Received: 18 November 2022 Revised: 17 March 2023 Accepted: 12 April 2023
DOI: 10.1002/pds.5630

Real-world treatment patterns and outcomes for patients with advanced melanoma treated with immunotherapy or targeted therapy

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Funding information
University Cancer Research Fund via State of North Carolina

Abstract

Objective: To identify real-world patterns of first line treatment, treatment sequence and outcomes for older adults diagnosed with advanced melanoma who received immunotherapy or targeted therapy.

Methods: The study population included older adults (ages 65+) diagnosed with unresectable or metastatic melanoma between 2012 and 2017 and who received first line immunotherapy or targeted therapy. Using the linked surveillance, epidemiology, and end results-medicare data, we described patterns of first line treatment and treatment sequence through 2018. We used descriptive statistics to report patient and provider characteristics by first line treatment receipt and changes in first line therapy use over calendar time. We also described overall survival (OS) and time to treatment failure (TTF) by first line treatment using the Kaplan–Meier method. For patterns of treatment sequence, we reported commonly observed treatment switch patterns by treatment sub-category and calendar year.

Results: The analyses included 584 patients (mean age = 76.3 years). A majority ($n = 502$) received first line immunotherapy. There was a sustained increase in immunotherapy uptake, most notably from 2015 to 2016. The estimated median OS and TTF were longer with first line immunotherapy than with targeted therapy. Individuals treated with CTLA-4 + PD-1 inhibitors had the longest median OS (28.4 months). The most common treatment switch pattern was from a first line CTLA-4 inhibitor to a second line PD-1 inhibitor.

Conclusions: Our findings inform understanding of treatment patterns of currently used immunotherapies and targeted therapies in older adults with advanced melanoma. Immunotherapy use has increased steadily with PD-1 inhibitors becoming a dominant treatment option since 2015.

KEYWORDS
immunotherapy, melanoma, older adults, SEER-Medicare, targeted therapy, treatment patterns

Plain Language Summary

The objective of this study was to describe patterns of treatments used in older adults with advanced melanoma. The study population included older adults (ages 65+) in the U.S. diagnosed with advanced melanoma between 2012 and 2017 and who received

immunotherapy or targeted therapy as first line treatment. Using a large database containing detailed treatment information, we reported patterns of first line treatment and trends over calendar time. We also reported survival by treatment group and the time to treatment failure (TTF). Treatment failure was defined as either a patient needing a different treatment, starting hospice care, or death. We also reported commonly observed treatment switch patterns by treatment group and calendar year. The analyses included 584 patients (average age 76.3) and a majority ($n = 502$) received immunotherapy as first line treatment. Use of immunotherapy steadily increased through the study period. Observed survival and TTF were longer with immunotherapy than with targeted therapy. Patients receiving combination immunotherapy – which was a combination of two different types of immunotherapy, had the longest survival (28.4 months).

Key Points

- There was a sustained increase in use of immunotherapy in our study population (Medicare beneficiaries age 65+) diagnosed with advanced melanoma between 2012 and 2017.
- Single agent PD-1 inhibitors became the most used first line treatment option in 2015, with increasing popularity over calendar time.
- Observed median OS and TTF with first line treatment were longer with immunotherapy than with targeted therapy. Patients treated with CTLA-4 + PD-1 inhibitors had the longest OS (28.4 months, 95% CI, 9.6-NA) and those treated with PD-1 inhibitors had the longest TTF (16.7 months, 95% CI, 10.6–24.0).
- About 60% ($n = 348$) of patients had one line of treatment only, highlighting the importance of selecting first line treatment.
- Among those who had two or more lines of treatment, the most common treatment switch pattern was from a first line CTLA-4 inhibitor to a second line PD-1 inhibitor. In presumed BRAF positive patients, the most common switch pattern was from a first line PD-1 inhibitor to a second line BRAF+MEK inhibitor combination therapy.

1 | INTRODUCTION

Immune checkpoint inhibitors (e.g., anti-CTLA-4 & anti PD-1/PD-L1 antibodies) and targeted therapies (e.g., BRAF and MEK inhibitors) are currently recommended as first line treatments for unresectable or metastatic melanoma (Figure 1). Since Food and Drug Administration (FDA) approval of the CTLA-4 antibody (ipilimumab) in 2011, new treatments for advanced melanoma have evolved rapidly, increasing the options for first line treatment.[1–6] PD-1 inhibitors (nivolumab, pembrolizumab) and combination therapy of CTLA-4 and PD-1 inhibitors (ipilimumab + nivolumab) were approved in 2014 and 2015 respectively, demonstrating superior clinical response compared to anti CTLA-4 (ipilimumab) monotherapy.[7,8] BRAF inhibitors (vemurafenib, dabrafenib) that target the BRAF V600E mutation were approved in 2011 and 2013 and combination therapies of BRAF and MEK inhibitors (dabrafenib + trametinib, vemurafenib + cobimetinib, encorafenib + binimetinib) were introduced between 2014 and 2018.[8]

While randomized clinical trials have shown significant improvements in clinical outcomes of immunotherapy and targeted therapy,[9–11] there are limited data available about real-world use of these treatments.[12–15] Furthermore, there is a general lack of data for older melanoma patients.[16] More than 50% of all melanoma cases are diagnosed in patients aged 65 or older and more than half of those patients are 75 years or older.[17] Treatment selection in older cancer patients can be complicated by the presence of comorbidities, increased frailty and different treatment goals.[18–20]

Using a large database linking cancer registry and healthcare encounter data for adults over age 65, this study aimed to describe recent treatment patterns and outcomes in older adults with unresectable or metastatic melanoma. The primary objectives of this study were to identify real-world (1) treatment patterns of first line treatment and (2) patterns of treatment sequence in older adults who received immunotherapy and targeted therapy as first line treatment for unresectable or metastatic melanoma from 2012 to 2018. The secondary objective was to describe overall survival (OS) and time to treatment failure (TTF) associated with first line treatment in this population.

2 | METHODS

2.1 | Data source

This study used the Surveillance, Epidemiology, and End Results (SEER)-Medicare data. SEER-Medicare is a linkage between the SEER cancer registries and Medicare claims and enrollment data, which

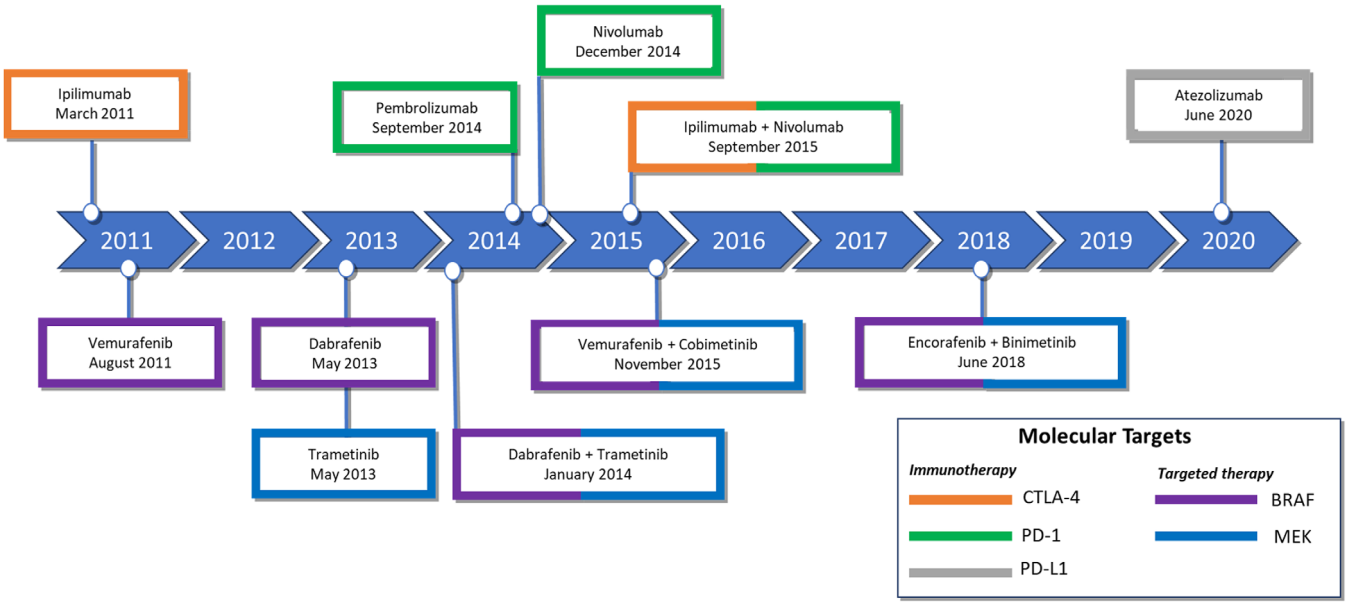

FIGURE 1 Food and Drug Administration (FDA) approvals of immunotherapy and targeted therapy. *Source*: FDA approval history.[8]

provides a wide range of information about Medicare beneficiaries with cancer.[21] The geographical coverage of the SEER registry has expanded to about one third of the US population in 2018.[22] This study used data that included all Medicare fee-for-service beneficiaries residing in SEER registry areas diagnosed with cancer from 2012 through 2017 and their Medicare claims through 2018. The beneficiaries enrolled in Medicare Advantage plans (Part C) were not included as their claims are incompletely captured in the Medicare claims data.[22] The SEER-Medicare database contains clinical, demographic and vital status information as well as medical and pharmacy claims for Medicare covered health care services.

2.2 | Study sample

The study included Medicare beneficiaries aged ≥65 years who were diagnosed with melanoma (Supplemental Table 1A) between January 2012 and December 2017 and started with immunotherapy or targeted therapy within 90 days of diagnosis (Figure 2). The date of diagnosis was assigned as the first day of the month of diagnosis. Patients were excluded if they (1) were diagnosed with early-stage melanoma (Stage 0–II), (2) were discontinuously enrolled in Medicare Parts A, B, or D or enrolled in HMO for 1 year prior to diagnosis, or (3) died within the month of diagnosis. Among the studied treatments, ipilimumab has been used for adjuvant melanoma treatment since October 2015. Therefore, we excluded patients if they were (1) diagnosed with melanoma as stage III or unknown stage after October 2015, (2) had ipilimumab within 90 days of diagnosis as first line treatment, and (3) had lymph node dissection between melanoma diagnosis date and ipilimumab treatment or followed the pattern of adjuvant therapy (4 doses of 3 weeks cycle followed by maintenance therapy every 12 weeks). Lymph node dissection was identified using relevant CPT codes (Supplemental Table 1B).

2.3 | Study design and key variables

All patients were indexed to the date of their initial first line treatment, defined as the first treatment (immunotherapy or targeted therapy) that started within 90 days of their diagnosis date. In conjunction with clinical input, different lines of treatment were defined when there was a switch of treatment or a gap of more than 3 months between same treatments. For example, if there was a gap of more than 3 months between two nivolumab administrations, we considered that nivolumab was re-initiated as second line treatment. National Drug Codes (NDC) and Healthcare Current Procedural Classification System (HCPCS) codes were used to identify melanoma treatment claims for immunotherapy and targeted therapy (Supplemental Table 1C,D).

In addition to treatment patterns, we described OS and TTF. TTF was defined as the time from treatment initiation to (1) start of the next melanoma therapy, (2) hospice, or (3) death, whichever occurred first. The implementation of TTF in literature and how we defined *next melanoma therapy* is described in Supplemental Table 2 and 3. For example, if the first line therapy and the subsequent therapy were both PD-1 inhibitor monotherapies (either nivolumab or pembrolizumab), the subsequently used PD-1 inhibitor was not considered the next melanoma therapy that defined treatment failure. If the first line therapy was PD-1 inhibitor monotherapy (nivolumab or pembrolizumab) and the subsequent therapy was CTLA-4 + PD-1 inhibitor combination (e.g., ipilimumab+nivolumab), this was considered a treatment failure (Supplemental Table 3). OS was defined using vital

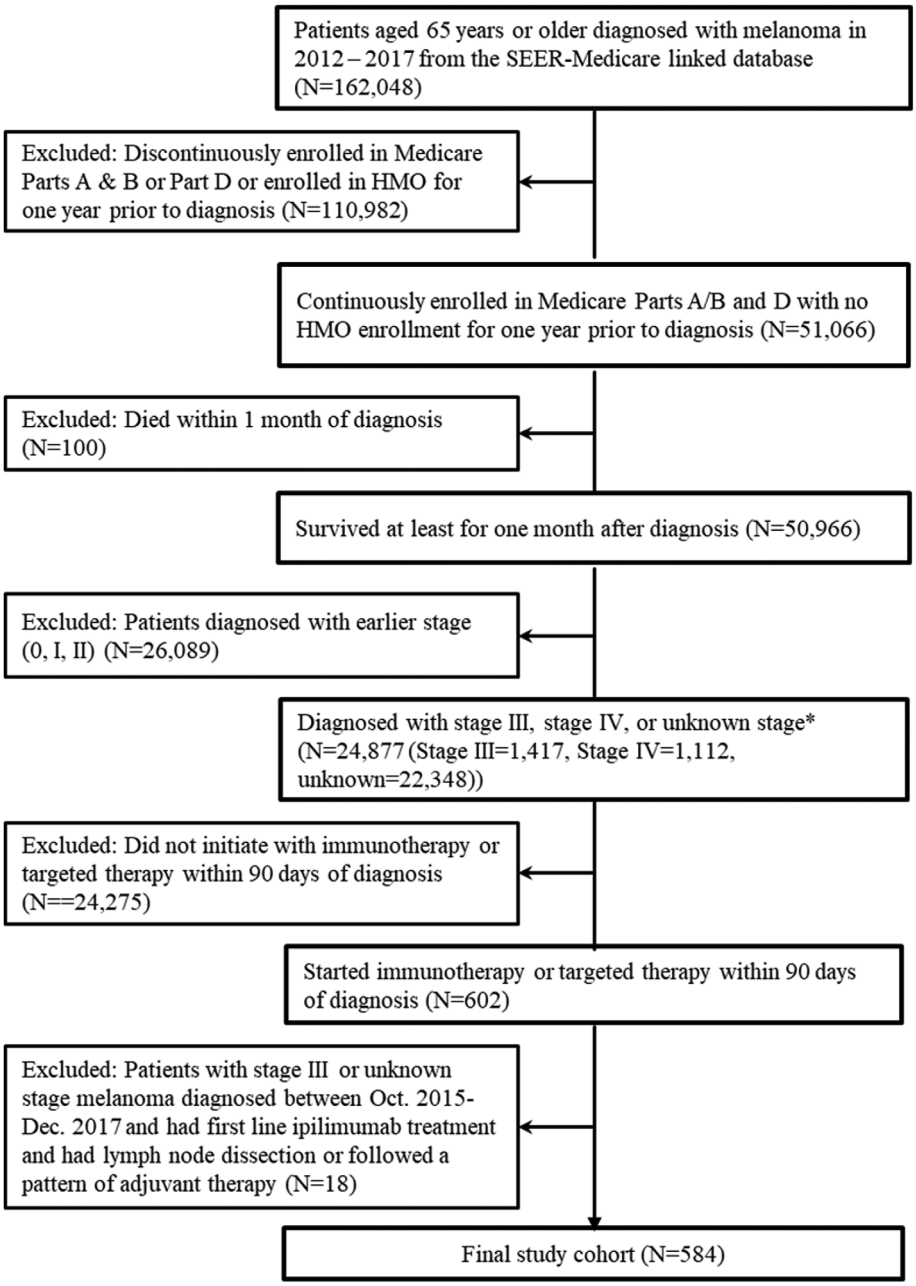

FIGURE 2 Sample identification flow chart. * We included melanoma patients with unknown stage when defining the study cohort as we assumed patients were being treated for advanced melanoma if they received immunotherapy or targeted therapy as first line treatment. However, the proportion of eligible patients (i.e., those who started with immunotherapy or targeted therapy) with unknown stage was minimal (<70). This explains the significant reduction in the number of eligible patients described in the flow chart. The large proportion of melanoma patients with unknown stage is also observed elsewhere.[38]

status and date of death reported by Medicare through December 31, 2018. Death data reported from Medicare has high accuracy, as 99% of death dates have been validated against the Social Security Administration death index.[23]

We defined covariates as described by category below.

2.3.1 | Sociodemographic characteristics

We described patient and area-level characteristics including age at diagnosis (65–70, 71–75, 76–80, or ≥80 years), sex (female or male), race (white, other, or unknown), marital status (married, not married, or unknown), Medicare Part D low-income subsidy (LIS) status (full or partial LIS or no LIS), and census tract poverty status. The LIS is designed to reduce low-income patients' out of pocket cost for Medicare Part D covered prescription drugs (e.g., oral targeted therapy). Census track poverty status (percentage of residents living below the federal poverty level) is an area-level measure that indicates socioeconomic disparities and was divided into quartiles: < 4%, 4 – <7%, 7 – <13%, and ≥13%.

2.3.2 | Clinical characteristics

Patient-level clinical characteristics were also described, including comorbidity, frailty, and the number of hospitalizations in the 3 months prior to melanoma treatment. For comorbidities, the Charlson Comorbidity Index (excluding cancer) was applied.[24] The study adopted a 1-year look back period prior to diagnosis to

TABLE 1 Patient characteristics

Patient characteristics	First line immunotherapy, *n* (%), *N* = 502	First line targeted therapy, *n* (%), *N* = 82	All patients, *n* (%) *N* = 584
Age			
Mean (SD)	76.3 (6.9)	75.4 (7.1)	76.2 (6.9)
Median	75	73.5	75
65–70	120 (23.9)	21 (25.6)	142 (24.3)
71–75	134 (26.7)	25 (30.5)	159 (27.2)
76–80	113 (22.5)	16 (19.5)	129 (22.1)
81+	135 (26.9)	20 (24.4)	155 (26.5)
Sex			
Female	154 (30.7)	30 (36.6)	184 (31.5)
Male	348 (69.3)	52 (63.4)	400 (68.5)
Race			
White	483 (96.2)	78 (95.1)	561 (96.1)
Other	[b]	[b]	[b]
Unknown	[b]	[b]	[b]
Marital status			
Married	246 (49.0)	39 (47.6)	285 (48.8)
Not married	99 (19.7)	21 (25.6)	120 (20.6)
Unknown	157 (31.3)	22 (26.8)	179 (30.7)
Part D low-income subsidy (LIS)			
Full or partial LIS	60 (12.0)	13 (15.9)	73 (12.5)
No LIS	442 (88.0)	69 (83.1)	511 (87.5)
% of residents living below poverty			
13%+	127 (25.3)	21 (25.6)	148 (25.3)
7% – <13%	128 (25.5)	23 (28.0)	151 (25.9)
4% – <7%	116 (23.1)	20 (24.4)	136 (23.3)
<4%[a]	131 (26.1)	18 (22.0)	149 (25.5)
Melanoma stage			
Stage III	92 (18.3)	[b]	[b]
Stage IV	353 (70.3)	65 (79.3)	418 (71.6)
Unknown	57 (11.4)	[b]	[b]
Year of diagnosis			
2012–2013	77 (15.4)	18 (21.9)	95 (16.3)
2014–2015	143 (28.4)	35 (42.7)	178 (30.5)
2016–2017	282 (56.2)	29 (35.4)	311 (53.3)
Charlson Comorbidity Index (CCI)			
0	231 (46.4)	35 (43.2)	266 (45.9)
1	107 (21.5)	26 (32.1)	133 (23.0)
2+	160 (32.2)	20 (24.7)	180 (31.0)
Predicted probability of frailty			
<5%	56 (11.2)	16 (19.5)	72 (12.3)
5 – <10%	230 (45.9)	19 (23.2)	249 (42.6)
10 – <20%	126 (25.1)	24 (29.3)	150 (25.7)
20 – <40%	62 (12.4)	12 (14.6)	74 (12.7)
40%+	28 (5.6)	11 (13.4)	39 (6.7)

TABLE 1 (Continued)

Patient characteristics	First line immunotherapy, *n* (%), *N* = 502	First line targeted therapy, *n* (%), *N* = 82	All patients, *n* (%) *N* = 584
Brain metastasis			
Brain metastasis	140 (27.9)	33 (40.2)	173 (29.6)
No brain metastasis	362 (72.1)	49 (59.8)	411 (70.4)
Number of metastatic regions			
0–1	210 (41.8)	27 (32.9)	237 (40.6)
2	121 (24.1)	13 (15.9)	134 (22.9)
3+	171 (34.1)	42 (51.2)	213 (36.5)
Number of hospitalizations for 3 months prior to diagnosis			
0	352 (70.1)	45 (54.9)	397 (68.0)
1	118 (23.5)	26 (31.7)	144 (24.7)
2+	32 (6.4)	11 (13.4)	43 (7.4)
Teaching hospital status			
Teaching	358 (71.3)	42 (51.2)	400 (68.5)
Non-teaching	144 (28.7)	40 (48.8)	184 (31.5)
NCI-designated cancer center			
Yes	196 (39.0)	23 (28.0)	219 (37.5)
No	306 (61.0)	59 (72.0)	365 (62.5)

[a]For % of residents living below poverty, missing category is included in the lowest category (<4%).
[b]All cell size of <11 patients were suppressed.

identify comorbidities. Frailty was quantified as the predicted probability of frailty (<5%, 5–<10%, 10–<20%, 20–<40%, or ≥40%) using a validated Medicare claims-based algorithm.[25,26]

2.3.3 | Cancer characteristics

Direct measures for symptom severity or disease progression status of cancer are not available in the SEER registry or claims database. In this study, history of brain metastasis and number of metastatic regions were used as variables that represented severity of symptoms and tumor burden. Stage of melanoma was also reported.

2.3.4 | Provider characteristics

Teaching hospital status and whether hospitals were National Cancer Institute (NCI)-designated cancer centers or not were also reported.

2.4 | Data analysis

Descriptive statistics were used to summarize patient demographic and clinical characteristics, cancer characteristics and provider type by first line treatment. Changes in the number of patients who received immunotherapy and targeted therapy as first line treatment over the study period were reported. Changes in the distribution of first line therapy over calendar time was also reported by treatment sub-category (CTLA-4 inhibitor, PD-1 inhibitor monotherapy, CTLA-4 + PD-1 inhibitor combination therapy, BRAF inhibitor monotherapy, and BRAF+MEK inhibitor combination therapy). As part of the descriptive analysis, the unadjusted estimates of median OS and TTF with 95% confidence interval were reported by treatment sub-category using the Kaplan–Meier method.

Patterns of treatment sequence were also described. The proportion of patients who completed one line, two lines or three or more lines of therapy was reported. The most common treatment switch patterns (first to second line treatment) and associated calendar time trends were reported by treatment sub-category.

Treatment sequences up to third line treatment were identified among those who had ≥2 lines of treatment. Patients receiving their first- or second-line treatment until the end of the study period were excluded from sequential analysis because their second- or third-line treatment status could not be defined. Additionally, patterns of treatment sequence were identified for those who had at least one targeted therapy in their treatment continuum: these patients were considered to have BRAF-mutant melanoma in the absence of BRAF mutation status in the SEER-Medicare database.

Patients who did not maintain their Medicare Parts A and B fee-for-service enrollment and Part D enrollment were censored as treatment information could have been missing otherwise. All cell sizes <11 were suppressed in accordance with the SEER-Medicare confidentiality policy. All analyses were conducted using SAS 9.4 and STATA 17.

3 | RESULTS

3.1 | Study population

A total of 584 eligible melanoma patients who started with immunotherapy or targeted therapy were identified and included in the analysis (Figure 2). The baseline patient characteristics by first line treatment are presented in Table 1. The mean age of the patients was 76 years (SD: 6.9, median 75 years). Most patients (86.0%, $n = 502$) initiated treatment with immunotherapy. About two-thirds (68.5%) of patients were treated in teaching hospitals. More patients who initiated treatment with immunotherapy were from teaching hospitals compared to those initiating with targeted therapy (71.3% vs. 51.2%). There was a higher proportion of patients with an increased predicted probability of frailty in the targeted therapy group than in the immunotherapy group. We did not observe defining patterns of comorbidity burden between two treatment groups.

3.2 | Pattern of first line treatment

Among 502 patients who received first line immunotherapy, the percentage of patients who received a PD-1 inhibitor, CTLA-4 inhibitor, and CTLA4 + PD-1 inhibitor combination therapy was 50.2% ($n = 252$), 35.7% ($n = 179$), and 14.1% ($n = 71$), respectively. Among 82 patients who received first line targeted therapy, 65.9% ($n = 54$) had BRAF+MEK inhibitor combination therapy and 34.1% ($n = 28$) had single agent BRAF inhibitor. Use of immunotherapy as first line treatment has been continually increasing since 2012 with a marked increase between 2015 and 2016 (Figure 3A). Use of first line targeted therapy increased between 2012 and 2014, then became steady and started declining in 2017 (Figure 3A).

Figure 3B shows the distribution of first line therapy by treatment sub-category in 2015–2017 when compared to 2012–2014. Ipilimumab monotherapy was largely replaced by PD-1 inhibitors from 2015 onwards. The combination therapy of CTLA-4 + PD-1 inhibitor

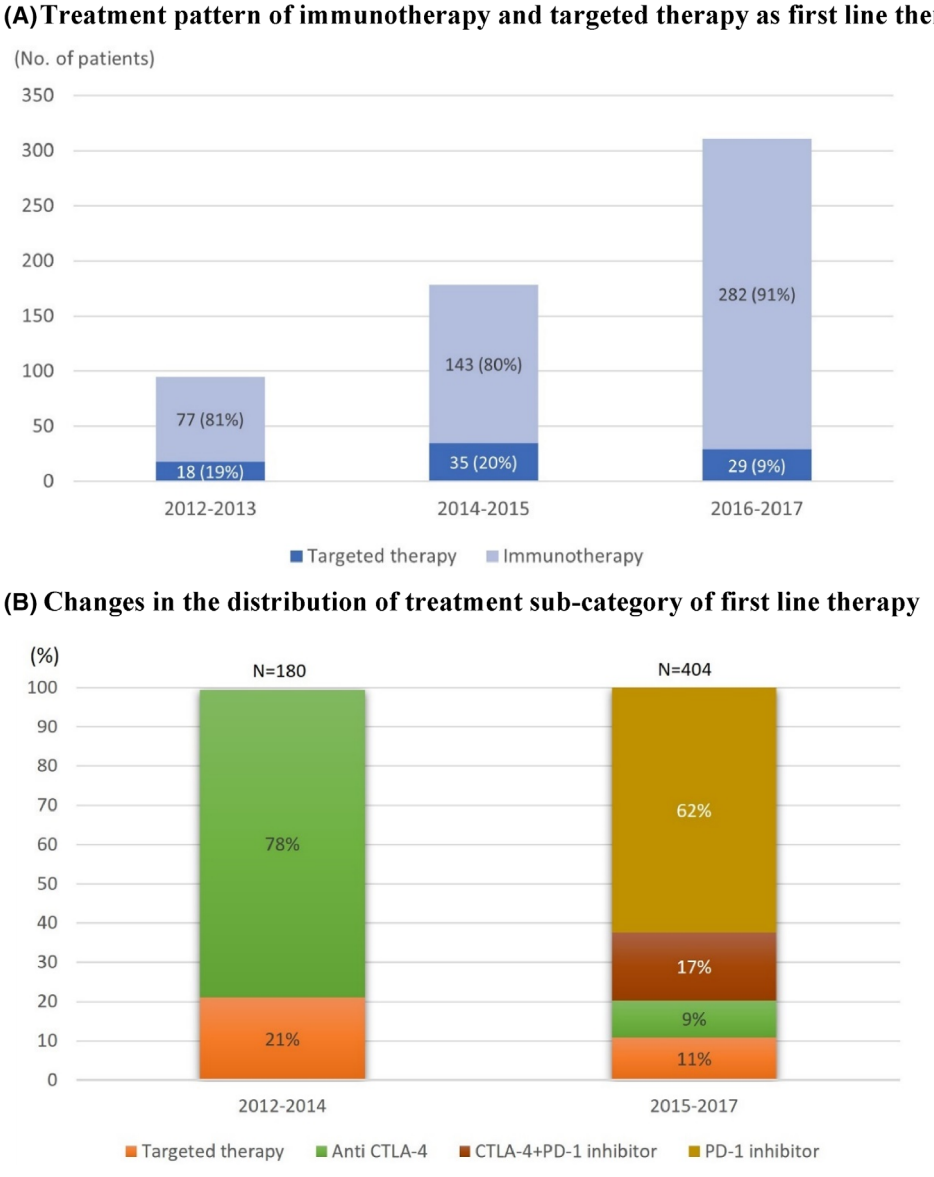

FIGURE 3 First line therapy for patients who were diagnosed with unresectable or metastatic melanoma in 2012–2017. (A) Treatment pattern of immunotherapy and targeted therapy as first line therapy. (B) Changes in the distribution of treatment sub-category of first line therapy. Targeted therapies (BRAF inhibitor monotherapy and combination therapy) are reported as one combined category. PD-1 inhibitors were approved by Food and Drug Administration (FDA) in late 2014, followed by CTLA-4 + PD-1 inhibitor combination therapy in 2015.

TABLE 2 Kaplan–Meier estimates of overall survival (OS) and time to treatment failure (TTF) by treatment category for patients who received first-line immunotherapy or targeted therapy

A. Overall survival by first line treatment	
First line treatment	**Overall survival**
BRAF inhibitor	*N* = 28
Median OS (95% CI)	7.2 months (3.1–9.2)
1-year survival rate (95% CI)	28.6% (13.5%–45.6%)
2-year survival rate (95% CI)	17.9% (6.5%–33.8%)
BRAF + MEK inhibitor	*N* = 54
Median OS (95% CI)	6.2 months (4.9–7.9)
1-year survival rate (95% CI)	30.8% (19.1%–43.3%)
2-year survival rate (95% CI)	18.5% (9.3%–30.1%)
CTLA-4 inhibitor	*N* = 179
Median OS (95% CI)	18.5 months (12.4–26.7)
1-year survival rate (95% CI)	58.7% (51.1%–65.5%)
2-year survival rate (95% CI)	45.6% (38.1%–52.7%)
PD-1 inhibitor	*N* = 252
Median OS (95% CI)	25.9 months (19.6-NA)
1-year survival rate (95% CI)	66.4% (60.1%–70.0%)
2-year survival rate (95% CI)	52.7% (45.7%–59.2%)
CTLA-4 + PD-1 inhibitor	*N* = 71
Median OS (95% CI)	28.4 month (9.6-NA)
1-year survival rate (95% CI)	57.5% (45.1%–68.0%)
2-year survival rate (95% CI)	53.5% (40.9%–64.6%)
B. Time to treatment failure by first line treatment	
First line treatment	**Time to treatment failure**
BRAF inhibitor	*N* = 27
Median TTF (95% CI)	3.6 months (2.3–7.0)
1-year without TF (95% CI)	14.8% (4.7%–30.5%)
2-year without TF (95% CI)	7.4% (1.3%–21.0%)
BRAF + MEK inhibitor	*N* = 53
Median TTF (95% CI)	4.9 months (3.5–5.7)
1-year without TF (95% CI)	18.9% (9.7%–30.3%)
2-year without TF (95% CI)	14.7% (6.7%–25.6%)
CTLA-4 inhibitor	*N* = 176
Median TTF (95% CI)	5.8 months (4.8–8.3)
1-year without TF (95% CI)	33.5% (26.7%–40.5%)
2-year without TF (95% CI)	21.2% (15.6%–27.6%)
PD-1 inhibitor	*N* = 243
Median TTF (95% CI)	16.7 months (10.6–24.0)
1-year without TF (95% CI)	54.5% (47.9%–60.1%)
2-year without TF (95% CI)	42.0% (35.1%–48.8%)
CTLA-4 + PD-1 inhibitor	*N* = 71
Median TTF (95% CI)	9.5 month (3.8–18.3)
1-year without TF (95% CI)	41.8% (30.3%–53.0%)
2-year without TF (95% CI)	38.0% (26.6%–49.4%)

Abbreviations: TF, treatment failure; TTF, time to treatment failure.

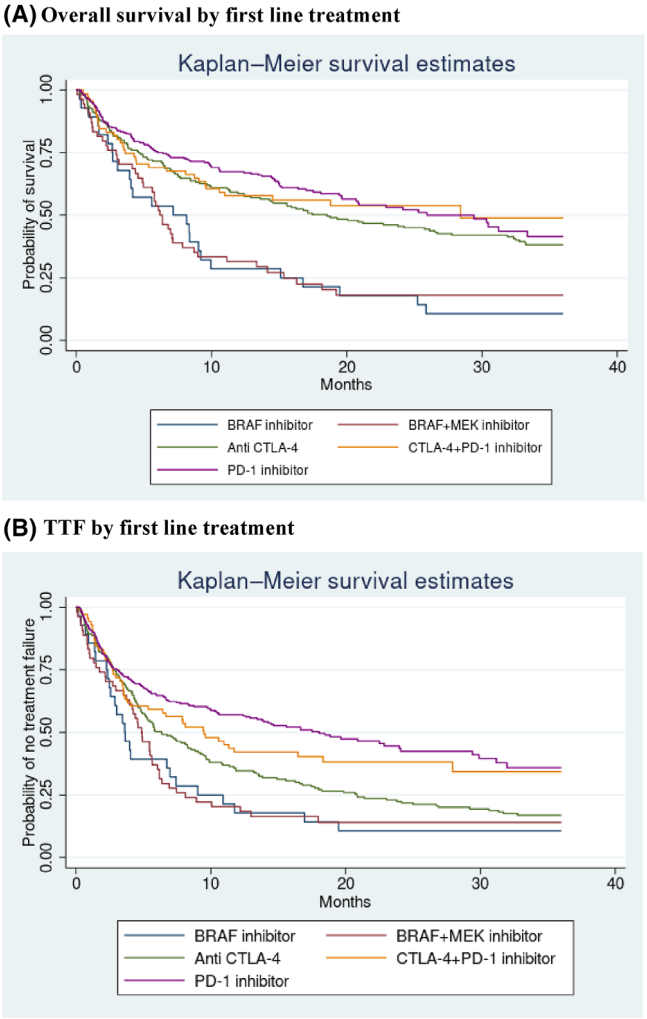

FIGURE 4 Kaplan–Meier plot for overall survival and time to treatment failure by first-line treatment category. (A) Overall survival by first line treatment. (B) Time to treatment failure (TTF) by first line treatment.

became widely used from 2016. There was a significant decrease in proportion of targeted therapy in 2015–2017 when compared to 2012–2014 (Figure 3B). BRAF inhibitors were the main targeted therapies in use until 2013 with BRAF+MEK inhibitor combination therapies becoming more commonly used from 2014.

3.3 | Overall survival and time to treatment failure

Table 2 presents Kaplan–Meier estimates of OS and TTF by treatment category for patients who received first-line immunotherapy or targeted therapy. The median OS estimates from the treatment initiation were longer with immunotherapy when compared to targeted therapy with the median OS for CTLA-4 + PD-1 inhibitor being the longest (28.4 months, 95% CI: 9.6-NA) among all categories. PD-1 inhibitor had the longest median TTF (16.7 months, 95% CI: 10.6–24.0). All three categories of immunotherapy treatment had longer observed

median TTF compared to targeted therapies. Kaplan–Meier plots for OS and TTF by first line treatment category are presented in Figure 4.

3.4 | Treatment sequence

The median follow-up time for the cohort was 13 months (Q_1: 4 months, Q_3: 24 months). The distribution of follow-up time by calendar years is presented in the Supplemental Table 4. Among 584 patients, 59.6% ($n = 348$) had only a single line of treatment, 16.3% ($n = 95$) had two lines of treatment and 11.1% ($n = 65$) received three or more lines of treatment. Among patients who received one line of treatment, 85.1% ($n = 296$) received first line immunotherapy and 47.6% ($n = 140$) of those patients died within 1 year of treatment initiation. Among the patients who had one line of treatment and initiated with targeted therapy ($n = 52$), 80.8% ($n = 42$) died within 1 year of treatment initiation.

The most common treatment switch pattern among patients who received at least two lines of treatment ($n = 176$) was from first line CTLA-4 inhibitor to second line PD-1 inhibitor (Table 3A). In a subgroup analysis of those who were presumed to be BRAF positive (meaning they had received targeted therapy at least once during the observation period) and received at least two lines of treatment ($n = 77$), the most common switch pattern was from first line PD-1 inhibitor to second line BRAF+MEK inhibitor combination therapy (Table 3A). About two-thirds (68%, $n = 52$) of patients who were presumed to be BRAF positive received immunotherapy as first line treatment. The changes in first to second line patterns were identified over the study period (2012–2013, 2014–2015, and 2016–2017) (Table 3B).

Figure 5A shows the treatment sequence of up to third line treatment in all patients ($n = 140$) who had multiple lines of treatment. Most patients received immunotherapy in each line of treatment. Figure 5B depicts the treatment sequence in the subgroup of presumed BRAF positive patients. In this subgroup, more patients had immunotherapy than targeted therapy as first line treatment and more than 90% of patients had at least one immunotherapy in their treatment continuum through third line treatment.

TABLE 3 Treatment switch pattern (first to second line) in patients with ≥2 lines of treatment

A. Treatment switch patterns (in all patients diagnosed in 2012–2017)

Rank[a]	All patients ($N = 176$)	Presumed BRAF positive patients ($N = 77$)[e]
1	CTLA-4[b] → PD-1[b]	PD-1 → BRAF+MEK
2	PD-1 → PD-1[c]	CTLA-4 → BRAF[b]
3	PD-1 → BRAF+MEK[b]	PD-1 → PD-1
3	PD-1 → CTLA-4	BRAF+MEK → PD-1
5	CTLA-4 → Other[d]	CTLA-4 → BRAF+MEK

B. Treatment switch patterns by rank and calendar period

	All patients ($N = 176$)		Presumed BRAF positive patients ($N = 77$)[e]	
Years	Rank	First → Second line	Rank	First → Second line
2012–2013	1	CTLA-4 → Other	1	CTLA-4 → BRAF
	2	CTLA-4 → BRAF	2	CTLA-4 → PD-1
	3	CTLA-4 → PD-1	2	CTLA-4 →BRAF+MEK
			2	BRAF → CTLA-4
2014–2015	1	CTLA-4 → PD-1	1	CTLA-4→ BRAF
	2	CTLA-4 → BRAF	1	CTLA-4 → PD-1
	3	CTLA-4 → Other	2	CTLA-4 → BRAF+MEK
			2	PD-1 → BRAF+MEK
2016–2017	1	PD-1 → PD-1	1	PD-1 → BRAF+MEK
	2	PD-1 → CTLA-4 + PD-1	2	CTLA-4 + PD-1 → BRAF+MEK
	3	PD-1 → BRAF+MEK	2	BRAF+MEK → PD-1
	3	PD-1 → CTLA-4		

[a]Rank is reported in order of the most to least common patterns. All cell sizes are suppressed due to several cells being <11, in accordance with the confidentiality policy.
[b]CTLA-4: CTLA-4 inhibitor, PD-1: PD-1 inhibitor, BRAF: BRAF inhibitor, BRAF+MEK: BRAF+MEK inhibitor.
[c]When there was a ≥3 months gap between same treatments, they were considered different lines of treatment.
[d]Other category included old chemotherapy medications (e.g., dacarbazine, cisplatin, carboplatin), interferon alpha 2B, and talimogene laherparepvec (T-Vec).
[e]Presumed BRAF-positive patients are those who have received at least one targeted therapy in the study period.

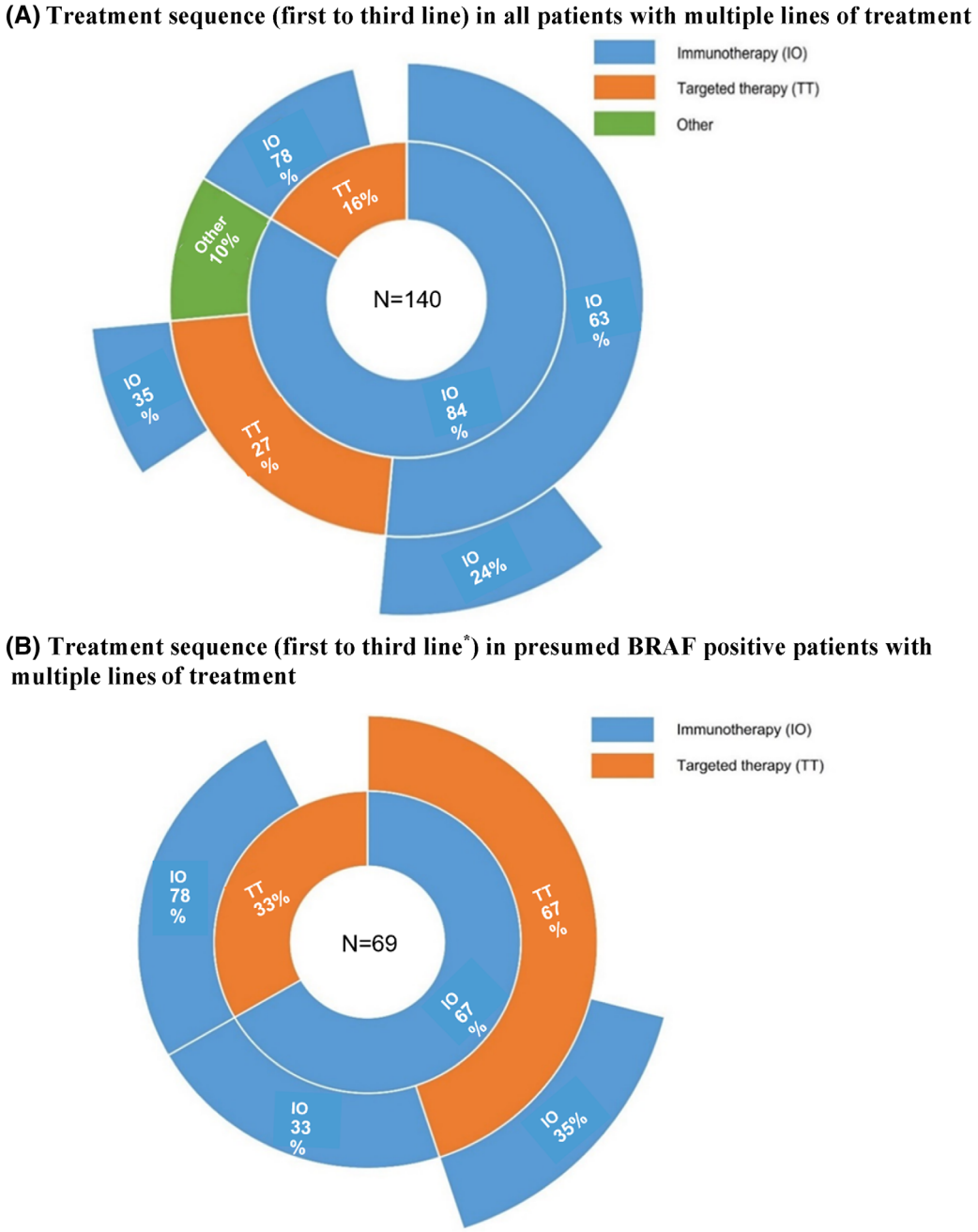

FIGURE 5 Treatment sequence in patients with multiple (2+) lines of treatment. (A) Treatment sequence (first to third line) in all patients with multiple lines of treatment. (B) Treatment sequence (first to third line) in presumed BRAF positive patients with multiple lines of treatment. The three rings indicate different lines of treatment (First through third line from the inner-most to the outer ring). The total number of patients receiving the prior line of therapy is the denominator for calculating the percentage of patients receiving the next line of therapy. For example, of patients who received first line immunotherapy in Figure 5A, 63% chose immunotherapy as second line and 24% of those who had the second line immunotherapy chose immunotherapy as third line treatment. Line of therapy is presented in the charts where groups had ≥11 patients.

4 | DISCUSSION

In this study, we described real-world treatment patterns and outcomes by first line treatment with immunotherapy and targeted therapy in older patients with advanced melanoma, using SEER-Medicare data (2012–2018). We observed distinct patterns of use of immunotherapy and targeted therapy and trends over time. There was a continual increase in use of immunotherapy in patients diagnosed with advanced melanoma between 2012 and 2017, which was not the case with targeted therapy (Figure 3A). Clinical trial data published since 2015 showing favorable progression-free survival and OS outcomes of PD-1 inhibitors and CTLA-4 + PD-1 inhibitor combination therapy likely had an impact on uptake of these immunotherapies.[27,28]

Changes in the distribution of first line therapy generally reflected the introduction (FDA approvals) of new immunotherapies and targeted therapies.[8] Among immunotherapies, it was notable that PD-1 inhibitor monotherapy was much more frequently used when compared to CTLA-4 + PD-1 inhibitor combination therapy as first line therapy in 2016 (79 vs. 28 patients) and 2017 (125 vs. 37 patients). Previous observational studies have described treatment patterns in younger patients (18 years or older), primarily from community cancer practices using electronic health records (EHR) or commercial claims database.[12–15] Similar to our findings, PD-1 inhibitor monotherapy was more commonly used than the combination checkpoint inhibitor but with varied ratios in different studies. In our study, greater use of PD-1 inhibitor monotherapy may be mainly due to an increased concern about the impact of toxicities associated with the use of combination immunotherapy in older and more frail patients.[29] In a qualitative study that examined the decision-making process for advanced melanoma, most clinicians mentioned they would choose PD-1 inhibitor monotherapy more frequently over the combination therapy for older patients with poor performance status because of such concerns.[30]

Current literature indicates targeted therapy is a preferred option when patients have more symptomatic disease which often accompanies a high tumor burden.[30–32] Patients who received targeted therapy as first line treatment were more likely to have brain metastasis, a higher predicted level of frailty, and a more frequent number of hospitalizations prior to diagnosis in our data when compared to those who had first line immunotherapy. We did not observe any trend in comorbidity burden across the use of first line treatment. The frailty measure used in our study may be closely related to the cancer-related characteristics that indicate severity of the disease as frailty is considered to be associated with adverse health outcomes.[26] The percentage of patients diagnosed at stage IV was higher in those who initiated treatment with targeted therapy than with immunotherapy, although stage IV patients were the majority in both treatment groups. We also observed that a greater proportion of patients receiving first line immunotherapy were treated in teaching hospitals when compared to patients treated with first line targeted therapy (71.3% vs. 51.2%). This may suggest academic cancer centers have led the uptake of immunotherapy with non-academic centers following, but this dynamic requires more scrutiny. While using different study populations, the proportion of first line targeted therapy use in the previous studies that used the EHR from community cancer practices tended to be higher than that of ours.[12,14,15]

When compared to previous clinical studies, the median OS observed across different first line treatment categories were much shorter within our population. This was not surprising since for most clinical trials of these treatments, more than 60% of patients were younger than 65 years and median age ranged from 50 to 60 years.[4,27,33,34] In our analysis, median age was 75 years. In our study, CTLA-4 + PD-1 inhibitor use had the longest median OS, followed by PD-1 inhibitor, CTLA-4 inhibitor, BRAF inhibitor, and BRAF+MEK inhibitor use. In the recent 5-year follow up clinical trials, the median OS of BRAF+MEK inhibitor use was significantly longer than that of BRAF inhibitor use but we had different results.[3–5] Median OS was 7.2 months with BRAF monotherapy and 6.2 months with BRAF+MEK inhibitor in our study. Our study sample was neither randomized nor adjusted for head-to-head comparisons, as such, these results are purely descriptive and do not represent causal relationships between treatment and outcomes. All three categories of immunotherapy had longer median OS and TTF when compared to targeted therapies. Although this was expected based on previous data, some of the observed difference may be due to systematic bias, including confounding by indication.

In our study, we found that the number of patients who received a single line of treatment was high (about 60%). This highlights the importance of selecting first line treatment as it relates to survival and risk of side effects. To identify treatment sequences, we have conducted a subgroup analysis by creating a presumed BRAF positive group by selecting patients who had targeted therapy at least once in their treatment continuum. It was notable that immunotherapy was still the dominant first line treatment option in this sub-group and substantially used in second- and third-line therapy. As the data could only underestimate the use of immunotherapy in this group—by potentially excluding patients who had immunotherapy only despite having BRAF mutant melanoma, it seems that immunotherapy was a preferred first choice of treatment regardless of BRAF status. The recently released results from two clinical trials suggest better outcomes if patients with a BRAF mutation are given first line immunotherapy rather than starting with targeted therapy. The DREAMseq and SECOMBIT trials aimed to address the optimal sequencing of immunotherapy and targeted therapy in treatment naïve patients with a BRAF mutation.[35,36] In the DREAMseq trial, in which patients were randomized to receive either combination checkpoint inhibitor or BRAF+MEK inhibitor and received the alternate therapy at disease progression, patients who started with immunotherapy had superior two-year landmark OS than those who initiated with BRAF+MEK inhibitor.[35] The SECOMBIT trial was composed of three randomized arms (immunotherapy first, targeted therapy first, or an approach of 8 weeks of targeted therapy followed by planned switch to immunotherapy followed by targeted therapy at time of progression) and the results showed the same trend, although the trial was a phase II non-comparative study.[36] Extrapolation of these clinical trial findings to the Medicare population is challenging, as treatment switches can be triggered by many different factors in real-world practice. Nonetheless, these trial results provide robust evidence supporting the current clinical trend, particularly in teaching hospitals, to lead with immunotherapy and may encourage a change in treatment practices across the broader treating community.

This study has several limitations. As the treatment related information was only available through billing codes required for Medicare reimbursement, we were not able to capture treatments provided through clinical trials or patient assistance programs. There were many ongoing clinical trials of new immunotherapies and targeted therapies during our study period and missing such information could have affected our classification of lines of therapy and analyses of TTF. It is also possible that claims database studies like ours could be affected by immeasurable time bias that could potentially cause a

treatment gap issue, especially with oral medications when patients are hospitalized.[37] Although the effect of immeasurable time bias was deemed minimal in our analyses, future studies based on a large claims database should consider this limitation. Secondly, the SEER-Medicare data do not contain information about BRAF gene status. The subgroup analysis we conducted for treatment sequence may have excluded patients who had BRAF mutant melanoma and have received immunotherapies only through second line and beyond. Lastly, most patients in our sample were treated from teaching hospitals and the generalizability of our findings to community-based, non-teaching hospitals may be limited.

5 | CONCLUSION

Using Medicare claims data, we have described recent patterns of first line treatment and treatment sequence among older adults with advanced melanoma treated with immunotherapy or targeted therapy. We observed a sustained increase in use of immunotherapy over the study period (2012–2018). Notably, PD-1 inhibitor monotherapy became a dominant systemic treatment option around 2015 in this population, increasing the gap relative to other treatment options over calendar time in terms of first line treatment. In contrast, the proportion of patients who received first-line targeted therapy decreased in the second half of the study period. We also noted that immunotherapy was still the most used first line therapy in a subgroup of patients who were considered to have BRAF mutant melanoma and had multiple lines of treatment. In our study, most patients who started with immunotherapy or targeted therapy also received either of those therapies for second line or third line treatment.

ACKNOWLEDGMENTS

The study was supported by the Cancer Information and Population Health Resource, UNC Lineberger Comprehensive Cancer Center, with funding provided by the University Cancer Research Fund via the state of North Carolina.

CONFLICT OF INTEREST STATEMENT

Dr. Lund reports research support from AbbVie to UNC, research support from Roche Genentech to UNC, outside the submitted work. Dr. Betof Warner has received institutional research funding from Iovance, consulting fees from Bristol-Myers Squibb, BluePath Solutions, Immatics, Iovance, Instil Bio, Lyell Immunopharma, Novartis, Pfizer. Dr. Betof Warner has been reimbursed by Iovance for international conference attendance. All other authors declare no potential conflict of interest.

ETHICS STATEMENT

The study was approved by the University of North Carolina institutional review board (IRB Study #21–0335).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lee S, Bennett AV, Zhou X, et al. Real-world treatment patterns and outcomes for patients with advanced melanoma treated with immunotherapy or targeted therapy. *Pharmacoepidemiol Drug Saf*. 2023;32(9):988-1000. doi:10.1002/pds.5630