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Original Article

Unmet need for previously untreated metastatic triple-negative breast cancer: a real-world study of patients diagnosed from 2011 to 2022 in the United States

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Abstract

Background: This real-world study describes the treatment landscape evolution after targeted therapy approval and associated survival outcomes for previously untreated metastatic triple-negative breast cancer (mTNBC) in the United States.

Patients and Methods: This retrospective analysis used de-identified electronic health record-derived data of patients diagnosed with mTNBC (January 2011-July 2022; index date was first-line [1L] treatment start date). Patient characteristics, treatment patterns, real-world overall survival (rwOS), and time to next treatment or death (TTNTD) were determined. Outcomes before (2011-2017, early cohort) and after (2018-2022, late cohort) targeted therapy approval were evaluated.

Results: Among 2004 eligible patients, 21% were classified as Black, 13% had Eastern Cooperative Oncology Group performance status ≥2, and 63% were diagnosed with recurrent disease; median age was 60 years. First-line chemotherapy-only (single- and multiple-agent chemotherapy) use decreased with the introduction of targeted therapies from 96% before 2018 to 65% between 2019 and 2022. From 2019, 33% of patients received programmed death-(ligand) 1 inhibitor-based regimen; ~2% received poly (ADP-ribose) polymerase inhibitors. Median 1L treatment duration was 2.6 months and this did not change over time. Of all 1L patients, 34% died before second-line (2L) and 51% subsequently received 2L treatment. Median (95% CI) 1L rwOS and TTNTD were 11.3 (10.7-12.0) months and 4.3 (4.1-4.6) months, respectively. Median 1L 5-year survival [95% CI] showed statistically significant but small improvement from the early (10.9 [10.3-11.6] months) to late cohort (11.9 [10.7-13.1] months; HR [95% CI], 0.87 [0.78-0.96]).

Conclusion: This analysis demonstrated that, despite changes in care over time, survival improvements were not clinically meaningful; thus, a substantial unmet need for more efficacious treatments in previously untreated patients with mTNBC remains.

Key words: triple-negative breast cancer; real-world clinical outcomes; first-line; metastatic; treatment patterns; unmet need.

Implications for practice

This real-world study demonstrated that despite the introduction of targeted therapies after 2018, standard cytotoxic chemotherapy-only (including both single- and multiple-agent chemotherapy) remains the backbone systemic treatment for patients with previously untreated metastatic triple-negative breast cancer (mTNBC). First-line treatment duration was short and survival outcomes showed a small improvement over time; attrition rates between lines of therapy remain high with approximately one-third of the patients dying without receiving a second-line treatment. Together, these data highlight the substantial unmet need for new, more efficacious treatment options for patients with previously untreated mTNBC.

Introduction

Breast cancer (BC) is the most common cancer in women worldwide with approximately 2.3 million new cases (~275 000 in the United States) and 666 000 deaths (~43 000 in the United States) in 2022.[1] In 2024, it is estimated that approximately 314 000 new cases of invasive BC will be diagnosed in the United States.[2] Triple-negative BC (TNBC) is defined by American Society of Clinical Oncology (ASCO)/

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College of American Pathologists (CAP) guidelines as hormone receptor (HR)-negative (<1% of tumor nuclei being immunoreactive for estrogen receptor [ER] and progesterone receptor) and human epidermal growth factor receptor 2 (HER2) negative determined by immunohistochemistry (IHC) as HER2 0, 1+, or 2+ and confirmed as negative by in situ hybridization.[3,4] TNBC accounts for 15%-20% of all BCs and is characterized by a higher incidence in early onset BC (<40 years; ~1.5-4 times more frequent than in other subtypes) and in Black women (~2 times more frequent than in White women); in addition, *BRCA1/2* mutations are reported in 10%-25% of TNBCs and programmed death-(ligand) protein 1 (PD-[L]1) is assessed as positive in approximately 45%-50% of this subgroup.[5-17] TNBC is highly aggressive (with a 35%-45% risk of developing distant metastases within 3 years after diagnosis) and the 5-year survival rate for patients with distant metastasis is 12%.[18-20]

Prior to 2018, patients with previously untreated metastatic TNBC (mTNBC) received chemotherapy.[21] Since then, treatment options have improved with the approval of poly (ADP-ribose) polymerase inhibitors (PARPi) in 2018, atezolizumab (a PD-L1 inhibitor) plus nab-paclitaxel in 2019 (withdrawn in the United States in 2021 after IMpassion131 did not meet its primary end point), and pembrolizumab (a PD-1 inhibitor) plus chemotherapy in 2020; however, these treatments are limited to patients with *BRCA1/2* mutations (ie, PARPi) or a specific PD-L1 expression level (ie, PD-L1 combined positive score ≥10 for pembrolizumab and PD-L1 staining of any intensity covering ≥1% of the tumor area for atezolizumab).[22-26] Furthermore, due to the recent approval of pembrolizumab plus chemotherapy for treatment of TNBC in the curative setting, the treatment landscape for first-line (1L) mTNBC is likely to evolve.[27] It is important to understand how these treatments are used in clinical practice and to what extent they improve patient outcomes.

This real-world study aims to assess patient characteristics, treatment strategies, and survival outcomes of patients diagnosed with mTNBC between 2011 and 2022, as well as their evolution over this decade, before and after the approval of targeted therapies.

Methods

Data Sources and Study Design

This study was reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort studies. Electronic health record (EHR)-derived data from the longitudinal Flatiron Health database, including data on patient demographics, diagnosis, biomarkers, and outcomes from approximately 280 cancer clinics in the United States (~800 sites of care) was used. The database includes structured and unstructured records, curated via technology-enabled abstraction.[28,29] The de-identified data were subject to obligations to prevent re-identification and protect patient confidentiality.

Patients (≥18 years) with a mTNBC diagnosis as defined by ASCO/CAP[3,4] who had initiated oncologist-defined, rule-based 1L treatment with systemic treatment between January 1, 2011, and July 31, 2022 (index period) were eligible. The follow-up period was defined as time from the index date (start of 1L treatment) until death, end of study period (January 31, 2023), or loss to follow-up, whichever occurred first. Patients who received hormonal therapy and/or HER2-targeted treatment were excluded from this analysis; patients receiving trastuzumab-deruxtecan (T-DXd) for HER2-low (IHC1+ or IHC2+/ISH–) disease were allowed. Patients who were missing recordings of visits, vital information, medication administration date, or laboratory tests/results surrounding the metastatic diagnosis date (30 days prior to and 90 days after diagnosis), or who had other primary cancers (excluding non-metastatic, non-melanoma skin cancers) within 5 years prior to mTNBC diagnosis were also excluded. Patients who received sacituzumab govitecan (SG) in 1L or a clinical study drug were also excluded (**Figure 1A**). In this analysis, patients with mTNBC diagnosed as recurrent disease were included regardless of their responses to (neo) adjuvant treatment (early or late relapsers). Furthermore, data on disease-free or treatment-free intervals after (neo) adjuvant treatment were not captured.

Treatment patterns

The description of treatment patterns included all systemic treatments received in the metastatic setting. The number and proportion of patients receiving various treatment classes and regimens, and treatment duration (from start to end of each line of therapy [LoT]) were described by LoT. The start of therapy and advancement to next LoT were determined with an oncologist-defined, rule-based framework. Briefly, the start of a LoT was defined as the initiation of a new regimen. The end of this line was triggered by the switch to a subsequent treatment or a gap of more than 120 days between 2 sequential treatments. Receiving maintenance treatment in the 1L setting was considered the same line of therapy.

Single-agent and multiple-agent chemotherapy are grouped under the term "chemotherapy-only" to differentiate from PD-(L)1 inhibitor regimens that are given in combination with chemotherapy.

Effectiveness

Real-world overall survival (rwOS) was defined as the time (months) from index date until death from any cause, loss to follow-up, or end of study period, whichever occurred first. Time to next treatment or death (TTNTD) was defined as the time (months) from 1L treatment start date (index date) until start of the next line of therapy or death, loss to follow-up, or end of study period, whichever came first. OS was also assessed among patients who were subsequently treated in second line (2L) and third line (3L) during the index period (indexed to the start of 2L and 3L treatments, respectively). Patients treated with a clinical study drug in 2L and 3L were excluded from these analyses.

Subgroup analyses

Subgroup analyses included PD-L1 expression status at index date (status was defined as positive or negative based on qualitative data provided in the database), age at index date (<45 years, 45 to <65 years, and ≥65 years), HER2 expression status (HER2-IHC0 and HER2-low [IHC1+, or IHC2+/ISH–]), Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 and ≥2), and disease type (recurrent and de novo metastatic). Survival outcomes were described for each subgroup.

For the subgroup analysis according to period of diagnosis, patients were stratified into those diagnosed with mTNBC from January 1, 2011, to December 31, 2017 (early cohort) and to those diagnosed from January 1, 2018, to July 31, 2022 (late cohort). The cutoff date of January 2018 between

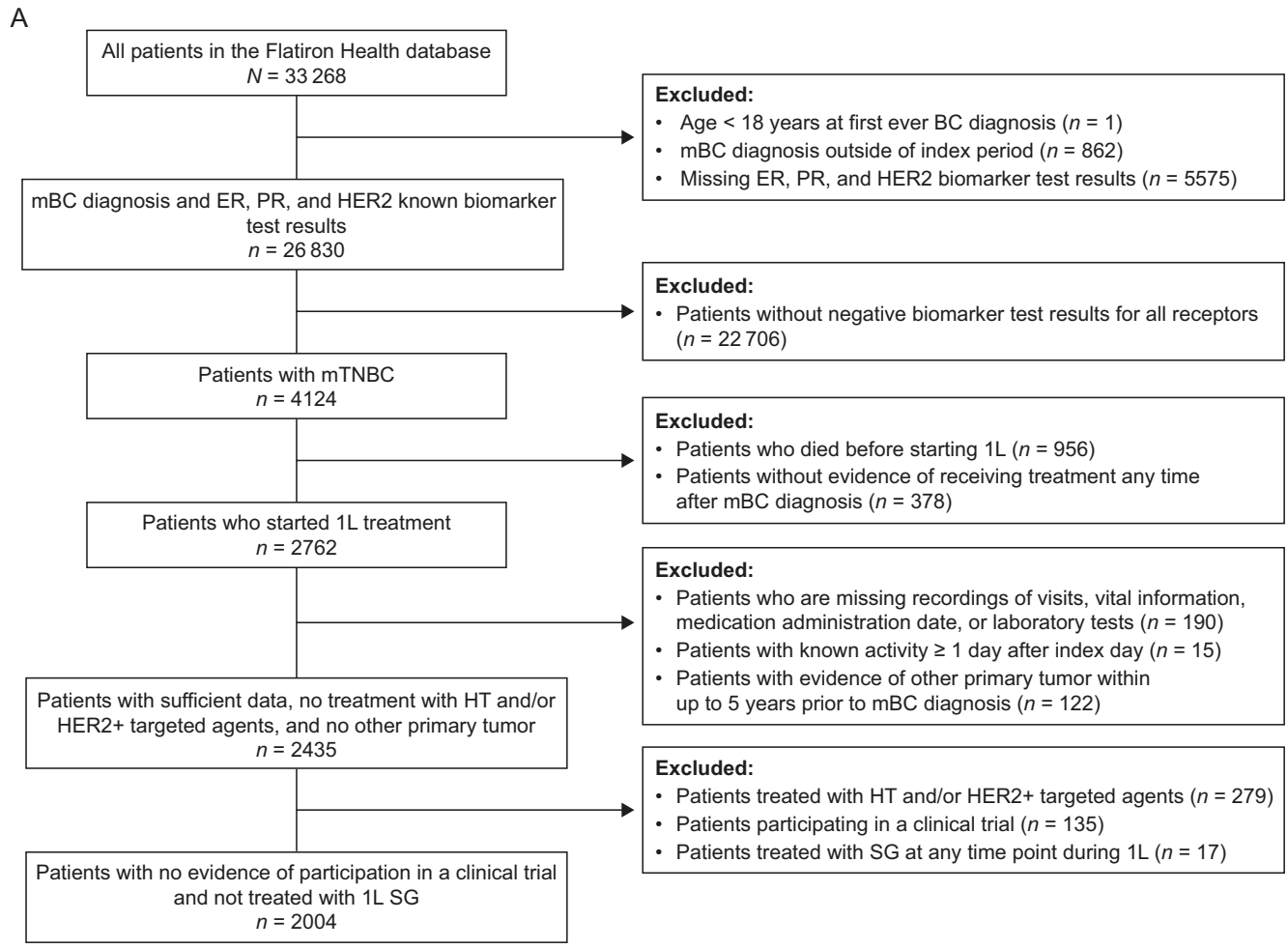


Figure 1. Patient selection (A) and disposition (B). [a]Patients who received a next line of treatment outside index period, or whose next line of treatment started on the date of last activity date, or patients who participated in a clinical trial at any point during next line of treatment were censored from outcomes analysis only. All available data were used for treatment patterns analysis. Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HT, hormone therapy; LoT, line of therapy; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; PR, progesterone receptor; SG, sacituzumab govitecan.

the two sub-cohorts was determined based on the approval of targeted therapies in the United States (PARPi [olaparib in January 2018; talazoparib in October 2018] and PD-(L)1 inhibitors [atezolizumab plus nab-paclitaxel in March 2019; pembrolizumab plus chemotherapy in November 2020]) for the treatment of mTNBC.[22-25] Temporal changes in patient characteristics, treatment patterns, and survival outcomes were described for each cohort.

Statistical analysis

Data were summarized using descriptive statistics. Continuous data were summarized as mean (standard deviation) or median (interquartile range [IQR]), and categorical variables were described as a number (percentage). Missing data were not imputed but number (percentage) of patients with missing data were reported for categorical and continuous variables.

Kaplan-Meier method was used to describe median (95% CI) time-to-event for rwOS and TTNTD. For rwOS analyses, patients who were alive at the end of study or lost to follow-up were censored at their last confirmed activity date; patients for whom a date of death was not recorded were censored at their last known date alive before the end of study period (data cutoff). For TTNTD analyses, patients who were still on their 1L, 2L, or 3L treatment or who were alive at the end of the study period, or who were lost to follow-up were censored at the last confirmed activity date.

Cox proportional hazards regression was used to measure the association between mTNBC diagnosis period (early vs late cohort) and 1L 5-year survival. A right censoring rule mirroring the maximum follow-up duration available in the late cohort (ie, 5 years) was implemented in the early cohort to account for the extended follow-up time available and to standardize observability across both cohorts. Median (95% CI) 1L 5-year survival was estimated, and unadjusted and adjusted hazard ratio (HR) estimates (95% CI) were reported. The covariates used for adjustment in the Cox proportional hazards regression model included age, race, region, treatment setting, disease type, and ECOG performance status. The missing indicator method was used to retain patients with missing covariate data in the analysis.

Results

Patients

Out of 26 830 patients with a metastatic BC (mBC) diagnosis during the index period and available biomarker data in the database, 15% (n = 4124) were diagnosed with mTNBC. Of these, 49% (n = 2004) initiated 1L treatment, satisfied all eligibility criteria, and were included in the analysis (**Figure 1A**). One-third of patients with mTNBC (n = 1362) had no evidence of receiving 1L treatment in the database. Of these, 70% (n = 956) had a documented death and the median (IQR) time from mBC diagnosis to death was 4.7 (2.0-13.3) months. Of all mTNBC patients, 8% (n = 339) had a death date within 3 months from mBC diagnosis (**Supplementary Table 1**).

Among 2004 patients who received 1L treatment, 51% (n = 1030) and 26% (n = 524) subsequently received a 2L and 3L treatment, respectively, during the patient identification period, and met the remaining eligibility criteria. Between each LoT, on average about 34% of the patients did not survive to receive next LoT (**Figure 1B**).

Of the 2004 eligible patients (>99% female), with median (IQR) age of 60 (51-70) years, 57% (n = 1145) were White and 21% (n = 421) were Black, 13% (n = 254) had an ECOG performance status≥2, and 86% (n = 1726) were treated in the community setting. Furthermore, 30% (n = 599) of patients had de novo mTNBC. Among patients with available quantitative HER2 data (n = 1370), 63% (n = 869) and 37% (n = 501) had their tumors classified as HER2-IHC0 and HER2-low (IHC1+ or IHC2+/ISH-), respectively. Of the patients with available *BRCA1/2* mutation status (n = 831), 10% (n = 86) had a germline mutation. Among the patients with known PD-L1 status (n = 190) at index date, 37% (n = 70) had PD-L1 positive disease (**Table 1**).

Among patients with mTNBC, 53% (n = 1071) and 47% (n = 933) of patients were diagnosed before and after 2018, respectively. Most patient demographic and disease characteristics did not change over time (**Table 1**). The proportion of patients with obesity (early cohort: 34%; late cohort: 38%), aged ≥ 65 years (early cohort: 34%; late cohort: 43%), and with de novo mTNBC (early cohort: 27%; late cohort: 33%) increased in the late cohort. The proportion of patients with documented *BRCA1/2* and PD-L1 testing increased over time, but was unknown for a substantial proportion of patients in the late cohort either due to missingness or not being performed (*BRCA1/2*: 47%; PD-L1: 82%). In the late cohort, among patients tested for *BRCA1/2* mutations, 54% (n = 265) were tested in the curative setting and 40% (n = 200) before/around mTNBC diagnosis/start of 1L treatment. Among patients with known PD-L1 status, 77% (n = 247) were tested before/around mTNBC diagnosis/start of 1L treatment, 10% (n = 33) in the curative setting, and 12% (n = 39) in later lines.

Treatment patterns

Median (IQR) time from mTNBC diagnosis to start of 1L treatment was 0.92 (0.49-1.64) months, and this did not change over time (Table 1). Use of chemotherapy-only in the 1L setting decreased with the introduction of targeted therapies from 96% (monotherapy: 53%; combination: 43%) in the early cohort to 65% (monotherapy: 40%; combination: 25%), on average, from 2019 to 2022 (**Figure 2A**). On average, 33% of patients received PD-(L)1 inhibitor-based regimens and ~2% received PARPi from 2019 to 2022. The most frequent chemotherapy regimens used as monotherapy included capecitabine (20%) and taxane (17%; paclitaxel 7%, protein bound paclitaxel [nab-paclitaxel] 8%, docetaxel 1%, taxane monotherapy sequencing <1%). Furthermore, 22% of patients received platinum-based chemotherapy (gemcitabine/carboplatin 9%, carboplatin+ [nab-] paclitaxel 7%, other platinum-based chemotherapy combination 3%, platinum monotherapy 2%) and 11% of patients received anthracycline-based chemotherapy (doxorubicin/cyclophosphamide 8%, anthracycline + taxane <1%, other anthracycline-based chemotherapy combination 1%, anthracycline monotherapy 1%). The median (IQR) 1L treatment duration was 2.6 (1.4-4.9) months and this did not change over time (**Supplementary Table 2**).

Among patients who subsequently received 2L treatment during the study period (n = 1030), on average, 53% received chemotherapy-only regimens and 26% received PD-(L)1 inhibitor–based regimens between 2019 and 2022. The proportion of patients treated with SG increased from 7% in 2020 to 22% in 2022 (**Figure 2B**). Among patients who subsequently received a 3L treatment during the study period, use of chemotherapy-only regimens decreased from 91% before 2018 to 49% on average between 2019 and 2022. SG was the most used agent in 3L (41%) from 2021 to 2022 (**Figure 2C**).

Survival outcomes

In the overall population, median (95% CI) rwOS was 11.3 (10.7-12.0) months in patients with mTNBC initiating 1L treatment (**Figure 3A**) and decreased to 9.7 (9.1-10.4) months

Table 1. Baseline demographics and clinical characteristics.

	All patients 2011-2022 (*N* = 2004)	**Metastatic disease diagnosis 2011-2017 (*n* = 1071)**	**Metastatic disease diagnosis 2018-2022 (*n* = 933)**
Median age,[a] years (IQR)	60 (51-70)	59 (50-69)	62 (52-71)
<45, *n* (%)	301 (15)	170 (16)	131 (14)
45-65, *n* (%)	942 (47)	538 (50)	404 (43)
≥65, *n* (%)	761 (38)	363 (34)	398 (43)
Sex, *n* (%)			
Female	1997 (> 99)	1067 (> 99)	930 (> 99)
Race, *n* (%)			
White	1145 (57)	628 (59)	517 (55)
Black	421 (21)	222 (21)	199 (21)
Asian	44 (2)	24 (2)	20 (2)
Other/unknown	394 (20)	197 (18)	197 (21)
Treatment provider type, *n* (%)			
Community	1726 (86)	949 (89)	777 (83)
Academic	244 (12)	109 (10)	135 (14)
Unknown	34 (2)	13 (1)	21 (2)
Region, *n* (%)			
Northeast	265 (13)	145 (14)	120 (13)
Midwest	232 (12)	138 (13)	94 (10)
South	858 (43)	460 (43)	398 (43)
West	245 (12)	131 (12)	114 (12)
Other/unknown/missing	404 (20)	197 (18)	207 (22)
Median BMI at index date, kg/m^2 (IQR)	27.7 (24.0-32.6)	27.6 (24.2-32.5)	27.8 (23.9-32.6)
Underweight/normal (<25), *n* (%)	593 (30)	301 (28)	292 (31)
Overweight (25–<30), *n* (%)	597 (30)	314 (29)	283 (30)
Obese (≥30), *n* (%)	718 (36)	366 (34)	352 (38)
Unknown, *n* (%)	96 (5)	90 (8)	6 (1)
ECOG performance status, *n* (%)			
0-1	1252 (62)	584 (54)	668 (72)
≥2	254 (13)	126 (12)	128 (14)
Unknown	498 (25)	361 (34)	137 (15)
Stage at first ever diagnosis, *n* (%)			
Stage I	203 (10)	118 (11)	85 (9)
Stage II	554 (28)	300 (28)	254 (27)
Stage III	513 (26)	292 (27)	221 (24)
Stage IV	599 (30)	288 (27)	311 (33)
Unknown	135 (7)	73 (7)	62 (7)
Disease type, *n* (%)			
De novo metastatic disease[b]	599 (30)	288 (27)	311 (33)
Recurrent disease[b]	1270 (63)	710 (66)	560 (60)
Unknown	135 (7)	73 (7)	62 (7)
Median time from mBC diagnosis to index date, months (IQR)	0.92 (0.49-1.64)	0.89 (0.46-1.74)	0.95 (0.56-1.61)
Patients with ≥1 metastasis site recorded, *n* (%)	1006 (50)	498 (46)	508 (54)
Median number of metastasis sites, *n* (IQR)	1 (1-2)	1 (1-2)	1 (1-2)
Metastasis sites (among patients with metastasis site recorded), *n* (%)			
Bone	431 (43)	229 (46)	202 (40)
Brain	126 (13)	63 (13)	63 (12)
Liver	177 (18)	90 (18)	87 (17)
Lung	291 (29)	135 (27)	156 (31)
Lymph nodes	346 (34)	145 (29)	201 (40)

Table 1. Continued

	All patients 2011-2022 (*N* = 2004)	Metastatic disease diagnosis 2011-2017 (*n* = 1071)	Metastatic disease diagnosis 2018-2022 (*n* = 933)
Visceral metastases, *n* (%)	588 (58)	280 (56)	308 (61)
HER2– expression status, *n* (%)[c,d]			
HER2-IHC0	869 (63)	391 (59)	478 (68)
HER2-low (IHC1+ or IHC2+/ISH-)	501 (37)	274 (41)	227 (32)
Germline *BRCA1/2* pathogenic variant status (over all time), *n* (%)[c,e]			
Wildtype	745 (90)	294 (87)	451 (91)
Pathogenic variant	86 (10)	43 (13)	43 (9)
PD-L1 status (at index date), *n* (%)[c,f]			
Negative	120 (63)	16 (84)	104 (61)
Positive	70 (37)	3 (16)	67 (39)
PD-L1 status (over all time), *n* (%)[c,g]			
Negative	277 (70)	61 (80)	216 (68)
Positive	118 (30)	15 (20)	103 (32)

If multiple values were available during the baseline period (from initial BC diagnosis to index date), patient demographics and disease characteristics were described using values closest to the index date.
Marker result at index date refers to the most recent result from start of data availability up to, and inclusive of, the index date; results over all time refers to the most recent result among all data available, before or after the index date.
[a]Patients born in 1938 or earlier may have an adjusted birth year in Flatiron Health datasets due to patient de-identification requirements.
[b]De novo metastatic disease was defined as first ever breast cancer diagnosis as stage IV; breast cancers that were first diagnosed as stages I-III and as metastatic breast cancer during the study period were considered recurrent disease.
[c]Among patients with known status.
[d]634 patients have unknown HER2– expression status (2011-2017, *n* = 406; 2018-2022, *n* = 228).
[e]1173 patients have unknown germline *BRCA1/2* status over all time (2011-2017, *n* = 734; 2018-2022, *n* = 439).
[f]1814 patients have unknown PD-L1 expression status at the index date (2011-2017, *n* = 1052; 2018-2022, *n* = 762).
[g]1609 patients have unknown PD-L1 expression status over all time (2011-2017, *n* = 995; 2018-2022, *n* = 614).
Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IQR, interquartile range; mBC, metastatic breast cancer; PD-L1, programmed death-ligand 1.

(2L) and 7.9 (7.0-9.0) months (3L) as patients advanced to subsequent LoTs. Median (95% CI) TTNTD was 4.3 (4.1-4.6) months in 1L (**Figure 4A**), 4.4 (4.1-4.9) months in 2L, and 3.7 (3.5-4.2) months in 3L.

Subgroup analyses of rwOS and TTNTD for patients who had received 1L treatment for mTNBC, including across age groups, PD-L1 status, HER2-IHC0 and HER2-low (IHC1+ or IHC2+/ISH-) status, ECOG performance status, and disease type (de novo metastatic and recurrent), are presented in **Figure 5**. Median rwOS (95% CI) among patients with an ECOG performance status ≥2 and ≤1 was 5.7 (4.4-7.0) months and 12.2 (11.3-13.1) months, respectively, and in patients with PD-L1 positive and negative disease at index date, was 15.1 (10.7-21.4) months and 10.1 (7.8-11.3) months, respectively. Similar results were observed for TTNTD.

Median (95% CI) 5-year survival was 10.9 (10.3-11.6) months in the early cohort and 11.9 (10.7-13.1) months in the late cohort for those who received 1L treatment (**Figure 3B**). HR (95% CI) after adjustment for confounding factors was 0.87 (0.78-0.96).

Discussion

This retrospective, observational cohort study investigated the characteristics, treatment patterns, and clinical outcomes of 2004 patients with previously untreated mTNBC in the United States from 2011 to 2022. Chemotherapy remained the treatment of choice for most previously untreated patients with mTNBC; the uptake of PD-(L)1 inhibitor-based regimens after 2019 was in line with the expected number of eligible patients. Despite changes in the standard of care since 2018, survival outcomes only showed a small improvement of approximately 1 month over time.

One-third of patients with mTNBC selected from the database did not have documentation of receiving 1L treatment; 8% died within 3 months from mTNBC diagnosis. Although the exact reasons for not receiving 1L treatment are unknown, explanations may include missing data, patients declining treatment, choice to proceed solely with palliative care, or death shortly after diagnosis. In addition, patients may have received treatment in a clinic outside the Flatiron Health network or outside the study period; thus, the proportion of patients not receiving 1L treatment reported in this study may be overestimated. There are few real-world studies reporting attrition rates in mTNBC. In two retrospective, real-world studies of females with mTNBC in the United States, 14%-17% did not receive 1L treatment; the reasons provided were similar to the hypotheses mentioned for the current study.[30,31]

Among the 2004 patients with mTNBC who started 1L treatment, 51% were subsequently treated with a 2L and 26% with a 3L within the study period; approximately 34% did not survive to receive next-line treatment after 1L or 2L. Similar high attrition rates were previously reported. In two retrospective, observational studies of patients with mTNBC, 57%-60% received 2L treatment and 34% received 3L treatment; no specific reasons were provided for the patients who

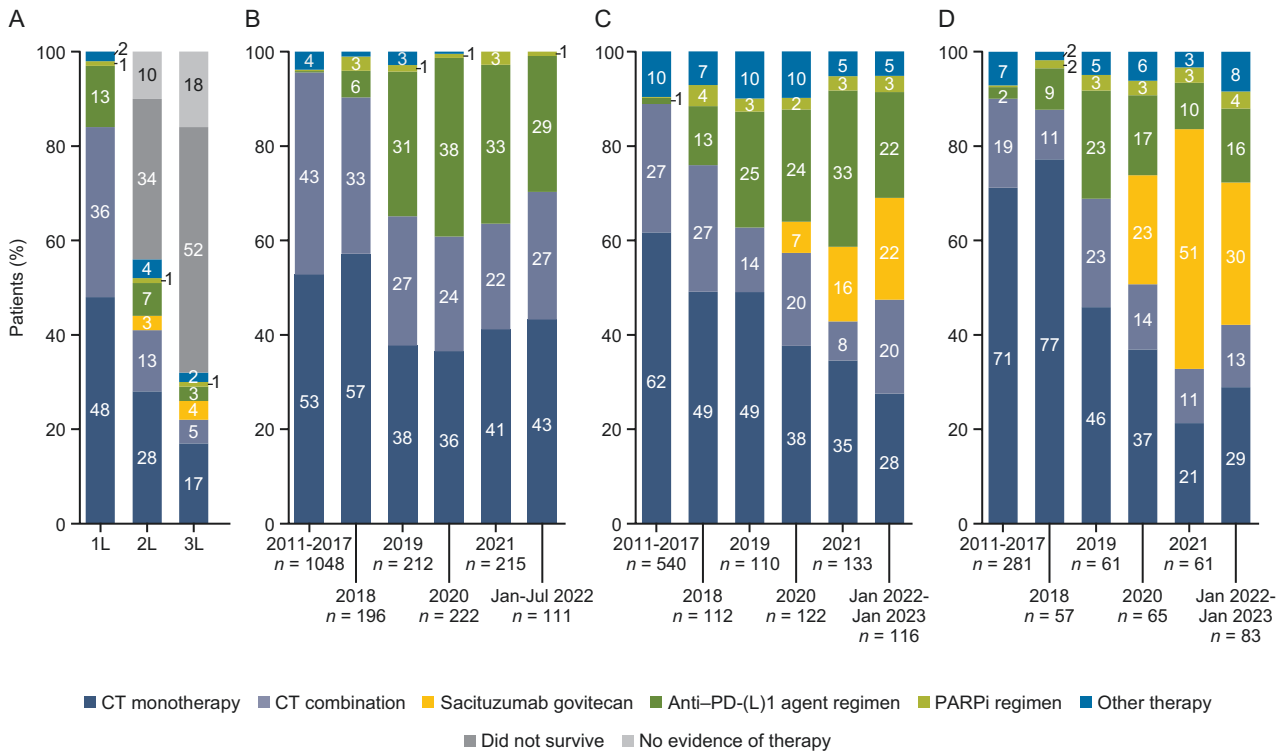
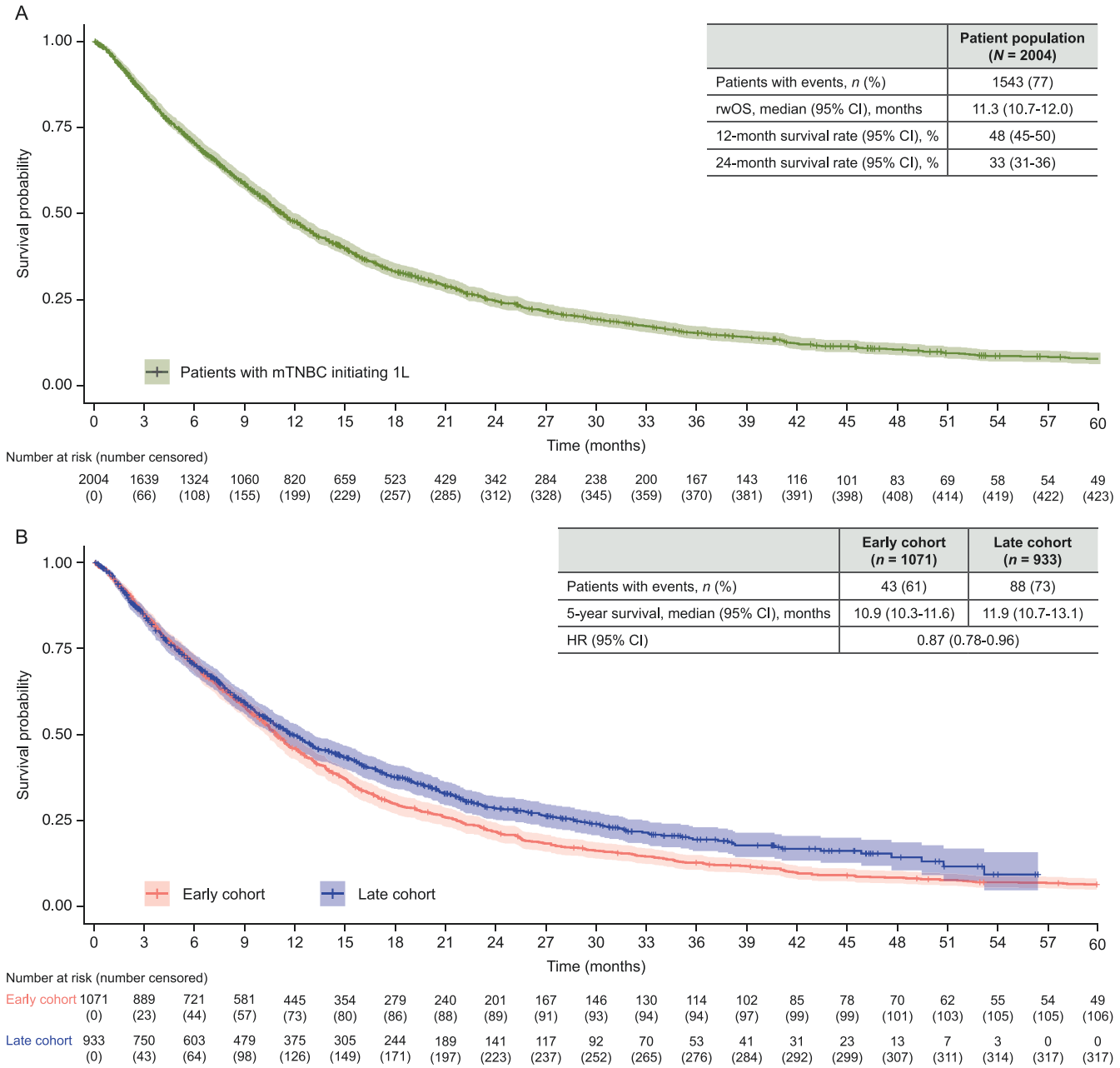


Figure 2. Treatment patterns by metastatic line (A) and evolution of metastatic treatment landscape among patients with mTNBC from 2011 to 2022 in 1L (B), 2L (C), and 3L (D). Other therapies included bevacizumab-based regimens, CDK4/6i monotherapy, clinical study drug and other monotherapy/combination therapy not classified above. Patients diagnosed in each period may not have been treated in the same period. 1L, first-line; 2L, second-line; 3L, third-line; CT, chemotherapy; mTNBC, metastatic triple-negative breast cancer; PARPi, poly (ADP-ribose) polymerase inhibitors; PD-(L)1, programed death-(ligand) 1.

did not receive a subsequent LoT.[32,33] These data highlight the need for additional treatment options and patient education on available options to improve outcomes.

While chemotherapy-only use decreased with the introduction of targeted therapies, chemotherapy-only remained the 1L treatment of choice for most patients with mTNBC, which is consistent with the use of chemotherapy-only as a preferred treatment option for patients without PD-L1 expression or *BRCA1/2* pathogenic variants.[34] PD-(L)1 inhibitor-based regimens were rapidly adopted in routine care and reached an average of 33% after 2019, consistent with the 45%-50% of patients expected to have PD-L1 expression.[15,16] The difference between observed and expected rates of PD-(L)1 inhibitor use may be due to the approval of pembrolizumab in combination with chemotherapy for patients with high-risk, early-stage TNBC in July 2021; use in the early setting may affect the use of this drug for mTNBC as there are no data to support an additional line of therapy with another PD-(L)1 inhibitor after recurrence of disease.[27,34] Use of PD-(L)1 inhibitor-based regimens increased after their approval in 2019-2020 based on the results of the IMpassion130 (atezolizumab) and KEYNOTE-355 (pembrolizumab) studies and remained stable even after the withdrawal of atezolizumab (2021) for this indication in the United States.[24,25] Following approval in 2018 based on the EMBRACA (talazoparib) and OlympiAD (olaparib) studies,[22,23] use of 1L PARPi ranged from 1% to 3% between 2019 and 2022. This is lower-than-expected based on the estimated 10% of patients with germline *BRCA1/2* mutation who would be eligible to receive a PARPi.[35,36] As mTNBC treatment with a PARPi is also recommended in later line, PARPi use in the 1L setting may be limited.[34,37] In the current study, the use of PARPi in 2L and 3L was approximately 3% on average in the late cohort. These treatment patterns are consistent with what was observed in other real-world studies in the United States; PARPi and PD-(L)1 inhibitor use was extremely low (≤3% overall), possibly due to the inclusion of patients with a mTNBC diagnosis between 2006 and 2019 and later approval of these drugs in Europe.[30,31,33,38-43]

The proportion of patients with *BRCA1/2* and PD-L1 testing results was low overall but increased over time, as expected with the requirement that an FDA-approved test is performed prior to treatment.[44-47] However, a large proportion of patients in the late cohort had unknown results, which may reflect low rates of testing during the data collection period or poor recording in the database. In addition, a high proportion of patients were treated in community centers where biomarker testing may have been less available to them than to patients treated in an academic setting.[48] Similarly, in an observational study of patients diagnosed with cancer in California and Georgia, the proportion of patients undergoing germline testing was 26% for females and 50% for males with breast cancer, below the expected rates based on guidelines.[49,50] The ethnic diversity in the current study may also have impacted testing; it has been shown that *BRCA1/2* germline mutation testing is underutilized in Asian, Black, and Hispanic patients compared with White patients.[50] As the proportion of patients with *BRCA1/2* mutation and those who express PD-L1 are enriched in the population of patients with mTNBC compared with other subtypes, testing for



	Patient population (*N* = 2004)
Patients with events, *n* (%)	1543 (77)
rwOS, median (95% CI), months	11.3 (10.7-12.0)
12-month survival rate (95% CI), %	48 (45-50)
24-month survival rate (95% CI), %	33 (31-36)

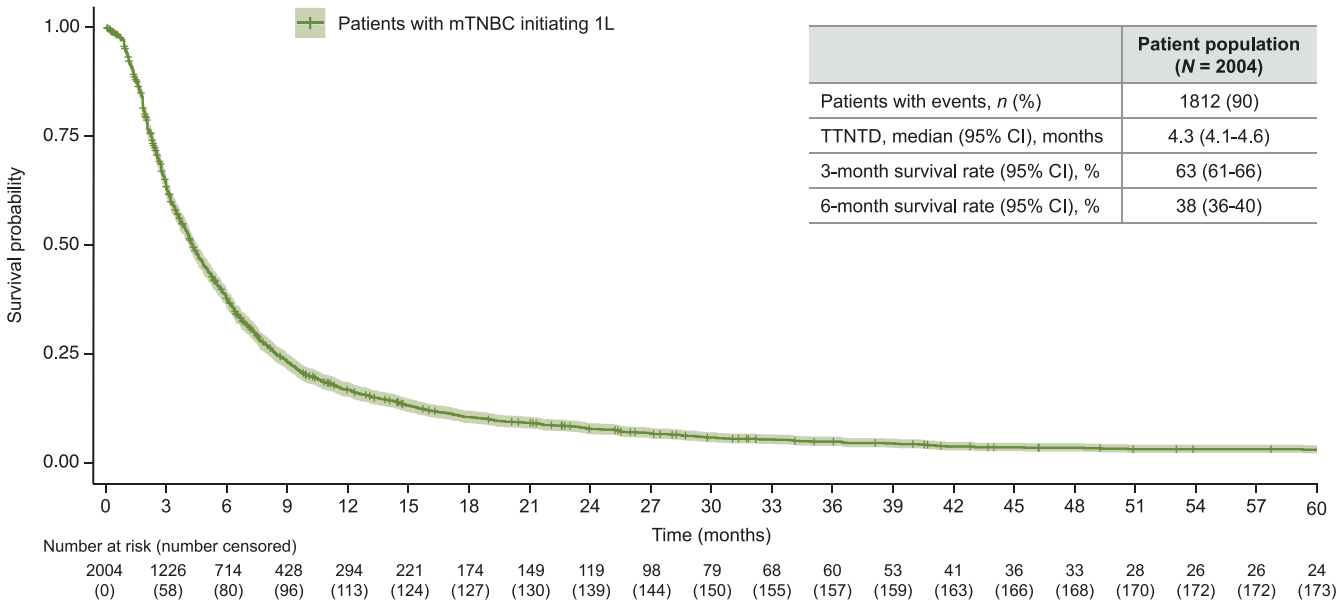
	Early cohort (*n* = 1071)	Late cohort (*n* = 933)
Patients with events, *n* (%)	43 (61)	88 (73)
5-year survival, median (95% CI), months	10.9 (10.3-11.6)	11.9 (10.7-13.1)
HR (95% CI)	0.87 (0.78-0.96)	

Figure 3. Kaplan-Meier analysis of real-world overall survival for the overall population (A) and 5-year survival by period of mBC diagnosis (B) for 1L mTNBC treatment. For visualization purposes the KM plot in panel A was truncated to present data through month 60. Of note, the real-world overall survival >60 months observed in the small subset of patients (*n* = 49) may be attributable to isolated metastatic disease (eg, brain only metastases), prolonged response to treatment, or to a transition to HR + mBC. 1L, first-line; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer.

these biomarkers is critical to determine the best treatment options.[5,14-16]

In April 2021, SG received full approval in the United States for patients with mTNBC who received two or more prior systemic therapies, with at least one in the metastatic setting based on the results of the ASCENT study.[51] With this approval, SG became the standard of care for 2L treatment of patients with mTNBC. In the ASCENT study, SG improved survival vs chemotherapy of physician's choice.[52] T-DXd was recently approved for the subgroup of patients with HER2-low (IHC1+ or IHC2+/ISH-) mBC who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant treatment, based on the DESTINY-Breast04 study.[53] After 2019 in the current study, chemotherapy-only use in 2L was observed for 53% of patients, on average, despite treatment advances. SG use in 2L after approval increased over time to reach 22% in 2022; however, most patients were still treated with chemotherapy-only, suggesting low uptake of novel therapies and a missed opportunity for some patients to benefit from the recommended standard of care.[54] T-DXd use was observed in < 1% of patients in 1L to 3L and may have reflected off-label use since US FDA approval was not granted until August 2022.[53]

Median rwOS in this study was 11.3 months. Other real-world studies (across various databases) have reported rwOS



	Patient population (*N* = 2004)
Patients with events, *n* (%)	1812 (90)
TTNTD, median (95% CI), months	4.3 (4.1-4.6)
3-month survival rate (95% CI), %	63 (61-66)
6-month survival rate (95% CI), %	38 (36-40)

Figure 4. Kaplan-Meier analysis of time to next treatment or death for the overall population. For visualization purposes the KM plot was truncated to present data through month 60. Of note, only a small subset of patients (*n* = 24) had median time to next treatment or death >60 months. Abbreviations:1L, first-line; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; TTNTD, time to next treatment or death.

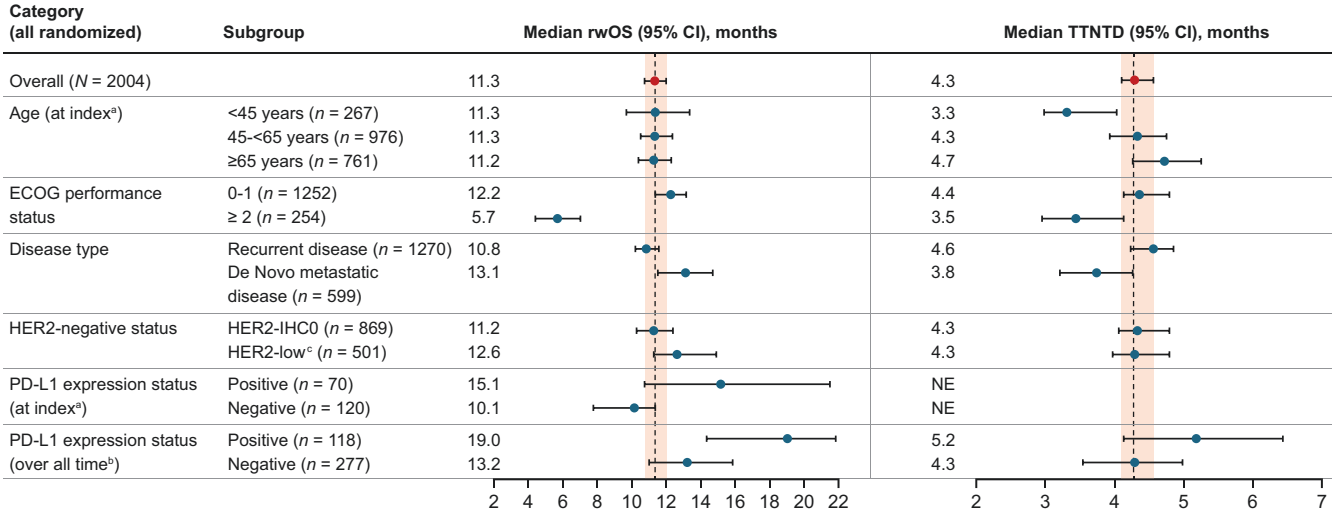


Figure 5. Subgroup analyses of clinical outcomes in patients receiving first-line treatment for mTNBC. The shading represents the 95% CI for the overall population. [a]"at index date" refers to the most recent data from start of data availability up to, and inclusive of, the index date. [b]"over all time" refers to the most recent data among all data available, before or after the index date. [c]IHC1+ or IHC2+/ISH−. Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mTNBC, metastatic triple-negative breast cancer; NE, not evaluated; PD-L1, programmed death-ligand 1; rwOS, real-world overall survival; TTNTD, time to next treatment or death.

from 8.2 months to 14.6 months, consistent with the current analysis.[30,33,38,39,55,56] In the current analysis, patients with an ECOG performance status of 0 or 1 had substantially longer OS than patients with a poorer performance status (12.2 vs 5.7 months), consistent with previous real-world evidence reports.[30,33] An improvement in rwOS was also observed for patients with PD-L1 positive but not PD-L1 negative disease compared to the overall population; these data reflect the benefit of PD-(L)1 inhibitors and the potential intrinsic prognostic value of PD-L1 positivity in this population. Median 5-year survival showed a statistically significant, but small, 1-month improvement in the late vs early cohorts; this is consistent with the small improvement of 0.5 years in survival for ER–/HER2– mBC reported in a recent simulation modeling analysis in the CISNET consortium.[57]

TTNTD is commonly used as a proxy in real-world studies as progression is often not well captured.[58-60] Median TTNTD was 4.3 months among all patients in the study. This is consistent with the TTNTD observed in another study, which ranged from 3.1 to 4.1 months and primarily included patients with mTNBC treated with chemotherapy.[38] In a study of patients treated with atezolizumab plus nab-paclitaxel, TTNTD was 8.1 months.[32] Most real-world studies reporting clinical outcomes for patients with mTNBC took place prior to the approval of PARPi and PD-(L)1 inhibitors and some enrolled very few patients who received these treatments[30,33,38,39,55,56,61];

thus, the current analysis provides valuable information on clinical outcomes for patients treated with targeted therapies. However, longer follow-up of this cohort may be required to fully observe the impact of these new treatments on clinical outcomes.

Limitations of this study include data entry errors and missing data (eg, biomarker testing results, ECOG performance status, metastasis sites) commonly associated with EHR, which may have impacted patient selection and clinical outcomes. Progression from one line of therapy to the next and disease progression cannot be assessed on a strict schedule, as in clinical trials, and was subject to the interpretation of available data. Furthermore, these results focused on the United States population mainly treated in the community setting and may not be generalizable to all patients with mTNBC and the small number of patients in some subgroups of the stratified analyses may limit data interpretation. Finally, this study included patients who were treated during the COVID-19 pandemic, which may have impacted routine clinical care and treatment decisions.

In conclusion, this large-scale, real-world analysis of >2000 patients with previously untreated mTNBC diagnosed over the last decade demonstrated a small improvement in survival over time. Systemic 1L treatment patterns in mTNBC reflected clinical guidelines, with most patients receiving single-agent chemotherapy, combination chemotherapy, and PD-(L)1 inhibitor-based regimens (after 2019). Approximately one-third of patients initiating 1L treatment for mTNBC did not survive to receive 2L treatment. Together, these results demonstrate that a substantial unmet need for more efficacious treatment options persists. While the use of new therapies was consistent with treatment guidelines, PD-(L)1 inhibitor-based regimen, PARPi, and ADC use remains lower than expected. A better uptake of recent treatment advances into routine clinical practice may improve the care of patients with mTNBC.

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Conflicts of interest

KP reports consultancy or advisory functions for AstraZeneca, Eli Lilly, Gilead Sciences, Inc., Exact Sciences, Focus Patient, Medscape, MSD, Mundi Pharma, Need Inc., Novartis, Pfizer, Hoffmann/La Roche, Sanofi, and Seagen; travel fees from Gilead Sciences, Inc., and MSD; nonfinancial interests with Belgian Society of Medical Oncology (BSMO, Vice President), EORTC Breast Cancer Task Force (Steering Committee Member), European Society of Medical Oncology (ESMO, officer), Commission Personalized Medicine Federal Government Belgium (Advisory Role), European Medicines Agency (External Scientific Advisor), and several oncology clinical trials (Steering Committee Member). AK reports no conflicts. IN was an employee of Gilead Sciences Europe, LTD at the time of the study conduct, and is now an employee of Novartis Pharmaceuticals UK, LTD. She reports stocks/shares from Gilead Sciences, Inc. and Novartis Pharmaceuticals. NS and CL are employees of Gilead Sciences, Inc. and report stocks/shares from Gilead Sciences, Inc. AE and ED are employees of Aetion Inc. and report stocks/shares from Aetion Inc., and funding, to Aetion Inc., for the conduct of this study. SH reports grants or consulting fees, to her institution, from Ambrx, Amgen, Arvinas, AstraZeneca, Bayer, Beigene, Boehringer Ingelheim, BriaCell, Celcuity, Cytomx, Daiichi-Sankyo, Dantari, Dignitana, Eli Lilly, Genentech/Roche, G1-Therapeutics, Gilead Sciences, Inc., Greenwich Life Sciences Inc, GSK, Immunomedics, Jazz, LOXO, MacroGenics, Menarini, Mersana, Novartis, OBI Pharma, Orinove, Orum, Pfizer, Phoenix Molecular Designs, Ltd., Pieris, PUMA, Radius, Samumed, Sanofi, Seattle Genetics/Seagen, and Zymeworks; royalties from Wolters Kluwer, Elsevier, McGraw Hill, and Sage; nonfinancial interests with Alliance Foundation, Quantum Leap, and InClin/Atossa. PR, the medical writer, is an employee of Parexel, which was compensated for the work on this manuscript.

Data availability

The data that support th findings of this study were originated by and are the property of Flatiron Health, Inc., which has restrictions prohibiting the authors from making the data set publicly available. Requests for data sharing by license or by permission for the specific purpose of replicating results in this manuscript can be submitted to PublicationsDataAccess@flatiron.com.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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