracycline/taxane-based neo-adjuvant therapy, with higher pCR

TABLE I Lowest hormone receptor (HR) expression considered negative

ER/PR Level	*% Respondents (n=44)*
10%	11
5%	23
0%	66

ER = estrogen receptor; n = number of patients; PR = progesterone receptor

rates[10,21] than non-TNBC patients. However, treatment standards for use of these neo-adjuvant regimens in TNBC have yet to be established.

Although numerous large randomized trials have established the benefit of adjuvant anthracyclines and taxanes in breast cancer[22-26], the benefit of anthracyclines in TNBC subpopulations remains unclear. Findings from a pooled subgroup analysis of eight adjuvant anthracycline trials assessing outcomes by HER2 status was conducted by Gennari and colleagues, and indicated a lack of benefit for anthracyclines in HER2-negative disease[26]. Moreover, subgroup analyses of individual trials have indicated mixed results for anthracycline-based therapy in TNBC subpopulations; some studies indicate a favorable effect in basal-like or TN tumors[27,28], while others indicate a lack of benefit[23]. Even more recently, preliminary findings from a meta-analysis of five randomized trials assessing the benefits of adjuvant anthracycline-based therapy indicate a role for anthracyclines in TNBC[29].

The benefit of adjuvant taxanes is well established in the general breast cancer population. Findings from multiple subgroup analyses of large phase III adjuvant trials support a role for taxanes in the adjuvant treatment of TNBC[30-36]. In the CALGB9344/INT1048 trial, patients with TNBC or HER2-positive breast cancer attained the greatest benefit from the addition of paclitaxel to doxorubicin and cyclophosphamide[36]. Likewise, in the BCIRG 001 trial, addition of a taxane to adjuvant chemotherapy was associated with a trend towards improved three-year DFS compared to non-taxane treatment among patients with TNBC[30]. However, a recent pooled subgroup analysis of seven randomized adjuvant anthracycline-taxane trials, conducted by De Laurentiis and colleagues, suggests that the benefit of taxane-based treatment is limited to HER2-positive patients, while no significant benefit is observed among those with TNBC[37].

Further efforts to evaluate the benefit of adjuvant chemotherapy in the TNBC population are required. The ongoing phase III BEATRICE trial, now closed to accrual, is a prospective study investigating the effects of adding bevacizumab to three adjuvant chemotherapy cohorts (A alone, AT or T alone) in TNBC. Chemotherapy selection was left to the discretion of the treating physician. Although not randomized, comparison of the three chemotherapy cohorts was stratified, and may offer insight into the benefit of adjuvant anthracyclines and taxanes in TN disease[15]. Moreover, the role of individual agents, such as capecitabine, platinum-based agents and ixabepilone, are currently being evaluated in the adjuvant setting[38-42]. Findings from a recent subgroup analysis of two large, randomized adjuvant capecitabine trials indicate that the addition of capecitabine to anthracyclines and taxanes may be particularly effective in TNBC populations[39,43].

When respondents were surveyed to see which adjuvant chemotherapy they would use to treat TNBC patients in the early disease setting, the majority selected an anthracycline-taxane regimen regardless of nodal status. However, a substantial proportion of respondents considered TC a good option for node-negative disease (Table II).

Clinical Opinion: In the absence of clear guidelines, and due to the increased risk of recurrence, use of a third-generation chemotherapeutic regimen should be considered for the treatment of TNBC, regardless of nodal status. Given the higher risk of relapse in TNBC, clinicians should generally have a lower threshold to consider chemotherapy. In this context, TC may be an appropriate choice for some patients, such as the elderly, those with considerable comorbidity, and those with favorable pathology or low-grade (< grade 3) tumors. The roles of adjuvant platinum-based agents and novel agents such as ixabepilone, which have taxane-like modes of action, are areas of ongoing research.

3.2 Patient Profiling and Supportive Therapy

3.2.1 The Role of Adjuvant Bisphosphonates

The role of adjuvant bisphosphonates in early disease is unclear. Early data from the ABSCG12 trial indicates a potential benefit for zoledronic acid when combined with traditional adjuvant chemotherapy or hormonal therapy[44]. However, recently presented data from the large, randomized AZURE trial did not support these findings, as a disappointing lack of benefit was observed when zoledronic acid was combined with traditional adjuvant therapy[45]. Subgroup analyses investigating the effects of bisphosphonates in TNBC subpopulations are pending. Taking an

TABLE II Most commonly offered chemo regimens for triple-negative early breast cancer

Chemo Regimen	*Node-negative (%;* n=*45)*	*Node-positive (%;* n=*44)*
TC	40	2
AC	4	0
CMF	0	0
FEC 100	9	0
FEC 100 → Docetaxel	30	67
AC → weekly Paclitaxel	2	2
dd AC → Paclitaxel (dose alone)	15	29

AC = Adriamycin (doxorubicin), cyclophosphamide; Chemo = chemotherapy; CMF = cyclophosphamide, methotrexate, fluorouracil; FEC = fluorouracil, epirubicin, cyclophosphamide; n = number of patients; TC = Taxotere (docetaxel), cyclophosphamide

evidence-based approach, the majority of Canadian respondents did not offer adjuvant bisphosphonates to their patients. However, a small proportion of physicians (9%) did recommend bisphosphonate therapy.

3.3 Metastatic/Recurrent Disease

Clinical data suggest that a greater proportion of TNBC patients recur more rapidly than non-TNBC patients, and that recurrence more often involves the viscera and brain metastases[2,46]. Furthermore, a change in receptor profile has been observed in certain breast cancer subtypes, from the time of diagnosis to the time of relapse[47-49]. Current evidence suggests that the receptor profile of TNBC is more stable than other subtypes[48], and with fewer targeted therapeutic options, this may make the information obtained from re-biopsy of metastatic disease less useful. However, the basis for a decision to re-biopsy is multifactorial, and must include the ease of re-biopsy, suspicion of a new primary tumor, and unexpected characteristics of the disease course. When asked about their diagnostic practices for metastatic TNBC, few respondents (19%) routinely imaged the brain for metastases, and 27% routinely biopsied metastatic lesions upon relapse after adjuvant therapy. When asked whether patients were re-biopsied upon relapse, half of the respondents indicated that less than 15% of their patients were re-biopsied, while a quarter indicated that 15%–30% of patients were re-biopsied.

Clinical Opinion: As current evidence suggests that the receptor profile of TNBC is more stable than other subtypes, re-biopsy of metastatic disease may not be routinely required. However, re-biopsy should always be considered if there is a possibility of benign disease, if there is reason to suspect a new primary tumor or metastases from a different source, and any time there is clinical suspicion of a different natural history of breast cancer recurrence.

3.4 Treatment of Advanced TNBC

Historically, treatment standards for metastatic breast cancer have included re-challenging with a taxane if the disease-free interval has been sufficiently long (usually > 12 months)[50,51], and the use of single agent capecitabine or vinorelbine for those who relapse shortly (< 6-12 months) after completion of adjuvant taxane treatment[52]. However, there are no current standards for TNBC therapy in the advanced setting. When participants were asked about their recommendations for the treatment of metastatic TNBC, the majority of respondents indicated taxanes for first-line therapy (77%), while recommendations for second-line therapy were more commonly single agent capecitabine or a platinum-based regimen (Table III). The majority of respondents felt it appropriate to re-challenge with a taxane if the disease-free interval was 6 to 12 months (57%) or 13 to 24 months (37%), and most respondents indicated that they do not use bevacizumab in breast cancer. There is emerging evidence on the use of specific cytotoxics in TNBC populations. A pooled subgroup analysis of two large phase III trials assessed the benefit of adding ixabepilone to capecitabine in anthracycline-taxane pre-treated TNBC patients[53]. The study demonstrated a doubling in progression-free survival (PFS; 4.2 months vs. 1.7 months, hazard ratio = 0.63, $p < 0.0001$) and overall response rate (31% vs. 15%) with comparable overall survival (OS; 10.3 months vs. 9.0 months, hazard ratio = 0.87, $p = 0.1802$) in the 400 TNBC patients receiving ixabepilone.

TABLE III Most common treatment used for metastatic triple-negative breast cancer

Chemo Regimen	*First-line (%;* n=*46)*	*Second-line (%;* n=*44)*
Docetaxel q3w, Paclitaxel qw, Paclitaxel q3w	70	10
Nab-paclitaxel q3w	0	0
Nab-paclitaxel qw	7	4
Platinum-based chemo	13	28
Single agent capecitabine	4	38
Other single agent chemo	2	4
Anthracyclines	5	12
CMF	0	2
Doublet chemo (e.g. capecitabine + docetaxel)	0	2
Chemo + bevacizumab	0	0

CMF = cyclophosphamide, methotrexate, fluorouracil; Chemo = chemotherapy; n = number of patients; qw = weekly; q3w = every three weeks

Historically, platinum-based therapy has not figured prominently in the treatment of breast cancer; however, preclinical data suggest that TNBC may be sensitive to platinum-based regimens due to deficiencies in BRCA-associated DNA repair mechanisms[54]. Emerging clinical evidence on the use of these agents in locally advanced breast cancer and metastatic disease is summarized in Table IV and suggests favorable activity for platinum-based regimens in TNBC.

When specifically asked about the use of platinum-based therapy for advanced TNBC, the greatest percentage of respondents indicated that platinum-based agents were used in < 20% of patients receiving first or second-line treatment. In first-line therapy, 13% of respondents used platinum-based chemotherapy most often, while 28% of respondents preferred platinum-based regimens for second-line treatment (Table III). The most frequently selected

TABLE IV Results of platinum-based agent trials in early and advanced triple-negative breast cancer

Pre-operative

Trial Phase First Author	n	*Regimen*	*pCR (%)*	*ORR (%)*	*Median DFS (months)*	*Median OS (months)*
Phase II expansion - subgroup Frasci[68]	74	Cis + E + Pac with GCSF support	62	98.3	76% (5-year)	89% (5-year)
Phase II Ryan[69]	51	Cis + Bev	16	80	n/a	n/a
Phase II Silver[70]	28	Cis	21	64	n/a	n/a
Phase II Gronwald[7]	25[a]	Cis	72	100	n/a	n/a
Phase III subgroup Sirohi[41]	17	Plt + E + F(ci)	17[b]	100	68	65% (5-year)
Phase II Torrisi[71]	30	Cis + E + F(ci) → Pac	40	86	87.5% (2-year)	n/a

Advanced

Trial Phase First Author	n	*Regimen*	*ORR (%)*	*Median PFS (months)*	*Median OS (months)*
Phase III First-line+ O'Shaughnessy[64]	258	Cb + Gem	30	4.1	11.1
Rd Phase II First-line+ Baselga BALI-1[72]	58	Cis	10.3	1.5	9.4
Phase II First-line+ Kim[73]	62	Plt	27.6	4.1	10.8
Phase II First-line Wang[74]	45[c]	Gem + Cis	62.2	6.2	n/a

[a] All patients had BRCA1 mutation, 20 patients (80%) were TN.
[b] pCR rates could not be compared because 65% (11 of 17) of patients within the TN group did not undergo surgery due to CR. One out of six (17%) patients with TN tumors who underwent surgery had a pCR.
[c] Preliminary analysis of 45 patients out of 65 enrolled.
Bev = bevacizumab; Cb = carboplatin; ci = continuous infusion; Cis = cisplatin; CR = complete response; DFS = disease-free survival; E = epirubicin; F = fluorouracil; GCSF = granulocyte colony-stimulating factor; Gem = gemcitabine; n = number of patients; n/a = not available; ORR = overall response rate; OS = overall survival; Pac = paclitaxel; pCR = pathological complete response; PFS = progression-free survival; Plt = platinum-based regimens; Rd = randomized; TN = triple-negative; TTP = time to progression

platinum-based regimens for first-line therapy were cisplatin plus gemcitabine (32%), carboplatin plus paclitaxel (29%) and carboplatin plus gemcitabine (17%) (Table V). In second-line, cisplatin plus gemcitabine (30%), carboplatin plus gemcitabine (27%) and carboplatin plus paclitaxel (16%) were the most commonly used platinum-based regimens (Table V).

Clinical Opinion: Metastatic TNBC is more aggressive than other subtypes, with a median survival of less than one year. A diligent approach to the assessment, management, and treatment of this patient subgroup is therefore warranted. Clinicians should consider re-challenging with a taxane when appropriate, and platinum-based therapies may be a reasonable choice based on the emerging benefits of DNA damaging agents in the treatment of TNBC. However, much of the current data on platinum-based agents are from nonrandomized trials. Therefore caution is warranted regarding the use of platinum-based agents outside of a clinical trial, and participation in clinical trials should be encouraged.

TABLE V Most commonly used platinum-based treatment regimens

Chemo Regimen	*First-line (%; n=40)*	*Second-line (%; n=43)*
Single agent cisplatin	5	7
Single agent carboplatin	2	5
Cisplatin + gemcitabine	32	30
Cisplatin + paclitaxel	0	7
Cisplatin + vinorelbine	5	2
Carboplatin + gemcitabine	17	27
Carboplatin + paclitaxel	29	16
Carboplatin + vinorelbine	0	0
Other	10	7

Chemo = chemotherapy; n = number of patients

3.5 Targeted Therapies

TNBC has a specific biological profile with many potential molecular targets, including the overexpression of vascular endothelial growth factors (VEGFs) and EGFR and high rates of BRCA mutation or deficiency in BRCA function (a concept termed BRCAness)[55]. As a result, there is a growing body of data on the use of VEGF, EGFR, poly ADP-ribose polymerase (PARP), and mammalian target of rapamycin (mTOR) inhibitors for the treatment of TNBC.

Bevacizumab is the most widely researched of the anti-VEGF inhibitors. Multiple randomized trials have demonstrated improvements in PFS with the addition of bevacizumab to chemotherapy in first-line disease[56-58]. Recently, O'Shaughnessy and colleagues conducted a pooled subgroup analysis of 621 TNBC patients enrolled in phase III first-line bevacizumab trials[59]. The analysis demonstrated a marked improvement in PFS (8.1 months vs. 5.4 months, hazard ratio 0.68, $p < 0.0002$) with the addition of bevacizumab to chemotherapy for TNBC patients. Similar improvements in PFS among patients with TN disease were seen for the VEGF-inhibitor sorafenib. A subgroup analysis of the SOLTI-0701 trial indicated an improvement in median PFS with the addition of sorafenib to chemotherapy in TNBC (4.2 months vs. 2.5 months, hazard ratio = 0.596)[60]. Available prospective randomized data on the use of other targeted agents in TNBC is summarized in Table VI. The search for more specific and reliable biomarkers to identify patients who are more likely to benefit from treatment with anti-angiogenic agents is ongoing and critical to improving the risk- and cost-benefit ratios for anti-angiogenic therapy. The routine use of anti-angiogenic therapy in TNBC patients was not prevalent among survey respondents, although over one-third of respondents used bevacizumab in the first-line treatment of at least some of their TNBC patients, with 21% of respondents using it for more than 20% of their patients. Furthermore, fewer respondents considered bevacizumab for second-line therapy and, of those who used it, the majority did so to treat fewer than 5% of their patients.

PARP inhibitors target cells deficient in DNA repair via homologous recombination. Phase II studies of the PARP inhibitors olaparib (single agent) and veliparib in combination with temozolomide demonstrated that the benefits of these agents were limited to patients with BRCA-mutated disease, although many of these patients were also TN[61,62]. In contrast, the benefit of iniparib (BSI-201) added to chemotherapy was observed among TNBC patients regardless of BRCA-mutation status[63]. When survey respondents were presented with data from the randomized phase II trial evaluating the addition of the PARP inhibitor BSI-201 to chemotherapy (Table VII), which was presented at ASCO 2009, all respondents (100%; N = 46) described the findings as clinically meaningful.

Greater than 80% of respondents indicated that if the above findings were confirmed in a phase III trial, it would increase their use of platinum-based agents in combination with PARP-inhibitors in the first- and second-line disease settings. More recently, in the phase III trial testing the addition of BSI-201 to gemcitabine and carboplatin, the experimental arm failed to meet the co-primary endpoints of PFS (hazard ratio = 0.79 [0.65-0.98], $p = 0.027$; pre-specified alpha = 0.01) and OS (hazard ratio = 0.88 [0.69-0.1.12], $p = 0.28$; pre-specified alpha = 0.04)[64] (see Table VI). An exploratory sub-group analysis showed that improvements were apparent only in second- and third-line patients.

The identification of biomarkers and further evaluation of outcomes based on specific patient subgroups may provide insights into which patients are more likely to derive benefit from BSI-201. Moreover, a better understanding of the mechanism of action of BSI-201 may also be key to further improving outcomes, as it has been suggested that BSI-201 does not inhibit PARP 1/2, but may act through an alternate mechanism to prevent DNA double strand break repair[65].

4. SUMMARY

Clinical Opinion:

- There is a need to focus the definition of TNBC, including defining levels of ER/PR expression considered HR-positive in the context of identification and treatment of patients who may benefit from TNBC-directed therapy
- The receptor profile of TNBC is not likely to change, but re-biopsy if:
  - Access to tissue is not complicated
  - There is suspicion of a new primary tumor or potential of benign disease
  - Uncharacteristic disease course

TABLE VI Results of randomized targeted therapy trials in advanced breast cancer

	n	*Regimen*	*ORR (%)*	*PFS (months)*	*OS (months)*
PARP Inhibitors					
Rd Phase III First-line+ O'Shaughnessy[64]	261	Cb + Gem + BSI-201	34	5.1 p=0.027[a]	11.8 p=0.28[b]
	258	Cb + Gem	30	4.1	11.1
EGFR Targeted Therapies					
Rd Phase II First-line+ Carey TBCRC001[75]	31	Cetux to progression then Cetux + Cb	6[c]	2.0[d]	12[d]
	71	Cetux + Cb	17[c]		
Rd Phase II Baselga BALI-1[72]	115	Cetux + Cis	20.0	3.7	12.9
	58	Cis to progression then Cetux/Cis or Cetux	10.3	1.5	9.4
Anti-Angiogenic Agents					
Rd Phase II Heavily Pretreated Curgliano[76]	113	Sunitinib	2.7	2.0	9.4
	104	CT	6.7	2.7	10.5

[a] Prespecified alpha = 0.01
[b] Prespecified alpha = 0.04
[c] ORR measured prior to disease progression.
[d] Cetuximab + Cb cohort from both arms.
BSI-201 = iniparib; Cb = carboplatin; Cetux = cetuximab; Cis = cisplatin; CT = physician's choice chemotherapy; EGFR = epidermal growth factor receptor; Gem = gemcitabine; n = number of patients; n/a = not available; ORR = overall response rate; OS = overall survival; PARP = poly ADP-ribose polymerase; PFS = progression-free survival; Rd = randomized

TABLE VII Efficacy data for PARP inhibitors for the treatment of metastatic triple-negative breast cancer[77]

Treatment Regimen[a]	*ORR (%)*	*PFS (months)*	*OS (months)*
Chemo alone	16	3.3	5.7
Chemo + BSI 201	48	6.9	9.2

[a] Patients were randomized to receive either Carboplatin + Gemcitabine (chemo) alone or Carboplatin + Gemcitabine + BSI 201 (PARP-I; iniparib).
Chemo = chemotherapy; ORR = overall response rate; OS = overall survival; PARP = poly ADP-ribose polymerase; PFS = progression-free survival

- Treatment guidelines for early stage TNBC:
  - Adjuvant anthracycline-taxane based regimens should be considered
  - The roles of platinum-based agents and novel taxane-like agents remain to be defined
  - Treatment guidelines for advanced disease
  - The common current treatment of TNBC is chemotherapy, but there is an ongoing shift toward use of platinum-based regimens (Cisplatin/Gemcitabine or Carboplatin/Taxol)
  - Targeted therapies are in development
    - A reliable biomarker is needed to select TNBC patients likely to benefit from anti-angiogenic agents
    - PARP-inhibitors are in development and show promise for the treatment of second- and third-line TNBC

It is important to investigate common and disparate TNBC treatment strategies and practices among Canadian physicians to identify potential gaps in access to or understanding of diagnostic or therapeutic strategies that may benefit patients with TN disease. Our study addresses these questions, although limitations of the study include the small number of survey respondents ($n = 46$) and the concentration of respondents primarily in two Canadian provinces (Ontario and Quebec). The data are informative, although the lack of response from physicians in the western provinces and the Maritimes may result in a geographical bias. Another limitation of our study is the absence of survey questions regarding reimbursement for therapeutic agents, which often affects treatment choices.

To determine whether the results of our survey were comparable with the assessment of a similar group from another country, we reviewed the results of a recent survey of physicians in the United States (US) which assessed current knowledge and

barriers in the management of TNBC[66]. The U.S.-based survey was more extensive than our Canadian survey, with both qualitative (10 oncology practices) and quantitative components (completed by 67 physicians). Treatment patterns and practices were similar based on comparison of survey responses from Canadian and U.S. physicians, with most clinicians choosing anthracycline/taxane chemotherapy for early stage or locally-advanced breast cancer. Platinum-based agents and capecitabine monotherapy or combination therapy were common in the treatment of patients with metastatic TNBC, and respondents from both countries were familiar with the emerging data on the use of PARP inhibitors for TNBC. Unlike Canadian physicians, U.S. respondents more often used platinum-based or bevacizumab-based therapy for early stage TNBC, and carried out more frequent screening for brain metastases among TNBC patients who showed no neurological symptoms. Overall, these survey results indicate similar challenges in the management of TNBC among clinicians in the U.S. and Canada.

The continued development and use of targeted therapy is logical, considering the host of candidate molecular pathways that may be responsive to focused TNBC treatments. The candidate pathways include molecules such as VEGF, EGFRs, and PARPs[67], and there is a growing body of clinical research investigating novel agents. However, until these emerging agents are available for widespread clinical use, chemotherapy should remain the backbone of TNBC treatment, with specific regimen selection based on risk of relapse. It is also necessary that elegant biomarker research continue to be conducted to gain insight into the mechanisms of action of these agents, and to assess the particular subgroups of TN patients that are more likely to benefit from a given therapy.

The future holds many promising avenues for therapeutic development based on improvements in molecular profiling, advances in individualized treatment, and consideration of targets beyond the traditional receptor profile. There is an urgent need for clinicians, patients, researchers, and regulatory agencies to work together to facilitate research in TNBC populations, as treatment of this subtype is one of the foremost challenges facing the breast cancer community.

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6. CONFLICT OF INTEREST DISCLOSURES

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Correspondence to: Sunil Verma, University of Toronto, Sunnybrook Odette Cancer Centre, T-Wing, 2nd Floor, 2075 Bayview Avenue, Toronto, Ontario M2N 3E6.
E-mail: sunil.verma@sunnybrook.ca

* University of Toronto and Sunnybrook Health Sciences Centre, Toronto, ON.
† Centre des maladies du sein Dechênes-Fabia, CHA, Université Laval, Quebec City, QC.