Real-world treatment patterns and survival of patients with triple negative metastatic breast cancer in Canada

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Objective

- To generate real-world evidence on treatment patterns and overall survival by line of therapy among individuals with triple-negative *de novo* or recurrent metastatic breast cancer (mBC) diagnosed in Alberta, Canada, between 2015 and 2021

Conclusions

- These real-world data suggest persistently high unmet need among patients with triple-negative mBC (mTNBC)
- Historically, the only treatment options included conventional chemotherapy regimens, as reflected in this study
- Most patients in this study received single-agent chemotherapy as 1L and 2L, and few patients received combination chemotherapies across all lines
- Recently reimbursed therapies, such as chemotherapy with immuno-oncology agents for tumours with programmed death-ligand 1 expression, as well as utilizing antibody drug conjugates (ADC) in 2L and/or 3L, may help improve outcomes in subsets of this population; however, these could not be investigated due to the study period
- Given poor survival and short duration of treatment with current therapies in mTNBC, the need for new tumour-directed therapies is high to improve outcomes and delay recurrence

Plain Language Summary

Why did we perform this research?

- Patients with mTNBC have a poor prognosis, with an estimated median survival[a] of 9–21 months
- Few studies in Canada have explored the current types of treatments patients with mTNBC are receiving and their survival rates in Canada
- This information can help guide healthcare professionals, government bodies, and payers to inform optimal treatment decisions for patients with mTNBC

How did we perform this research?

- Researchers studied women aged ≥18 years who were diagnosed with mTNBC between 2015 and 2021
- Patients were followed from the date of diagnosis or disease (mTNBC) recurrence[b] to the earliest of December 31, 2022, last follow-up, or death from any cause
- Outcomes studied included treatment types and survival[c], by type and line (first-, second-, and third-line) of therapy

What were the findings of this research?

- First-line therapy was started in 69.5% of patients, 37.5% started a second-line therapy, and 19.2% started a third-line therapy during the study period
- Most patients received chemotherapy alone or in combination with another chemotherapy as first (90%) or second line (82.2%); however, in third-line therapy most patients received other therapies (63.6%)
- After starting first-line treatment, 33.2% of patients were still alive after 2 years and 15.9% after 5 years; these survival rates dropped even more with each new treatment line

What are the implications of this research?

- mTNBC remains an aggressive cancer, with more patients than expected being diagnosed with metastatic disease at initial diagnosis
- Traditional chemotherapy, particularly single-agent options, is associated with poor survival in patients with mTNBC
- Future research should elucidate how new tumour-directed therapies improve overall outcomes for patients with mTNBC

[a] Median survival is the amount of time after which 50% of people have died and 50% are still alive. [b] Recurrent breast cancer is cancer that has come back as metastatic (i.e., it was initially diagnosed as early stage and had not spread outside the primary location of the cancer and now it has spread). [c] Overall survival was reported as median survival and survival rates. Survival rate is a statistic that describes how long an "average" person with cancer will survive for a particular amount of time.

This study was funded by AstraZeneca. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

Poster presented at ISPOR 2025; May 13-16, 2025; Montreal, Quebec, Canada

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Introduction

- Population-based studies conducted in Canada estimate that approximately 9% of breast cancer cases are TNBC, defined as negative for the human epidermal growth factor receptor 2 (HER2) and for the hormone receptors for estrogen and progesterone[1-3]
- While most patients with TNBC are diagnosed early (only 5-6% of all TNBC cases are stage IV at diagnosis), Canadian studies have reported up to 34% patients with TNBC will recur with distant metastases[1,2,4-6]
- Prognosis among patients with mTNBC is poor, with an estimated median overall survival (OS) rate of 9–21 months, and median OS decreasing with each subsequent treatment line[1,7,8]
- This retrospective, longitudinal, observational, population-based study described treatment patterns and OS in patients from Alberta, Canada, with mTNBC
- These data on historical outcomes are intended to assist with better understanding the unmet needs in mTNBC (e.g., access to treatment) and to inform and guide treatment strategies and health policy

Methods

Study Design

- Retrospective, longitudinal, observational, population-based study

Data Source

- Population-level databases in Alberta, Canada

Study Population

- Inclusion criteria:
  - Females aged ≥18 years
  - Diagnosis of *de novo* or recurrent mTNBC between 2015 and 2021
  - Information to derive HER2– status (immunohisto-chemistry [IHC] 0, 1+, or 2+ with negative *in situ* hybridization score) and HR status (positive or negative) captured at the time of initial diagnosis

Study Timeline and Outcomes

- Index date was defined as the date of initial diagnosis for *de novo* mTNBC or the date of being classified as having recurrent mTNBC[9]
- Patients were followed from index date to December 31, 2022, last follow-up, or death from any cause (**Figure 1**)
- Outcomes included treatment patterns and survival outcomes
  - Treatment patterns included proportion of patients by therapy, lines of systemic therapy initiated (0, 1, 2, ≥3), duration of each line of systemic therapy, and time to next line of systemic therapy, and were stratified by therapy, and line of systemic therapy
  - Survival outcomes included median OS and the proportion of patients alive at 24 and 60 months; by overall population and stratified by line of systemic therapy

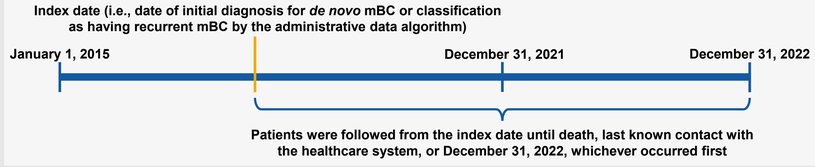
Statistical Analysis

- Demographic and clinical characteristics and treatment patterns were assessed using descriptive statistics (means, medians, standard deviations [SD], 95% confidence intervals [CI] interquartile ranges [IQR], counts, percentages)
- Variables with fewer than 10 patients/events were suppressed due to small frequency counts
- OS curves, median time-to-event estimates, and 95% CI were generated with the Kaplan-Meier method
- Log-rank *P*-values were provided where applicable

Ethical Approval

- This study was approved by the Health Research Ethics Board of Alberta and performed in accordance with the provisions of the Declaration of Helsinki and the Good Clinical Practice guidelines as defined by the International Conference on Harmonization. No patient contact was sought or made

Figure 1. Study timeline



Results

Baseline Demographics

- The study included 344 patients with mTNBC, including 120 (34.9%) with *de novo* disease (**Table 1**)

Table 1. Baseline demographic and clinical characteristics

Variable	mTNBC (N=344)
HER2 IHC score[a], n (%)	
0	122 (35.5)
1+	123 (35.8)
2+[b]	99 (28.8)
Age at diagnosis, mean (SD), years[a]	60.9 (14.7)
Rural residence (vs. urban), n (%)	47 (13.7)
Stage IV *de novo* mBC, n (%)[c]	120 (34.9)
Metastatic sites, n (%)[d]	
1	37 (39.4)
2	26 (27.7)
3+	31 (33.0)
Site of metastasis, n (%)	
Adrenal	<10
Bone	57 (48.3)
Brain	15 (12.7)
Liver	41 (34.7)
Lung	52 (44.1)
Lymph node	60 (50.8)
Peritoneal	<10
Skin	<10
Initiated treatment, n (%)[e]	239 (69.5)

[a]Refers to the index date (i.e., date of initial diagnosis for de novo cases or the date of being flagged by the algorithm as having recurrent disease). [b]IHC score of 2+ indicates HER2 IHC2+/ISH-. [c]Differentiated patients with recurrent mBC from patients with initial Stage I–III disease. [d]Captured at the time of initial (*de novo*) diagnosis, if available, and unavailable for recurrent cases. [e]Differentiated from patients who did not receive treatment for mBC.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; SD, standard deviation

Table 2. Systemic therapy and treatment duration

Line[a]	Regimen	n (%)	Duration, median (IQR), months
1L	**Total**	**239 (100.0)**	**3.0 (1.7-5.1)**
	Capecitabine	92 (38.5)	2.3 (1.6-4.6)
	Taxane	40 (16.7)	3.9 (2.4-6.5)
	Combination chemotherapy[b]	37 (15.5)	3.2 (1.8-4.6)
	Other[c]	24 (10.0)	4.3 (2.2-7.4)
	Taxane+chemotherapy	19 (7.9)	3.5 (2.3-5.3)
	Chemotherapy monotherapy[d]	17 (7.1)	3.0 (0.9-4.6)
	CEF	10 (4.2)	2.2 (2.0-2.7)
2L	**Total**	**129 (100.0)**	**2.6 (1.8-4.5)**
	Capecitabine	32 (24.8)	2.9 (1.7-4.5)
	Chemotherapy monotherapy[d]	32 (24.8)	2.0 (1.3-3.3)
	Taxane	29 (22.5)	3.2 (2.3-4.9)
	Other[c]	23 (17.8)	3.2 (2.1-7.9)
	Combination chemotherapy[b]	13 (10.1)	2.3 (1.8-3.3)
3L	**Total**	**66 (100.0)**	**3.8 (2.3-5.5)**
	Other[c]	42 (63.6)	4.6 (2.9-5.6)
	Eribulin	14 (21.2)	2.3 (1.8-3.7)
	Chemotherapy monotherapy[d]	10 (15.2)	2.8 (1.6-6.1)

[a]1L systemic therapy was classified by the start date—the earliest date of systemic therapy given on or after the index date—and the regimen—all systemic agents received within 30 days of the start date. The start date for the subsequent line of systemic therapy was defined using the earliest of the following two dates, if available: 1) date on which patient received any systemic agent not specified in the 1L regimen (note: switches in the type of taxane therapy or switches within the same class of hormone therapy were not flagged as a new line of systemic therapy); or 2) date on which there was a gap ≥240 days between successive nonhormonal systemic therapies. Agents received within 30 days of the 2L start date were used to define the 2L regimen (and so forth for 3L systemic therapy). The end date of each line of systemic therapy was defined as the earliest of the following four dates: (1) start date of the subsequent line of systemic therapy minus 1 day; (2) date of the last agent received within the line of systemic therapy, plus 28 days; (3) date of death; (4) last known date of follow-up. [b]Chemotherapy combinations in systemic therapy groupings include azacitidine+hydroxycarbamide, capecitabine+cisplatin, capecitabine+cyclophosphamide+doxorubicin+fluorouracil, capecitabine+doxorubicin, capecitabine+everolimus, capecitabine+gemcitabine, capecitabine+methotrexate, carboplatin+doxorubicin, carboplatin+eribulin+gemcitabine, carboplatin+etoposide, carboplatin+gemcitabine, carboplatin+pemetrexed, cisplatin+etoposide, cisplatin+gemcitabine, cisplatin+pemetrexed, cisplatin+vinorelbine, cyclophosphamide+doxorubicin, cyclophosphamide+doxorubicin+fluorouracil, cyclophosphamide+epirubicin, cyclophosphamide+epirubicin+fluorouracil, cyclophosphamide+fluorouracil+methotrexate, cyclophosphamide+methotrexate, and gemcitabine+vinorelbine. [c]Other therapies include AI+SERD+alpelisib, AI+pembrolizumab, AI+rituximab, SERD+alpelisib, SERM+lenvatinib, SERM+pembrolizumab, atezolizumab+capecitabine, atezolizumab+carboplatin+etoposide, atezolizumab+cyclophosphamide+doxorubicin+taxane, atezolizumab+taxane, bendamustine+fluorouracil+rituximab, bendamustine+rituximab, carboplatin+gemcitabine+pembrolizumab, carboplatin+pembrolizumab+pemetrexed, carboplatin+pembrolizumab+taxane, cyclophosphamide+doxorubicin+pembrolizumab, lenvatinib, pembrolizumab, and pembrolizumab+taxane. [d]Chemotherapy monotherapies in systemic therapy groupings include azacitidine, carboplatin, cisplatin, cyclophosphamide, doxorubicin, epirubicin, eribulin, etoposide, everolimus, fluorouracil, gemcitabine, hydroxycarbamide, methotrexate, and vinorelbine.
1/2/3L, first/second/third-line; CEF, cyclophosphamide, epirubicin, and 5-fluorouracil; IQR, interquartile range; L, line; mTNBC, metastatic triple-negative breast cancer; SERD, selective estrogen receptor degrader

Treatment Patterns

- First-line (1L) therapy was initiated in 69.5% (n=239) of patients, 37.5% (n=129) initiated a second-line (2L) therapy, and 19.2% (n=66) initiated a third-line (3L) therapy during the study period **(Table 2)**
- Median (IQR) lines of therapy were 2.0 (1.0, 3.0)
- Median time to next treatment is shown in **Table 3**
- 62.0% of patients had a time to 2L treatment of <6 months

Table 3. Time to next line of systemic therapy

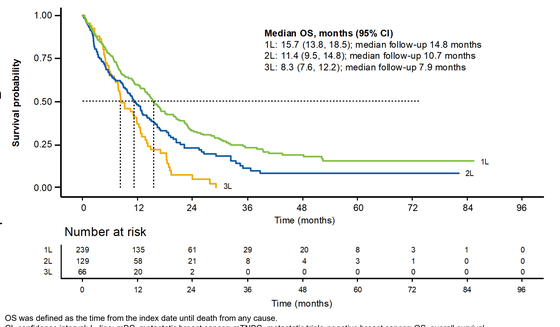
	Regimen	n	Initiated next line, n (%)	Median TTNT (IQR), months	TTNT >6 months, n (%)
1L	Overall	239	129 (54.0)	4.8 (2.6-8.4)	49 (38.0)
2L	Overall	129	66 (51.2)	4.9 (3.0-9.1)	30 (45.5)
3L	Overall	66	40 (60.6)	4.6 (2.9-7.6)	Supp.

Regimens that had <10 patients who initiated a subsequent line of systemic therapy were suppressed (Supp.) due to small cell counts.
1/2/3L, first/second/third-line; CEF, cyclophosphamide, epirubicin, and 5-fluorouracil; mTNBC, metastatic triple-negative breast cancer; IQR, interquartile range; mo, months; TTNT, time to next treatment

Survival

- Median OS (95% confidence interval) by each line of therapy is shown in **Figure 2**
- mOS by type of 1L, 2L, and 3L therapy is presented in **Table 4**
- 2- and 5-year survival rates by each line of therapy (overall, irrespective of type of therapy) were ≤40%
- There were no significant differences in median OS from initiation of 1L based on age at diagnosis (*P*=0.44), *de novo* or recurrent mTNBC (*P*=0.19), number of metastatic sites (*P*=0.23), or IHC score (*P*=0.94)

Figure 2. mOS in patients with mTNBC from initiation of 1L, 2L, and 3L systemic therapy



OS was defined as the time from the index date until death from any cause.
CI, confidence interval; L, line; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; OS, overall survival

Table 4. mOS by type of therapy

Line	Regimen	n	mOS, months (95% CI)	Survival rate, % (95% CI)	
				2 years	5 years
1L	Overall	239	15.7 (13.8, 18.5)	33.2 (27.4, 40.2)	15.9 (10.8, 23.3)
	Capecitabine	92	15.5 (13.8, 28.1)	38.0 (28.9, 50.1)	22.4 (13.9, 36.0)
	Taxane	40	20.0 (16.2, 38.1)	37.2 (24.1, 57.3)	11.6 (3.7, 36.5)
	Combination chemotherapy	37	11.2 (7.9, 16.8)	18.6 (9.0, 38.7)	9.9 (3.1, 32.0)
	Other	24	13.8 (8.0, 39.5)	35.2 (20.0, 61.7)	— (—, —)
	Taxane+chemotherapy	19	23.1 (14.3, —)	46.1 (27.9, 76.0)	27.6 (11.5, 66.2)
	Chemotherapy monotherapy	17	6.0 (5.0, 20.9)	— (—, —)	— (—, —)
	CEF	10	21.9 (15.0, —)	40.0 (18.7, 85.5)	30.0 (11.6, 77.3)
2L	Overall	129	11.4 (9.5, 14.8)	23.1 (16.4, 32.5)	8.5 (4.2, 17.4)
	Capecitabine	32	9.5 (4.7, 18.9)	18.4 (08.5, 39.8)	— (—, —)
	Chemotherapy monotherapy	32	6.7 (4.2, 13.2)	6.5 (01.7, 24.7)	6.5 (01.7, 24.7)
	Taxane	29	14.1 (12.0, 32.4)	31.0 (17.3, 55.6)	13.3 (04.1, 43.3)
	Other	23	13.3 (8.9, —)	40.1 (22.6, 71.2)	— (—, —)
	Combination chemotherapy	13	16.9 (3.2, —)	36.9 (17.7, 76.8)	18.5 (05.4, 62.8)
3L	Overall	66	8.3 (7.6, 12.2)	5.1 (1.4, 18.1)	— (—, —)
	Other	42	9.1 (7.8, 13.6)	6.2 (1.6, 23.6)	— (—, —)
	Eribulin	14	6.8 (4.9, —)	— (—, —)	— (—, —)
	Chemotherapy monotherapy	10	7.5 (1.5, —)	— (—, —)	— (—, —)

CEF, cyclophosphamide, epirubicin, and 5-fluorouracil; CI, confidence interval; mOS, median overall survival

Limitations

- The administrative data algorithm (used to identify patients with recurrent disease and to identify lines of systemic therapy) may have resulted in misclassification
- HER2 classification was based on expression at the time of initial diagnosis (i.e., at early-stage disease in those who went on to have recurrent disease) and may have changed in recurrent tumours[10]
- Small sample sizes may have reduced the confidence in clinical outcomes by treatment type
- Due to the timing of this study, treatment patterns of recently funded therapies such as ADCs directed at HER2 and TROP2 and immunotherapies plus chemotherapy could not be evaluated
- Clinical covariates of interest (e.g., performance status, smoking history, disease progression, low-grade toxicity) were not routinely captured due to the reliance on administrative data

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Acknowledgements

The authors thank Jeff Alexander (SNELL Medical Communication) for editorial assistance in the preparation of this poster.

Disclosures

JWH has received research funding from AstraZeneca, Pfizer, Rethink Breast Cancer and Novartis. **SS**, **APR**, and **ZSM** are employees of AstraZeneca. **WYC** has received research funding from AstraZeneca.