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# Treatment patterns, clinical outcomes, health resource utilization, and cost in patients with *BRCA*-mutated metastatic breast cancer treated in community oncology settings

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ABSTRACT

*Purpose:* This retrospective study of community oncology patients with breast cancer gene (*BRCA*)-mutated metastatic breast cancer (MBC) examined treatment outcomes and health resource utilization (HRU) and costs for a sample of patients with human epidermal growth factor receptor 2 (HER2)-negative disease who were either hormone receptor positive (HR+) or triple negative breast cancer (TNBC).

*Methods:* Evidence from the Vector Oncology Data Warehouse, a repository of electronic medical records/billing data and provider notes, was analyzed. Treatment outcomes were progression-free survival (PFS) and overall survival (OS) from start of first-line therapy in the metastatic setting. HRU and cost measures were collected from the time of MBC diagnosis to end of the record. HRU included hospitalizations, emergency room visits, infused/parenteral supportive care drugs, and outpatient visits. Costs were computed both as total and monthly costs.

*Results:* 57 HR+ and 57 TNBC patients (2013–2015) met inclusion criteria. Eight TNBC patients did not get treatment. HR+ patients had median first line PFS of 12.1 months and TNBC patients had 6.1 months. HR+ patients had median OS from start of first line of 38.4 months, and TNBC patients had 23.4 months. Rate of use of infused/parenteral supportive care drugs was 25.5% overall and 36.7% among TNBC patients with 15.8% among HR+ patients.

*Conclusion:* There is an unmet need in *BRCA*-mutated patients with MBC, including those with HR+ and TNBC disease. The unmet need among TNBC patients was most evident in that 12% were not treated and TNBC patients appeared to have poor treatment outcomes.

*Micro abstract:* Reviewed medical records for outcomes, resource utilization, and costs in 114 community patients with *BRCA* mutated metastatic breast cancer. 57 hormone positive (HP); 57 triple negative (TN). Results: median PFS: 12.1 months HP; 6.1 TN. HP OS was 38.4; TN 23.4. Rate of infused supportive care drugs: 25.5% HP; 36.7% TN. Patients with TN disease need better therapeutic options.

## Introduction

In 2018, it was estimated that 40,920 women in the USA will die of breast cancer, making it the second leading cause of cancer death for women after lung cancer [1]. Despite advances in the treatment of breast cancer, the prognosis for metastatic breast cancer (MBC) remains suboptimal with median survival of 20.5–60 months in first-line treatment Phase III trials depending on subtype [2–4], and slightly less in routine clinical practice [4].

Approximately 5–10% of breast cancers are attributable to pathogenic mutations in single genes that are inherited [5]. The most common breast cancer susceptibility genes, breast cancer gene 1 (*BRCA1*) and breast cancer gene 2 (*BRCA2*) are human genes that produce tumor suppressor proteins. When either of these genes is mutated, DNA damage may not be repaired properly. As a result, cells are more likely to develop additional genetic alterations that can lead to cancer. Inherited mutations in *BRCA1* and *BRCA2* increase the risk of female breast (and ovarian) cancers.

Patients with inherited *BRCA1*-mutated breast cancers are more likely to meet criteria for triple negative breast cancer (TNBC) disease

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(estrogen receptor [ER] negative, progesterone receptor [PR] negative, and human epidermal growth factor receptor 2 [HER2] negative) [6–8]. Among all breast cancers, about 12–15% are TNBC. For patients with BRCA mutation, the proportion with TNBC disease is greater than 20% [9]. In patients identified as triple negative, *BRCA1* mutations have ranged from 8.5% to 28% overall [5,10,11]. Among TNBC, *BRCA1* mutations are more commonly found than *BRCA2* [12]. In contrast, patients with *BRCA2* mutations are more likely to be ER positive [6,13].

In preclinical studies, poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors, which block the repair of DNA damage, have been found to arrest the growth of cancer cells that have *BRCA1* and/or *BRCA2* mutations [14]. PARP inhibitors have also shown substantial activity in cancer patients who carry *BRCA1/2* mutations [15,16]. Olaparib is the currently approved PARP inhibitor for *BRCA*-positive MBC. Results from another PARP inhibitor trial (EMBRCA) evaluated patients with advanced *BRCA1/2* mutation who were treated with talazoparib or physicians choice monotherapy. Progression-free survival (PFS) was significantly longer in the talazoparib group (8.6 months vs. 5.6 months; HR = 0.54, 95% CI 0.41–0.71, $P < .001$) [17]. Patients treated with this PARP inhibitor also showed less toxic effects of treatment compared to those who received traditional therapy [18]. It is expected that as more PARP inhibitors become available, the treatment landscape for patients with BRCA mutated cancers will change considerably.

The treatment patterns, effectiveness outcomes, health resource utilization (HRU) and costs in these patients are not well documented. This study examined these outcomes in real-world community oncology patients with *BRCA1/2*-mutated MBC.

## Material and methods

### *Study design*

This was a retrospective observational study using data from the Vector Oncology Data Warehouse, a repository of electronic medical record (EMR) data, billing data, and health care provider notes for cancer patients treated in community oncology settings in the United States. Over 30 practice sites from 10 oncology practices are included in the Vector Oncology Data Warehouse. These sites and practices are located primarily in Southern and Midwestern states. Specifically, records from over 250,000 cancer patients are available. The provider notes supported the collection of key information not otherwise available in structured data fields (e.g. performance status, confirmation of and dates for disease progressions, comorbidities) through review by experienced Clinical Research Nurses. The protocol for this study received institutional review board (IRB) approval from IntegReview (Austin, TX).

### *Patients*

Eligible patients met the following criteria: (1) International Classification of Diseases (ICD)-9 code of 174.x or ICD-10 code of C50.x (malignant neoplasm of breast); (2) diagnosis of Stage IV/MBC at any point in the patient record; (3) female sex; (4) documentation that the patient received *BRCA* mutation testing and was verified to be either *BRCA1* and/or *BRCA2* mutated in any location; (5) age greater than or equal to 18 years old at the time of Stage IV/MBC diagnosis. Further, eligible patients had to be confirmed to have been tested and documented to be HER2 negative. Patients with HER2-positive disease were excluded. The primary interest in this study was *BRCA*-mutated patients with MBC.

### *Study endpoints and assessments*

The primary outcome endpoints were progression-free survival (PFS) and overall survival (OS). PFS was defined as the interval from start of a line of therapy until occurrence of disease progression, death, or end of the medical record, whichever occurred first. Dates of all disease progressions after diagnosis of MBC were directly determined from radiological scan notes and medical progress notes. OS was defined as the interval from start of first-line therapy for MBC until death. Dates of death were determined from the medical record and Social Security Death Index.

HRU measures and cost measures were collected from the time of MBC diagnosis to the end of the medical record. HRU included frequency of hospitalizations, emergency room visits, infused/parenteral supportive care drugs (e.g., saline, granulocyte colony stimulating factor drugs, anti-anemia drugs, anti-emetic drugs, etc.), and outpatient office visits.

Costs were computed both as total and monthly costs and included hospitalization, emergency room visits, office visits, other procedures (e.g. radiographs, needle biopsies, urinalysis, scans, blood tests, portacath, etc.), other infused/parenteral supportive care drugs (see above), systemic anti-cancer drugs (chemotherapies, hormone therapies, targeted therapies), and all other drugs delivered (not supportive care and not anti-cancer). Hospitalization events were matched to breast cancer patients in the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) [19]. Events were matched by admission diagnoses or procedural reasons for hospitalization where admitting diagnosis was not reported, length of stay (LOS), age ± 3 years, sex, and race category, with priority of matching in the listed order. Median costs of matched HCUP events were used as cost estimates for study hospitalization events. The cost of procedures was estimated based on a published national median price schedule, with matching of procedure codes in the study to the published schedule. For procedures that did not have a match, billing records were utilized to estimate cost, with billing charged amounts multiplied by an average charge-to-cost ratio, which itself was calculated from those procedures that did have matches. Patient total procedure and office visit costs were calculated as the sum of costs for the study period. The average wholesale prices from Red Book for medications were used to estimate each medication cost [20].

Other study variables collected as part of this investigation included patient demographic (age, race, sex) and clinical characteristics (stage and year at initial diagnosis, histology, year of MBC diagnosis, tumor grade, menopausal status at initial and MBC diagnosis, ER and PR status, performance status, sites of distant metastases, *BRCA1* and *BRCA2* status, comorbidity summary). Treatment patterns were also examined for up to three lines of treatment following MBC diagnosis.

### *Statistical analysis*

Descriptive statistics were used to describe the patient sample and the rates of different treatment patterns.

Unadjusted PFS and OS were calculated using Kaplan–Meier methods. Multivariate Cox regression models with covariates (age, race [minority/unknown vs. white], performance status [impaired vs. unimpaired]), bone metastases (present vs. absent) were also used to examine PFS and OS.

Logistic regression analyses were used to identify predictors of hospitalization, emergency room visit, and use of qualifying infused/parenteral supportive care drugs, controlling for patient demographic and clinical characteristics. Poisson regression was used for modeling total number of office visits.

Per patient total cost for the study period was calculated as the sum of costs across the categories of cost described above. Average monthly cost of care in the study period was calculated. In addition to descriptive statistics, overall total cost and monthly total cost were analyzed using generalized linear regression with gamma distribution and log-link function by controlling for demographic and clinical covariates.

**Table 1**
Demographic and clinical characteristics of *BRCA*-mutated patients with TNBC or HR+ metastatic breast cancer.

| Characteristic | TNBC $n = 57$ | HR+ $n = 57$ | Overall $N = 114$ |
|---|---|---|---|
| Age (years) at mets diagnosis | | | |
| Mean (SD) | 48.2 (12.72) | 50.9 (11.52) | 49.5 (12.15) |
| Race category, *n* (%) | | | |
| Caucasian | 46 (80.7) | 44 (77.2) | 90 (78.9) |
| Minority/unknown | 11 (19.3) | 13 (22.8) | 24 (21.1) |
| BMI (kg/m$^2$) at mets diagnosis | | | |
| Mean (SD) | 29.0 (7.30) | 28.3 (6.76) | 28.7 (7.02) |
| Insurance category, *n* (%) | | | |
| Neither public nor private | 3 (5.3) | 3 (5.3) | 6 (5.3) |
| Private insurance only | 30 (52.6) | 22 (38.6) | 52 (45.6) |
| Private and public insurance | 13 (22.8) | 17 (29.8) | 30 (26.3) |
| Public insurance only | 10 (17.5) | 13 (22.8) | 23 (20.2) |
| Unknown/undocumented | 1 (1.8) | 2 (3.5) | 3 (2.6) |
| Region, *n* (%) | | | |
| Midwest | 19 (33.3) | 16 (28.1) | 35 (30.7) |
| South | 38 (66.7) | 41 (71.9) | 79 (69.3) |
| Age (years) at mets diagnosis | | | |
| Mean (SD) | 48.2 (12.72) | 50.9 (11.52) | 49.5 (12.15) |
| Stage of disease at initial diagnosis, *n* (%) | | | |
| Stage I | 7 (12.3) | 7 (12.3) | 14 (12.3) |
| Stage II | 28 (49.1) | 17 (29.8) | 45 (39.5) |
| Stage III | 11 (19.3) | 14 (24.6) | 25 (21.9) |
| Stage IV | 6 (10.5) | 12 (21.1) | 18 (15.8) |
| Undocumented | 5 (8.8) | 7 (12.3) | 12 (10.5) |
| Histology at initial diagnosis, *n* (%) | | | |
| Ductal | 52 (91.2) | 43 (75.4) | 95 (83.3) |
| Inflammatory | 3 (5.3) | 1 (1.8) | 4 (3.5) |
| Lobular | 0 | 5 (8.8) | 5 (4.4) |
| Mixed, lobular-ductal | 0 | 1 (1.8) | 1 (<1) |
| Other | 0 | 4 (7.0) | 4 (3.5) |
| Undocumented | 2 (3.5) | 3 (5.3) | 5 (4.4) |
| Year of initial BC diagnosis, *n* (%) | | | |
| ≤2000 | 7 (12.3) | 12 (21.1) | 19 (16.7) |
| 2001–2005 | 5 (8.8) | 8 (14.0) | 13 (11.4) |
| 2006–2010 | 24 (42.1) | 19 (33.3) | 43 (37.7) |
| 2011–2015 | 20 (35.1) | 17 (29.8) | 37 (32.5) |
| ≥2016 | 1 (1.8) | 1 (1.8) | 2 (1.8) |
| Year of MBC diagnosis, *n* (%) | | | |
| ≤2000 | 1 (1.8) | 1 (1.8) | 2 (1.8) |
| 2001–2005 | 2 (3.5) | 9 (15.8) | 11 (9.6) |
| 2006–2010 | 24 (42.1) | 13 (22.8) | 37 (32.5) |
| 2011–2015 | 27 (47.4) | 31 (54.4) | 58 (50.9) |
| ≥2016 | 3 (5.3) | 3 (5.3) | 6 (5.3) |
| Tumor grade at initial diagnosis, *n* (%) | | | |
| Grade 1 | | 1 (1.8) | 1 (<1) |
| Grade 2 | 9 (15.8) | 27 (47.4) | 36 (31.6) |
| Grade 3 | 46 (80.7) | 21 (36.8) | 67 (58.8) |
| Undocumented | 2 (3.5) | 8 (14.0) | 10 (8.8) |
| Menopausal status at initial BC diagnosis, *n* (%) | | | |
| N/A (*de novo* Stage IV/ metastatic breast cancer) | 6 (10.5) | 12 (21.1) | 18 (15.8) |
| Postmenopause | 9 (15.8) | 11 (19.3) | 20 (17.5) |
| Premenopause | 17 (29.8) | 13 (22.8) | 30 (26.3) |
| Undocumented | 25 (43.9) | 21 (36.8) | 46 (40.4) |
| Menopausal status at MBC diagnosis, *n* (%) | | | |
| Perimenopause | | 2 (3.5) | 2 (1.8) |
| Postmenopause | 33 (57.9) | 31 (54.4) | 64 (56.1) |
| Premenopause | 17 (29.8) | 14 (24.6) | 31 (27.2) |
| Undocumented | 7 (12.3) | 10 (17.5) | 17 (14.9) |
| Hormone receptor status, *n* (%) | | | |
| HR+ | 0 | 57 (100.0) | 37 (32.5) |
| ER+, PR- | 0 | 18 (31.6) | 18 (15.8) |
| ER+, PR undocumented | 0 | 1 (1.8) | 1 (0.9) |
| ER-, PR+ | 0 | 1 (1.8) | 1 (0.9) |
| ER-, PR- | 57 (100.0%) | 0 | 57 (50.0%) |
| ECOG, *n* (%) | | | |
| 0 | 18 (31.6%) | 15 (26.3) | 33 (28.9) |
| 1 | 12 (21.1%) | 9 (15.8) | 21 (18.4) |
| 2 | 2 (3.5%) | 4 (7.0) | 6 (5.3) |
| Undocumented | 25 (43.9%) | 29 (50.9) | 54 (47.4) |
| Composite performance status, *n* (%) | | | |
| Impaired | 2 (3.5) | 4 (7.0) | 6 (5.3) |
| Not impaired | 55 (96.5) | 53 (93.0) | 108 (94.7) |
| Site(s) of distant mets at MBC, *n* (%) | | | |
| Bone | 29 (50.9) | 22 (38.6) | 51 (44.7) |
| Brain | 7 (12.3) | 7 (12.3) | 14 (12.3) |
| Breast dermis | 0 | 1 (1.8) | 1 (0.9) |
| Chest wall | 9 (15.8) | 3 (5.3) | 12 (10.5) |
| Colon | 1 (1.8) | 0 | 1 (0.9) |
| Contralateral breast | 1 (1.8) | 0 | 1 (0.9) |
| Distant lymph node(s) | 13 (22.8) | 22 (38.6) | 35 (30.7) |
| Liver | 14 (24.6) | 16 (28.1) | 30 (26.3) |
| Lung | 11 (19.3) | 16 (28.1) | 27 (23.7) |
| Mediastinum | 1 (1.8) | 0 | 1 (0.9) |
| Other | 4 (7.0) | 5 (8.8) | 9 (7.9) |
| Pleural | 1 (1.8) | 5 (8.8) | 6 (5.3) |
| Uterus | 0 | 1 (1.8) | 1 (0.9) |
| *BRCA1* test, *n* (%) | | | |
| Negative | 10 (17.5) | 23 (40.4) | 33 (28.9) |
| Positive | 40 (70.2) | 18 (31.6) | 58 (50.9) |
| Positive or undocumented | 1 (1.8) | | 1 (<1) |
| Undocumented | 6 (10.5) | 16 (28.1) | 22 (19.3) |
| *BRCA2* test, *n* (%) | | | |
| Negative | 25 (43.9) | 11 (19.3) | 36 (31.6) |
| Positive | 16 (28.1) | 39 (68.4) | 55 (48.2) |
| Positive or undocumented | 1 (1.8) | | 1 (<1) |
| Undocumented | 15 (26.3) | 7 (12.3) | 22 (19.3) |
| *BRCA* status, *n* (%) | | | |
| *BRCA1* unknown, *BRCA2*+ | 6 (10.5) | 16 (28.1) | 22 (19.3) |
| *BRCA1*+, *BRCA2* unknown | 15 (26.3) | 7 (12.3) | 22 (19.3) |
| *BRCA1*+, *BRCA2*- | 25 (43.9) | 11 (19.3) | 36 (31.6) |
| *BRCA1*-, *BRCA2*+ | 10 (17.5) | 23 (40.4) | 33 (28.9) |
| Positive or undocumented | 1 (1.8) | | 1 (<1) |
| Comorbidity summary, *n* (%) | | | |
| Any comorbid condition | 18 (31.6) | 11 (19.3) | 29 (25.4) |
| Diabetes | 8 (14.0) | 5 (8.8) | 13 (11.4) |
| Chronic obstructive pulmonary disease | 5 (8.8) | 2 (3.5) | 7 (6.1) |

*BRCA*, breast cancer gene; BC, breast cancer; BMI, Body Mass Index; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HR, hormone receptor; MBC, metastatic breast cancer; PR, progesterone receptor; SD, standard deviation; TNBC, triple negative breast cancer.

## Results

The study sample included 114 *BRCA*-mutated patients with MBC and comprised 57 TNBC and 57 hormone receptor positive (HR+). All patients were confirmed to be HER2 negative. In the overall sample, 59 patients were *BRCA1* positive and 55 were *BRCA2* positive, and none had both mutations. This was a convenience sample of all available patients who met the aforementioned inclusion criteria, and it was coincidental that each of the two groups had an equal number of patients.

### *Patient characteristics*

Table 1 shows demographic and clinical characteristics of the patient sample. Average age was 49.5 years (range, 25–79), and the majority (79%) were Caucasian/white. The largest proportion (46%) had private insurance only. As would be expected from the Vector Oncology Data Warehouse, most of the patients (69%) were from the Southern region of the USA. Most patients (70%) were initially diagnosed from 2006 to 2015 with ductal carcinoma (83%). At MBC diagnosis, most

patients were unimpaired (95%) using either known Eastern Cooperative Oncology Group (ECOG) performance status 0–1 or absence of text-based EMR information indicating impairment.

For patients with HR+ disease, nearly half (47%) had Grade 2 tumors, and for patients with TNBC disease, Grade 2 tumors were observed in 16% of patients. Regarding Grade 3 tumors, the rate among patients with HR+ disease was 37% and for patients with TNBC disease, the rate of Grade 3 tumors was 81%. With respect to *BRCA1* mutation, 31.6% of the patients with HR+ disease had this form of the mutation, and 70.2% of the patients with TNBC disease had this form of the mutation. Regarding rates of *BRCA2*-positive disease, patients with HR+ disease showed 68.4% with this form of the mutation, and patients with TNBC disease showed a rate of 28.1% with this form of the mutation. The proportions of patients with any comorbidity were: HR+ 19.3% and TNBC 31.6%. The most common comorbidity overall was diabetes (11.4%) followed by chronic obstructive pulmonary disease (6.1%).

*Treatment patterns*

Eight patients with TNBC disease did not receive treatment in the metastatic setting. In patients with TNBC disease, the most common first line treatments in the metastatic setting were: bevacizumab containing ($n = 10$; 20.4%), capecitabine-containing ($n = 10$; 20.4%), carboplatin/gemcitabine ($n = 8$; 16.3%), carboplatin plus other ($n = 7$; 14.3%), and paclitaxel-containing ($n = 5$; 10.2%). In second line ($N = 34$), the most common treatments were capecitabine-containing therapy ($n = 7$; 20.6%) and carboplatin/gemcitabine ($n = 5$; 14.7%). In third line ($N = 28$), the most common treatments were capecitabine-containing therapy ($n = 7$; 25%) and paclitaxel-containing therapy ($n = 5$; 17.9%). For patients with TNBC, a sizeable proportion in both second line (23.6%) and third line (28.6%) received treatments labeled "Other therapies" because treatment regimens were mostly unique combinations not repeated ($n < 2$).

In patients with HR+ disease, the most common first line treatments were: endocrine therapies; aromatase inhibitors ($n = 14$; 24.6%) (anastrozole-containing $n = 3$, exemestane-containing $n = 4$, letrozole-containing $n = 7$); fulvestrant-containing ($n = 10$; 17.5%); tamoxifen ($n = 7$; 12.3%), and capecitabine-containing ($n = 5$; 8.8%). In second line ($N = 36$), the most common treatments were aromatase inhibitors ($n = 12$; 33.3%), fulvestrant-containing therapy ($n = 7$; 19.4%), and capecitabine-containing therapy ($n = 4$; 11.1%). In third line ($N = 30$), the most common treatments were aromatase inhibitors ($n = 15$; 50%), fulvestrant-containing therapy ($n = 3$; 10.0%), and capecitabine-containing therapy ($n = 4$; 13.3%).

To reflect more recent treatment patterns, we also conducted the analysis using data only from 2013 to 2015. The pattern showed that for patients with TNBC disease, the most common treatment in first line was carboplatin plus other agent. In second line, the most common treatment was carboplatin with gemcitabine, and, unlike in the full data set, there was no use of bevacizumab-containing regimens in first line. For patients with HR+ disease, the most common treatment (2013–2015) in first line was aromatase inhibitors or fulvestrant, and in second line was capecitabine or fulvestrant.

*PFS and OS in first, second, and third lines*

Analyses of outcomes excluded eight patients with TNBC disease who did not receive treatment. Patients with HR+ disease had median PFS in first line of 12.1 months (95% confidence interval [CI], 7.1–14.5) and patients with TNBC disease had median PFS of 6.1 months (95% CI, 4.2–9.4). As shown in Fig. 1 and confirmed by inspection of the life table (not shown), the Kaplan–Meier plot for HR+ never went below the plot for TNBC. Analyses of PFS respectively from start of second and third line showed shorter PFS than in first line.

As shown in Fig. 2, patients with HR+ disease had median OS of 38.4 months (95% CI, 28.9–67.4) and patients with TNBC disease had median OS of 23.4 months (95% CI, 15.4–26.4) from the start of first line treatment. As was the case for subsequent analyses of PFS, so for OS, there were shorter medians for OS from either start of second line or start of third line as compared with OS from the start of first line.

*Health resource utilization and cost*

HRU rates for different categories of care are shown in Table 2. HRU rates of care are shown for first line treatment for MBC. Overall, 40.6% of patients experienced hospitalization in this period. Most of the total patient sample (84.9%) did not have any emergency room visits. Rate of use of infused/parenteral supportive care drugs was 25.5% overall and 36.7% among TNBC patients with 15.8% among HR+ patients. Median number of office visits was 10.

Average monthly costs of care in first line treatment are shown in Table 3. Monthly average cost for hospitalization was $4291. Emergency department monthly costs were $626 among the HR+ patients and $217 among the TNBC patients. The average cost of office visits was $132 per month. Average monthly cost of other procedures was $1222 overall. Mean cost for other infused/parenteral supportive care drugs was $950 among TNBC patients and $309 among HR+ patients. For the cost of all other drugs, the average among HR+ patients was $1974 and $360 among TNBC patients. Mean monthly cost of anticancer systemic therapy was $9560. The overall average monthly cost of care for all categories and total sample was $17,354.

A generalized linear regression analysis to identify predictors of monthly total cost of care showed that performance status (impaired vs. not impaired) was associated with higher average monthly cost (estimate 1.114, $P = .041$), and racial status minority/unknown vs. Caucasian/white was also associated with higher average monthly cost (estimate .578, $P = .46$).

## Discussion

This retrospective observational study included patients with *BRCA*-mutated MBC treated in the community oncology setting. The study sample was relatively small. The goal of the study was to describe treatment patterns and outcomes without formal comparison for a convenience sample of *BRCA*-mutated patients. This included patients with HR+ disease and patients with TNBC disease, all of whom were confirmed to be HER2 negative.

In general, patients with TNBC are widely recognized to have worse outcomes than other breast cancer patients [21,22], and this general pattern was reflected in this sample of patients with germline *BRCA*-mutated MBC. Patients with TNBC disease did show PFS in first line treatment with a median of 11.53 months, and patients with HR+ disease showed a median PFS of 20.16 months. A similar pattern was observed descriptively for OS, with median OS from the start of first line of 23.43 months and 38.41 months for patients with TNBC and HR+, respectively. In this small sample, some 12% of patients with TNBC disease in the metastatic setting were not treated. In general, outcomes from *BRCA*-mutated patients seem to mirror those of the same subtype without mutation. For example, in clinical trials, patients with metastatic TNBC are known to have shorter median OS in the range of 12–14 months [23], compared to patients with HR+ disease where median OS ranges from 26 to 48 months [24,25].

As an observational retrospective study, this investigation had limitations. The sample size was relatively small, and in order to obtain data on a larger number of patients, we included the past 10 years of data. It is clear from subset analyses (2013–2015) that the treatment patterns were different in the most recent 3 years compared with previous years, reflecting dynamic shifts in treatment patterns over the course of this study. This sample was also restricted to patients treated in the community oncology setting and as a result, may not be representative of what could be expected from patients treated in other

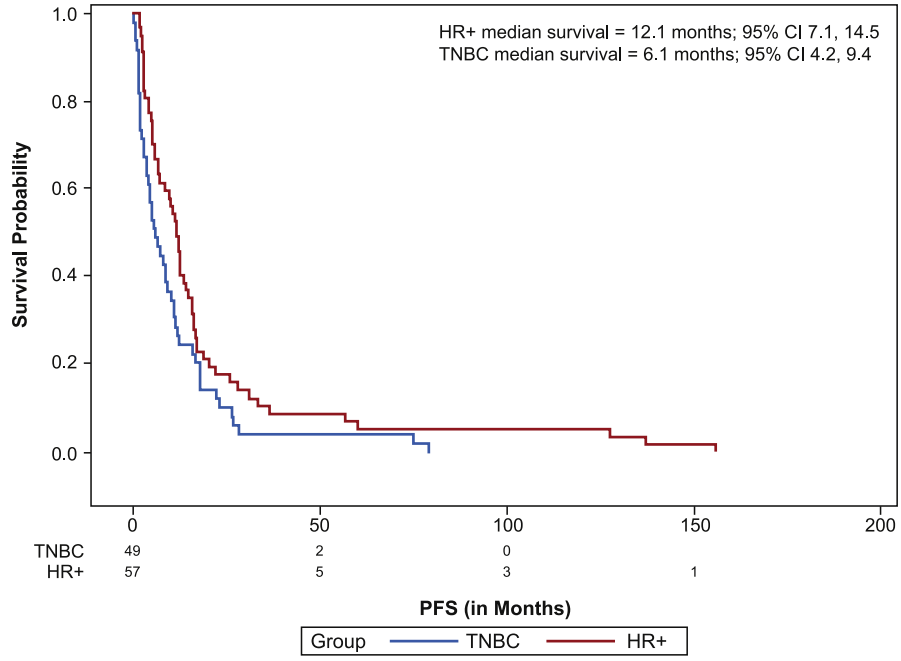


**Fig. 1.** Progression-free survival from initiation of first line treatment for patients with TNBC and HR+ *BRCA*-mutated metastatic breast cancer.

settings such as research and academic centers. The study period preceded the approval of newer therapies (e.g. PARP inhibitors), which may significantly influence future treatment practice patterns. Also, cost estimations used in this study may differ from cost values derived from actual payer records, which were not available for this sample of *BRCA*-mutated MBC patients.

## Conclusion

There is clearly an unmet need in treatment of *BRCA*-mutated MBC, and this is especially true for those with TNBC who do not have the options of hormone treatments and anti-HER2 agents. With the advent of agents that specifically target *BRCA1* and *BRCA2* mutations, the potential to improve outcomes for MBC patients carrying this genetic alteration is feasible, regardless of breast cancer subtype.

## Clinical practice points

- Results from this study of community oncology patients highlight an unmet medical need of patients with *BRCA* mutated metastatic breast cancer, especially those with triple negative (TN) disease.
- Median first line PFS for patients with hormone positive (HP) disease was 12.1 months and 6.1 months for TN patients. Median OS was 38.4 months for HP and 23.4 months for TN.
- Rate of use of infused/parenteral supportive care drugs was 25.5% overall and 36.7% among TN patients with 15.8% in HP patients.

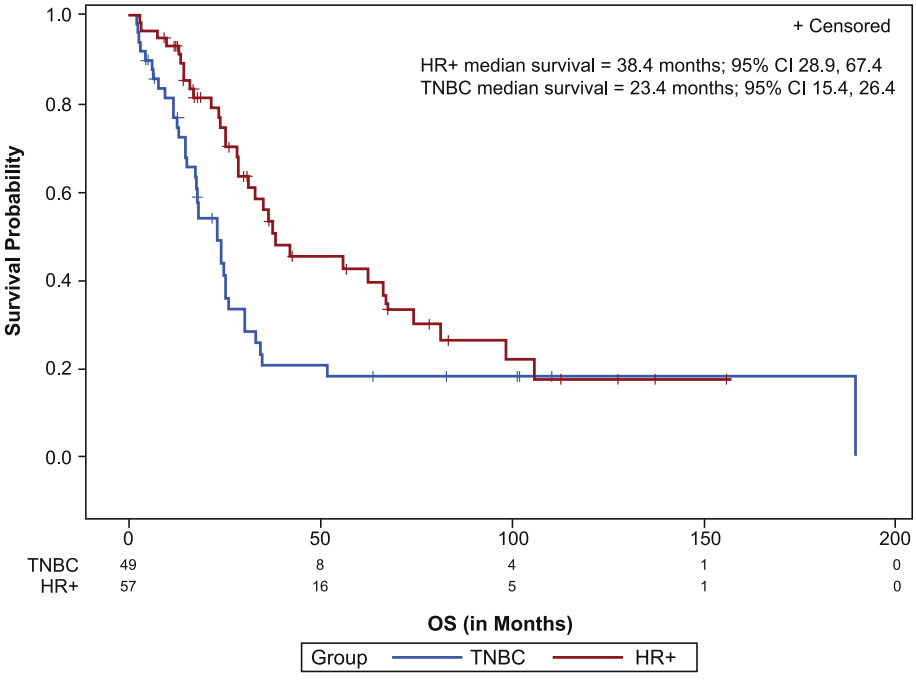


**Fig. 2.** Kaplan–Meier plot for median overall survival from initiation of first line treatment for patients with TNBC and HR+ *BRCA*-mutated metastatic breast cancer.

**Table 2**
Frequencies of different categories of health resource utilization for *BRCA*-mutated patients with TNBC or HR+ metastatic breast cancer.

| Category of health care | TNBC $n = 49$ | HR+ $n = 57$ | Overall $N = 106$ |
|---|---|---|---|
| Hospitalization | | | |
| No | 29 (59.2%) | 34 (59.6%) | 63 (59.4%) |
| Yes | 20 (40.8%) | 23 (40.4%) | 43 (40.6%) |
| Emergency room visits | | | |
| No | 45 (91.8%) | 45 (78.9%) | 90 (84.9%) |
| Yes | 4 (8.2%) | 12 (21.1%) | 16 (15.1%) |
| Infused/parenteral supportive care | | | |
| No | 31 (63.3%) | 48 (84.2%) | 79 (74.5%) |
| Yes | 18 (36.7%) | 9 (15.8%) | 27 (25.5%) |
| Office visits | | | |
| Mean | 13.5 | 11.2 | 12.2 |
| Median | 12.0 | 9.0 | 10.0 |

*BRCA*, breast cancer gene; HR+, hormone receptor positive; TNBC, triple negative breast cancer.

**Table 3**
Average Monthly Costs by Category of Care for *BRCA*-Mutated Patients with TNBC or HR+ Metastatic Breast Cancer.

| Category of health care | TNBC $n = 49$ | HR+ $n = 57$ | Overall $N = 106$ |
|---|---|---|---|
| Hospitalization | $4080.90 | $4472.00 | $4291.20 |
| Emergency room visits | $217.20 | $625.60 | $436.80 |
| Office visits | $159.50 | $108.40 | $132.00 |
| Other procedures | $1238.50 | $1208.50 | $1222.40 |
| Other infused/parenteral supportive care drugs | $950.20 | $309.30 | $605.60 |
| All other drugs delivered | $1973.50 | $360.20 | $1106.00 |
| Systemic anti-cancer therapy | $9069.80 | $9981.70 | $9560.20 |
| Total mean monthly cost | $17,689.60 | $17,065.60 | $17,354.10 |

*BRCA*, breast cancer gene; HR, hormone receptor positive; TNBC, triple negative breast cancer.

Mean cost for infused/parenteral supportive care drugs was $950 among TN patients and $309 among HP patients. Clinicians may anticipate higher toxicities in patients with TN disease.

- Outcomes for patients with *BRCA* mutated disease appear to mirror the general breast cancer outcomes which show that patients with TN disease have worse outcomes than patients with HP disease.
- In this sample, there were 8 patients with TN disease who did not get treatment. There is an unmet need in *BRCA* mutated breast cancer patients especially for patients with TN disease.
- In the future, clinicians may be able to lower toxicities and reduce cost of supportive care drugs as newer targeted treatments become available.
- A limitation of this study was that the study period preceded the approval of newer therapies such as PARP inhibitors and PD-L1 inhibitors.

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## Conflict of interest statement

A.C.H. reports no conflicts of interest. T.O. and R.S. are employed by AstraZeneca and own stock in AstraZeneca. M.S.W. reports no conflicts of interest. L.S.S. reports being on an advisory board for AstraZeneca.

## Research involving human participants and/or animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## Informed consent

This study involved retrospective analysis of existing data with no patient intervention or interaction.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2019.100121.

## Appendix. Multivariate Cox regression analysis results for first line PFS and OS from start of first line treatment

Multivariate survival analysis for PFS in first line identified presence of bone metastases (vs. no bone metastases) as a significant predictor of greater risk for disease progression (hazard ratio [HR]: 1.63, 95% CI, 1.039–2.561, $P = .033$).

Multivariate survival analysis for OS from the start of first line identified significantly higher risk for mortality associated with race (minority/unknown vs. white) (HR 2.04, 95% CI, 1.118–3.723, $P = .020$) and tumor grade (Grade 3 vs. other) (HR 3.01, 95% CI, 1.299–6.973, $P = .010$). It is important to note that the categorization of race as "minority/unknown vs. white" was formed due to relatively small sample size. The actual distribution of race by more granular categories is shown below. The proportions of different race groupings between TNBC and HR+ groups were not significantly different. However, in the multivariate analysis of OS, patients who were minority/unknown had significantly higher risk than patients who were white.

| Variables | Triple negative $N = 57$ | Hormone positive $N = 57$ | Overall $N = 114$ |
|---|---|---|---|
| Race, *n* (%) | | | |
| Black or African American | 9 (15.8%) | 10 (17.5%) | 19 (16.7%) |
| Hispanic or Latino | | 2 (3.5%) | 2 (1.8%) |
| White | 46 (80.7%) | 44 (77.2%) | 90 (78.9%) |
| Undocumented/unknown | 2 (3.5%) | 1 (1.8%) | 3 (2.6%) |
| Sub-total | 57 | 57 | 114 |
| *P* value | | 0.6635 | |

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