

# Treatment patterns and outcomes for patients with advanced melanoma in US oncology clinical practices

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**Aim:** To describe recent evolution in treatment patterns and outcomes for advanced melanoma (AMel).

**Methods:** This retrospective observational study analyzed de-identified electronic health record data from the Flatiron Health database for 1140 adult patients who initiated first-line therapy for AMel from 1 January 2014 to 30 June 2016 with follow-up through 28 February 2017. **Results:** The most common first-line regimens were ipilimumab-based therapies (34%), anti-PD-1 monotherapy (26%) and BRAF/MEK inhibitor(s) (20%). First-line ipilimumab-based and BRAF inhibitor regimens decreased after the third quarter of 2014 (3Q2014), and by 2Q2016, 55 and 91% of *BRAF*-mutant and *BRAF* wild-type cohorts, respectively, received a first-line anti-PD-1 regimen. Median overall survival from first-line initiation for all patients was 18.8 months (95% CI: 16.3–23.3). **Conclusion:** Results illustrate changing paradigms of therapy and real-world patient outcomes for AMel.

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**Keywords:** advanced melanoma • antineoplastic therapy • community oncology practice • immuno-oncology • observational study • overall survival • treatment pattern

The incidence rate of melanoma in the US has doubled in the past 40 years, a more rapid increase than for any other type of cancer [1,2], and similar trends have been observed in Europe and Australia [2,3]. Cutaneous melanoma represents 5.3% of all new cancer cases and is projected to be the fifth leading cause of cancer in the US in 2018 [4,5]. Historically, the median survival time for patients with advanced, unresectable (stage IV) melanoma was only 6–9 months, although this estimate is now becoming outdated with the introduction of newer therapies [2].

For many years, the primary systemic treatments for advanced melanoma (AMel) were chemotherapy – such as dacarbazine – and immunotherapy – such as IL-2. These therapies had low overall response rates ranging from 7 to 16%, often accompanied by associated side effects, and provided limited to no benefits on survival [6–9]. Indeed, no progress in improving survival rates was recorded during the last three decades of the 20th century [10]. Nonetheless, the potential of immunotherapy to treat melanoma has long been recognized, as high dose IL-2 can induce long-term remission, potentially cures, in a small number of patients with metastatic disease [11,12].

The promise of new immunotherapy agents and discoveries of isolated and treatable tumor-specific genetic mutations have now dramatically altered the landscape for systemic therapy of AMel. The start of a new era was heralded by the US FDA's approval of ipilimumab, an anti-CTLA-4 in March 2011, followed by approvals of targeted BRAF/MEK inhibitors, including vemurafenib, dabrafenib, trametinib and cobimetinib, and then two monoclonal antibodies directed against the PD-1 receptor, pembrolizumab and nivolumab in September 2014 and December 2014, respectively. These agents have all demonstrated significant improvements in progression-free and/or overall survival (OS) for patients with AMel in randomized controlled clinical trials [13–21].

Targeted therapy with BRAF/MEK inhibitors is indicated for patients with a *BRAF* V600 mutation, who comprise approximately 45% of patients with AMel [2,22,23]. The most recent data strongly suggest that combined therapy with BRAF and MEK inhibitors is more effective than monotherapy with either type of agent [24–26].

Treatments with these agents are characterized by rapid tumor shrinkage that is generally time limited, as the tumors often develop resistance [24,25]. Treatments with the so-called ‘checkpoint inhibitors’, such as ipilimumab, pembrolizumab and nivolumab, are associated with lower (but still impressive) response rates and less predictable kinetics of response but appear to have the potential for long-term clinical remissions and benefit [14,20,21,27]. Despite a fairly low-response rate and potentially severe toxicity with ipilimumab monotherapy, some patients can derive long-term clinical benefit and survival [28,29]. Anti-PD-1 therapy has demonstrated higher response rates with lower toxicity than ipilimumab although many patients do not respond [20,30–32]. Most recently, the combination of ipilimumab and nivolumab was approved by the FDA in 2016; however, its potential dramatic efficacy is offset by a heightened risk of toxicity [33,34].

The treatment of melanoma, more than that for any other cancer, has evolved so quickly over the past few years that it has been difficult for regulatory agencies, insurance payers and guideline committees to keep pace [35]. Yet the biggest challenge faced by physicians and patients is to select a treatment strategy from the lengthening list of effective therapies for what was previously a dismal prognosis. Additionally, patients seen in clinical practice may differ from those treated in randomized controlled clinical trials [36], and real-world evidence to complement trial findings can be useful to understand the outcomes of therapy in clinical practice [37]. The aims of this retrospective observational study were to understand the evolution of treatment patterns, time to next treatment line and associated OS for patients with AMel in US oncology clinical practices following the approval of these new therapies.

## Methods

### Data source

Our study population was identified from the Flatiron Health cloud-based longitudinal database derived from electronic health record (EHR) data from US cancer clinics [38]. At the time of the study, the Flatiron database contained EHR data available for analysis from over 265 cancer clinics across approximately 800 sites of care, including the active records of more than 1.7 million patients with cancer in the four US census regions. Refreshed monthly, the patient-level data are abstracted from EHRs and include structured data, such as laboratory values, limited biomarker information and prescribed drugs, in addition to unstructured data taken from physician’s notes in the medical record and other unstructured documents (e.g., detailed biomarker, radiology and pathology reports).

We included patients from the Flatiron AMel cohort (March 2017 analytic dataset, with mortality v1.0) [38], which includes patients with cutaneous melanoma at pathologic stage III or IV, either at initial diagnosis or at local or distant recurrence, and with at least two clinic encounters evident in the database occurring on or after 1 January 2011. To construct the cohort, a random, representative sample of patients is selected using a computer-based algorithm, and manual review of structured and unstructured data is conducted to ensure that those patients have the diagnosis of AMel. The diagnosis of melanoma is confirmed by review of pathology reports (International Classification of Diseases, Ninth Revision, Clinical Modification codes [ICD-9-CM] 172.0 through 172.9) [39], and melanoma is staged according to the treating physician’s charted notes plus radiology, pathology and surgical reports. Patients with noncutaneous melanoma (e.g., ocular, subungual, mucosal, palmar, plantar) are excluded.

Institutional review board approval of the study protocol was obtained through Flatiron procedure and approved by Copernicus Group institutional review board before study conduct and included a waiver of informed consent. Data provided to third parties were de-identified and provisions were in place to prevent re-identification in order to protect patients’ confidentiality.

### Patients

We included adult patients ( $\geq 18$  years) with a confirmed diagnosis of AMel who initiated first-line therapy for AMel from 1 January 2014, through 30 June 2016. These patients were followed until their last available medical record or to 28 February 2017, thereby providing minimum 8 months’ possible follow-up for each patient from the start of first-line therapy. Evidence in the structured data of enrollment in a clinical trial at any time was cause for exclusion.

### Data variables

Demographic variables available from the Flatiron database included sex, birth year, race and height and weight; age and BMI were derived from these data. Disease-related variables included melanoma stage at diagnosis, dates of initial melanoma and AMel diagnoses, Eastern Cooperative Oncology Group performance status (ECOG PS)

and presence of brain metastases (ICD-9-CM diagnosis code 198.3) and date. The Charlson Comorbidity Index score was derived from ICD-9 diagnostic data [40]; however, the Charlson Comorbidity Index was scored without consideration of AMel diagnosis since that was an entry criterion. The timing and results of *BRAF* mutation testing were captured by reviewing the relevant biomarker reports. Mortality data were captured through a combination of structured EHR data, unstructured EHR data (such as clinician notes and condolence letters), and external death data sources, including the US Social Security death index [41,42] and a commercial death dataset.

Treatment-related variables available in the database included drug names, route, dose and units, and the lines of therapy were determined by applying predefined algorithms. The first line of therapy for AMel was defined as the first systemic treatment regimen beginning either after or <14 days before the AMel diagnosis, and the index date was defined as the date of initiation of first-line therapy. Regimen components that began within 28 days of the first episode were considered to be part of a single line of therapy. A treatment line was advanced to the next line when a patient received new combinations of drugs or there was a gap in drug orders or administrations of >120 days. The line of therapy was not advanced if chemotherapy combinations were followed by a similar regimen in which one or more of the component drugs were suppressed for a period of time and then the drug(s) were subsequently reintroduced. A review of records indicated that treatments could change within the first month of initiation upon receipt of biomarker results. Therefore, if patients were switched to *BRAF*-targeted therapy during the first 28 days of a chemotherapy regimen (monotherapy or combination), the line of therapy was called *BRAF* therapy and the line number was not advanced. Not all Flatiron records contained days of supply data for oral drugs; when the information was missing, we assumed that the last prescription had 30 days' supply.

### Statistical analysis

Descriptive analyses were conducted to describe the patient population and treatment patterns, overall and according to *BRAF* mutation status at the index date. We determined frequencies and percentages for categorical variables and mean, standard deviation, median and range for variables measured on the continuous or interval scale. Patient characteristics and treatment patterns were described for all patients as well as according to *BRAF* status at the index date. The follow-up time was reported by summary statistics, and the median time to next treatment was reported using the Kaplan–Meier method. If a patient did not die nor initiate a next line of therapy, then this patient was considered still on the same line of therapy and was censored in the Kaplan–Meier estimate for time to next treatment line on the last visit date. OS was described using the Kaplan–Meier method, reporting median OS and associated 95% CI. Kaplan–Meier estimates of the percentage of patients on any therapy at 1 and 2 years were also reported.

Statistical analyses were performed using SAS 9.4 software (SAS Institute, Inc., NC, USA).

## Results

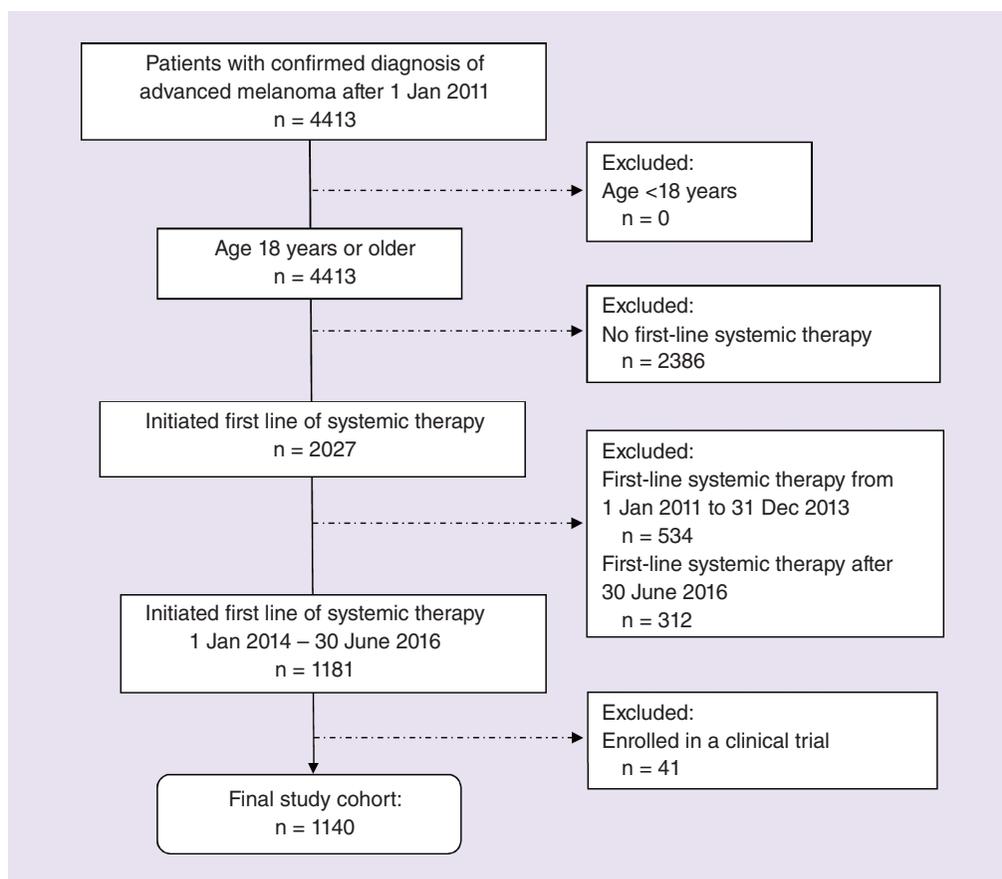
### Patients

Of the 4413 patients with a diagnosis of AMel from 2011 onward who were included in the Flatiron AMel cohort, 2027 (46%) initiated first-line systemic therapy and 1181 (27%) initiated the first line of systemic therapy during the study period from 1 January 2014 through 30 June 2016; all were  $\geq 18$  years of age. After excluding 41/1181 patients (3%) enrolled in clinical trials, the protocol-defined study cohort included 1140 eligible patients (97%) with AMel (Figure 1); of the 1140 patients, 78 (7%) were seen at academic centers and 1062 (93%) at community oncology clinics.

The median age at the index date was 68 years (range: 20–84 years): 68% of patients were male and 91% were white (excluding those with missing data; Table 1). The median ages were 63 and 71 years in *BRAF*-mutant and *BRAF* wild-type cohorts, respectively, and the sex distribution was 67 and 70% male, respectively.

Most patients (1037; 91%) were tested for *BRAF* mutation, and most patients (1014; 89%) had known *BRAF* mutation status, including 454 (45%) with *BRAF*-mutant melanoma and 560 (55%) with *BRAF* wild-type melanoma (Table 1). The 454 *BRAF*-mutant melanomas included 261 (57%), 68 (15%) and 24 (5%) with *BRAF* V600E, *BRAF* V600K and other *BRAF* mutation types, respectively; information on *BRAF* mutation type was unknown or missing for 101 (22%) tumors. The test types included PCR (43%), sequencing (35%) and other (missing or unknown, 22%).

Most patients who developed AMel received a first diagnosis of melanoma at stage III or later, including 327 patients (37%) overall with diagnosis at stage IV (Table 1). Of those with available data, 91 patients (17%) had ECOG PS of 2 or greater. An elevated LDH level at the index date was recorded for 29 and 22% of patients in



**Figure 1.** Selection of eligible patients in the database.

*BRAF*-mutant and *BRAF* wild-type cohorts, respectively, and history of brain metastases in 12 and 7%, respectively (Table 1).

### Treatment patterns

The median study follow-up was 9.9 months (range: 0.03–42.6 months) for all patients and 10.4 months in both *BRAF*-mutant and *BRAF* wild-type cohorts (Table 2). During follow-up, a total of 734 patients (64%) received only one line of therapy, 290 (25%) received two lines and 116 (10%) received three or more lines, as summarized by *BRAF* mutation status in Table 2.

The most commonly prescribed first-line regimens during the study period were ipilimumab as monotherapy or in combination with other than an anti-PD-1 agent (ipilimumab-based, 34%), anti-PD-1 monotherapy (26%) and regimens including a BRAF inhibitor (20%). The most commonly prescribed second-line regimens during the study were anti-PD-1 monotherapy (48%) and regimens including a BRAF inhibitor (20%; Table 3).

For all patients in the study (Figure 2A), the most common first-line regimens shifted during the study period from those including ipilimumab or BRAF inhibitors (49 and 28%, respectively, in the first quarter of 2014) to anti-PD-1 monotherapy or anti-PD-1 combination therapy (47 and 26% in the second quarter of 2016; percentages are rounded and may not be additive). The first-line treatment selected for patients with *BRAF*-mutated tumors shifted over the study period: the most common first-line regimen at the start of the study included a BRAF inhibitor (64%), and by the end of the index period, BRAF inhibitors (33%), anti-PD-1 monotherapy (30%) and anti-PD-1 combination therapy (25%) were utilized in similar proportions (Figure 2B). For *BRAF* wild-type melanoma (Figure 2C), an ipilimumab-based regimen was the most common first-line regimen at the start of the study, and by the end of the study, anti-PD-1 monotherapy (62%) and anti-PD-1 combination therapy (29%) were the most common regimens.

**Table 1. Patient demographic and clinical characteristics at the index date (initiation of first-line therapy).**

Variables	<i>BRAF</i> mutant (n = 454)	<i>BRAF</i> wild-type (n = 560)	<i>BRAF</i> status unknown (n = 126)	Total (n = 1140)
Male sex, n (%)	303 (66.7)	393 (70.2)	80 (63.5)	776 (68.1)
Median (IQR) age, years:	63 (53–73)	71 (61–80)	68 (60–79)	68 (58–77)
– Range	25–84	20–84	24–84	20–84
– <55 years, n (%)	125 (27.5)	69 (12.3)	18 (14.3)	212 (18.6)
– 55–64 years, n (%)	115 (25.3)	111 (19.8)	33 (26.2)	259 (22.7)
– 65–74 years, n (%)	113 (24.9)	151 (27.0)	26 (20.6)	290 (25.4)
– ≥75 years, n (%)	101 (22.2)	229 (40.9)	49 (38.9)	379 (33.2)
Race data available, n (%):	392 (86.3)	481 (85.9)	104 (82.5)	977 (85.7)
– White, n (%) <sup>†</sup>	362 (92.3)	441 (91.7)	86 (82.7)	889 (91.0)
– Other, n (%) <sup>†</sup>	30 (7.7)	40 (8.3)	18 (17.3)	88 (9.0)
Mean (SD) weight, <sup>‡</sup> kg	85.0 (20.7)	83.3 (19.0)	81.6 (18.2)	83.8 (19.6)
US CB region, data available, n (%):	427 (94.1)	516 (92.1)	112 (88.9)	1055 (92.5)
– Northeast, n (%) <sup>†</sup>	66 (15.5)	104 (20.2)	16 (14.3)	186 (17.6)
– Midwest, n (%) <sup>†</sup>	120 (28.1)	114 (22.1)	28 (25.0)	262 (24.8)
– South, n (%) <sup>†</sup>	159 (37.2)	209 (40.5)	50 (44.6)	418 (39.6)
– West, n (%) <sup>†</sup>	82 (19.2)	89 (17.2)	18 (16.1)	189 (17.9)
Adjusted CCI score, mean (SD):	2.9 (3.2)	2.8 (3.1)	3.1 (3.3)	2.9 (3.2)
– Median (IQR)	1 (0–6)	1 (0–6)	2 (0–6)	1 (0–6)
– Range	0–13	0–12	0–11	0–13
ECOG PS data available, n (%):	211 (46.5)	258 (46.1)	74 (58.7)	543 (47.6)
– ECOG 0–1, n (%) <sup>†</sup>	177 (83.9)	214 (82.9)	61 (82.4)	452 (83.2)
– ECOG ≥2, n (%) <sup>†</sup>	34 (16.1)	44 (17.1)	13 (17.6)	91 (16.8)
LDH level data available, n (%):	250 (55.1)	325 (58.0)	68 (54.0)	643 (56.4)
– Elevated LDH level, n (%) <sup>†,§</sup>	72 (28.8)	73 (22.5)	12 (17.6)	157 (24.4)
Stage available at first diagnosis, n (%): <sup>¶</sup>	340 (74.9)	440 (78.6)	106 (84.1)	886 (77.7)
– II or lower, n (%) <sup>†</sup>	121 (35.6)	153 (34.8)	37 (34.9)	311 (35.1)
– III, IIIA, IIIB, n (%) <sup>†</sup>	54 (15.9)	86 (19.5)	22 (20.8)	162 (18.3)
– IIIC, n (%) <sup>†</sup>	39 (11.5)	37 (8.4)	10 (9.4)	86 (9.7)
– IV, n (%) <sup>†</sup>	126 (37.1)	164 (37.3)	37 (34.9)	327 (36.9)
History of brain metastases, n (%):	55 (12.1)	41 (7.3)	9 (7.1)	105 (9.2)
– Tested for <i>NRAS</i>	86 (18.9)	110 (19.6)	10 (7.9)	206 (18.1)
– Positive <i>NRAS</i> status	1 (1.2)	43 (39.1)	4 (40.0)	48 (23.3)

<sup>†</sup> Patient percentages for race, region, ECOG PS, LDH level and stage at first diagnosis refer to those with available data.

<sup>‡</sup> Weight data were missing for 104 (9%) patients overall.

<sup>§</sup> Included were 20 (8.0%), 21 (6.5%) and 5 (7.4%) in the *BRAF*-mutant, *BRAF* wild-type and *BRAF* unknown cohorts, respectively, and 46 (7.2%) overall, with LDH levels ≥2 times the upper limit of normal.

<sup>¶</sup> Stage was a variable abstracted from the charts by trained abstractors; when missing, it was because of inadequate information available in the charts to determine stage (including inadequate information in the doctor's handwritten notes, pathology reports, etc.).

CCI: Charlson Comorbidity Index; ECOG PS: Eastern Cooperative Oncology Group performance status; IQR: Interquartile Range; LDH: Lactate dehydrogenase; US CB: US Census Bureau.

## Time to next treatment line & OS estimates

Table 4 summarizes the Kaplan–Meier estimates of time to next treatment line from first-line of therapy and overall by treatment category. The median time to next treatment line (including all treatment lines) for ipilimumab-based regimens was estimated at 4.9 months, anti-PD-1 monotherapy at 10.9 months, anti-PD-1 combination therapy at 8.2 months, *BRAF* inhibitor monotherapy at 4.7 months, *BRAF* inhibitor combination therapy at 6.8 months and other therapy at 4.5 months (Table 4).

From the time of initiation of first-line therapy, the Kaplan–Meier estimate of median OS for all patients was 18.8 months (95% CI: 16.3–23.3) with 1-year, 2-year and 3-year estimated survival rates of 60.7, 45.3 and 35.0%, respectively. The Kaplan–Meier estimate of median OS was 16.4 months (95% CI: 14.0–21.4) in the *BRAF*-mutant cohort and 24.7 months (95% CI: 18.4–not reached) in the *BRAF* wild-type cohort.

Table 2. Treatment summary.

Characteristics	<i>BRAF</i> mutant (n = 454)	<i>BRAF</i> wild-type (n = 560)	<i>BRAF</i> status unknown (n = 126)	Total (n = 1140)
Number of treatment lines received, n (%):				
– 1L only	259 (57.0)	379 (67.7)	96 (76.2)	734 (64.4)
– 1L + 2L	127 (28.0)	139 (24.8)	24 (19.0)	290 (25.4)
– 3 or more lines	68 (15.0)	42 (7.5)	6 (4.8)	116 (10.2)
Overview of treatment flow: <sup>†</sup>				
– Patients receiving 1L therapy, n (%)	454 (100)	560 (100)	126 (100)	1140 (100)
– Completed 1L, n (%)	321 (70.7)	325 (58.0)	75 (59.5)	721 (63.2)
– Advanced to 2L, n (% of 1L completers)	195 (60.7)	181 (55.7)	30 (40.0)	406 (56.3)
– Completed 2L, n (% of advancers)	127 (65.1)	102 (56.4)	16 (53.3)	245 (60.3)
– Advanced to 3L, n (% of 2L completers)	68 (53.5)	42 (41.2)	6 (37.5)	116 (47.3)
– Completed 3L, n (% of advancers)	46 (67.6)	24 (57.1)	5 (83.3)	75 (64.7)
– Advanced to 4L, n (% of 3L completers)	17 (37.0)	13 (54.2)	2 (40.0)	32 (42.7)
Received targeted therapy, n (%)	319 (70.3)	7 (1.3)	7 (5.6)	333 (29.2)
Months of follow-up, <sup>‡</sup> median (IQR):	10.4 (5.4–16.8)	10.4 (4.3–16.8)	7.3 (2.6–13.2)	9.9 (4.3–16.4)
– Range	0.03–42.6	0.3–37.9	0.03–35.0	0.03–42.6

<sup>†</sup>Patients were considered to have completed a line of therapy if there was a next line of therapy or a ≥60-day gap to the last visit date or if the patient died.  
<sup>‡</sup>Months of follow-up from the index date (start of first-line therapy) until death or loss to follow-up.  
 1L: First-line; 2L: Second-line; 3L: Third-line; 4L: Fourth-line; IQR: Interquartile range.

Median (95% CI) OS in months by first-line regimen type was 21.0 (15.7–28.7) for ipilimumab-based, 20.7 (19.7–not reached) for anti-PD-1 monotherapy, 17.4 (12.2–not reached) for anti-PD-1 combination therapy, 14.9 (8.8–31.0) for *BRAF* inhibitor monotherapy and 12.0 (9.1–15.7) for *BRAF* inhibitor combination therapy (Figure 3). The 1-year estimated survival rate by first-line regimen type was 62.0% (95% CI: 56.7–66.9%) for ipilimumab-based, 67.5% (61.4–72.8%) for anti-PD-1 monotherapy, 61.5% (51.6–70.0%) for anti-PD-1 combination therapy, 58.2% (45.2–69.2%) for *BRAF* inhibitor monotherapy and 48.9% (40.4–56.9%) for *BRAF* inhibitor combination therapy.

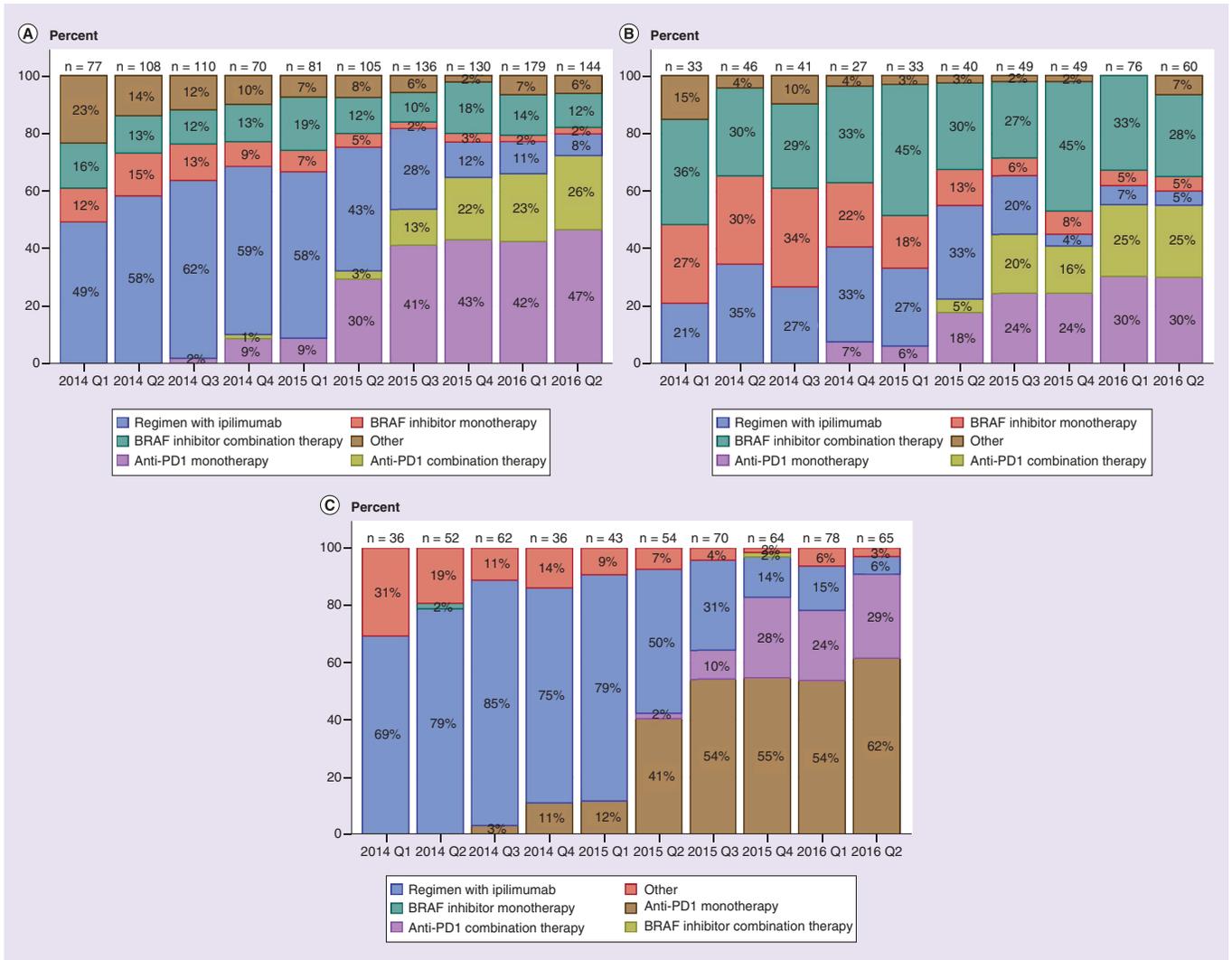
## Discussion

In this retrospective observational study, we observed that first-line treatment selection for AMel changed dramatically over the study period from 1 January 2014 through 30 June 2016. Specifically, ipilimumab-based and *BRAF* inhibitor monotherapy regimens were administered less frequently in the first-line setting after the third quarter of 2014, concurrent with FDA approval of anti-PD-1-based regimens beginning in the fourth quarter of 2014. The uptake of anti-PD-1 agents was observed in the *BRAF*-mutant cohort but was most dramatic for the *BRAF* wild-type cohort, 91% of whom received an anti-PD-1 agent as monotherapy or combination therapy in the second quarter of 2016.

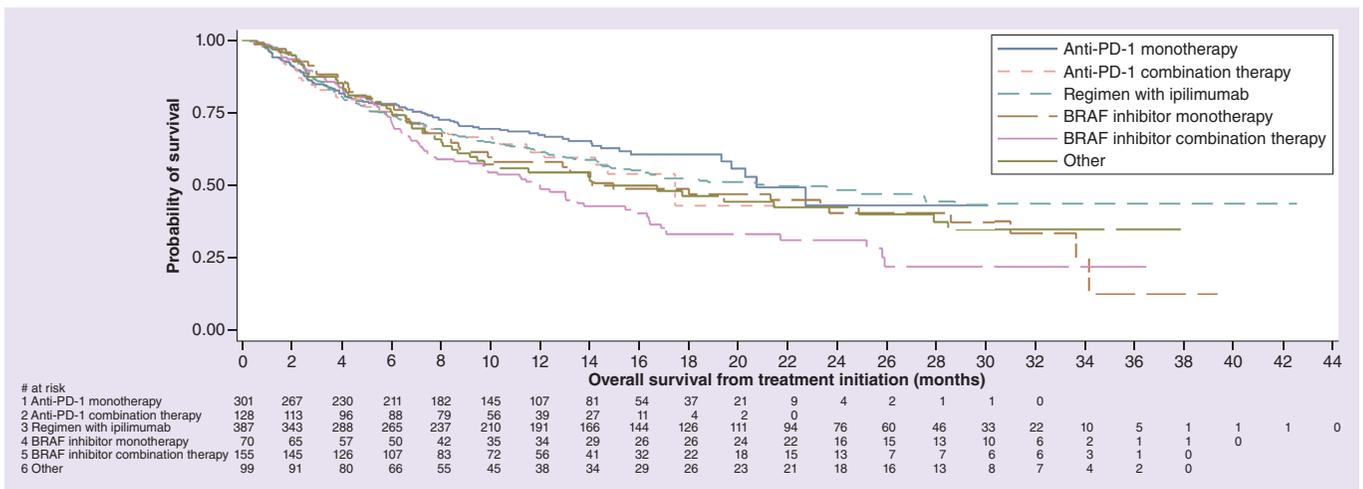
Observational data collected before the availability of immuno-oncology agents and *BRAF* inhibitor therapies are no longer relevant, as the treatment landscape and approved medicines are changing so quickly [43]. Several recent observational studies examine treatment patterns after the May 2011 approvals of ipilimumab and vemurafenib [28,44–47], but these observational data add only to our understanding of ipilimumab and do not reflect the incorporation of newer immuno-oncology agents.

In this descriptive, observational study, the median time to next treatment line was estimated overall at 10.9 months for anti-PD-1 monotherapy, 8.2 months for anti-PD-1 combination therapy and 6.8 months for *BRAF* inhibitor combination therapy. The median OS from initiation of first-line therapy for all patients was 18.8 months. The median OS for patients who received ipilimumab-based and anti-PD-1 monotherapy regimens was close to 2 years (21.0 and 20.7 months, respectively).

The median OS for first-line *BRAF* inhibitor combination therapy and first-line *BRAF* inhibitor monotherapy were 12.0 vs 14.9 months, respectively. This finding was unexpected. We reran the analyses at two institutions (Merck & Co., Inc. and Flatiron Health), and the results remained consistent. We note that differences in OS between *BRAF* cohorts and among regimens should be interpreted with caution because of the observational study design and because the OS results were not adjusted for baseline characteristics and may also be confounded by



**Figure 2. First-line therapy for patients with advanced melanoma from the first quarter of 2014 (2014Q1) through the second quarter of 2016 (2016Q2). (A) All patients with advanced melanoma (n = 1140); (B) patients with BRAF-mutant advanced melanoma (n = 454); (C) patients with BRAF wild-type advanced melanoma (n = 560). Percentages are rounded and may not add up to 100%.**



**Figure 3. Kaplan-Meier plot for overall survival from initiation of first-line therapy start by regimen type.**

**Table 3. Most common first- and second-line regimens for advanced melanoma administered to  $\geq 1\%$  of all patients, by *BRAF* status.**

Treatment category and regimen <sup>†</sup>	<i>BRAF</i> mutant (n = 454)	<i>BRAF</i> wild-type (n = 560)	<i>BRAF</i> status unknown (n = 126)	Total (n = 1140)
<b>First-line therapy</b>				
<b>Ipilimumab-based regimen</b>	<b>85 (18.7)</b>	<b>254 (45.4)</b>	<b>48 (38.1)</b>	<b>387 (33.9)</b>
Ipilimumab	69 (15.2)	247 (44.1)	48 (38.1)	364 (31.9)
<b>Anti-PD-1 monotherapy</b>	<b>76 (16.7)</b>	<b>188 (33.6)</b>	<b>37 (29.4)</b>	<b>301 (26.4)</b>
Pembrolizumab	39 (8.6)	98 (17.5)	22 (17.5)	159 (13.9)
Nivolumab	37 (8.1)	90 (16.1)	15 (11.9)	142 (12.5)
<b>BRAF inhibitor regimen</b>	<b>219 (48.2)</b>	<b>2 (0.4)</b>	<b>4 (3.2)</b>	<b>225 (19.7)</b>
Dabrafenib, trametinib	135 (29.7)	0	2 (1.6)	137 (12.0)
Vemurafenib	53 (11.7)	0	1 (0.8)	54 (4.7)
Dabrafenib	13 (2.9)	0	0 (0.0)	13 (1.1)
<b>Anti-PD-1 combination</b>	<b>54 (11.9)</b>	<b>64 (11.4)</b>	<b>10 (7.9)</b>	<b>128 (11.2)</b>
Ipilimumab, nivolumab	37 (8.1)	60 (10.7)	9 (7.1)	106 (9.3)
<b>Other</b>	<b>20 (4.4)</b>	<b>52 (9.3)</b>	<b>27 (21.4)</b>	<b>99 (8.7)</b>
Temozolomide	0	17 (3.0)	1 (0.8)	18 (1.6)
Interferon	7 (1.5)	5 (0.9)	2 (1.6)	14 (1.2)
Carboplatin, paclitaxel	2 (0.4)	6 (1.1)	4 (3.2)	12 (1.1)
<b>Second-line therapy</b>				
<b>Anti-PD-1 monotherapy</b>	<b>56 (28.7)</b>	<b>122 (67.4)</b>	<b>18 (60.0)</b>	<b>196 (48.3)</b>
Pembrolizumab	32 (16.4)	66 (36.5)	11 (36.7)	109 (26.8)
Nivolumab	24 (12.3)	56 (30.9)	7 (23.3)	87 (21.4)
<b>BRAF/MEK inhibitor regimen</b>	<b>76 (39.0)</b>	<b>2 (1.1)</b>	<b>1 (3.3)</b>	<b>79 (19.5)</b>
Dabrafenib, trametinib	52 (26.7)	1 (0.6)	1 (3.3)	54 (13.3)
Vemurafenib	7 (3.6)	0	0	7 (1.7)
Vemurafenib, cobimetinib	5 (2.6)	0	0	5 (1.2)
<b>Ipilimumab-based regimen</b>	<b>28 (14.4)</b>	<b>16 (8.8)</b>	<b>5 (16.7)</b>	<b>49 (12.1)</b>
Ipilimumab	23 (11.8)	15 (8.3)	5 (16.7)	43 (10.6)
<b>Anti-PD-1 combination therapy</b>	<b>27 (13.8)</b>	<b>18 (9.9)</b>	<b>2 (6.7)</b>	<b>47 (11.6)</b>
Ipilimumab, nivolumab	15 (7.7)	12 (6.6)	1 (3.3)	28 (6.9)
<b>Other</b>	<b>8 (4.1)</b>	<b>23 (12.7)</b>	<b>4 (13.3)</b>	<b>35 (8.6)</b>
Temozolomide	0	8 (4.4)	0	8 (2.0)

<sup>†</sup> Regimens administered to  $\geq 1\%$  of all patients are reported. Regimen categories were defined as follows: anti-PD-1 monotherapy; anti-PD-1-combination: any regimen containing pembrolizumab or nivolumab; ipilimumab-based regimen: any regimen containing ipilimumab but without an anti-PD-1 agent; BRAF/MEK inhibitor regimen: any regimen containing vemurafenib, trametinib, dabrafenib but without anti-PD-1 agent or ipilimumab; other: regimens not included in the prior categories.

second-line therapies. For example, 39% of patients who received ipilimumab-based regimens in first line received anti-PD-1 therapy in second line. In addition, follow-up is incomplete for some patients; many patients are receiving ongoing therapy and subsequent follow-up is planned. Further investigations are needed to explore the outcomes of various systemic therapies for AMel in the real-world setting.

Some data of clinical relevance that physicians may have considered in managing a patient's treatment were either limited or not available in the EHRs, including the number and location of sites of metastasis, disease progression, patient adherence to oral therapies, administration of regional therapies and information about adverse effects of therapy. Nonetheless, while some patient data were missing or incomplete, the cohort was well-characterized in many ways. Most patients (91%) in our study had been tested for the *BRAF* mutation, as currently recommended for AMel [35], and we were able to describe longitudinal treatment patterns, including first- and subsequent lines of therapy, according to *BRAF* mutation status. Almost half of patients tested in this study (45%) had *BRAF*-mutant melanoma, within reported ranges for the US, Australia and Italy [2,22,23], and on average, patients with *BRAF*-mutant tumors were younger than those with *BRAF* wild-type melanoma, as reported in prior studies [22,48], suggesting our population was representative of a general AMel population. However, the patient population included in our study may differ from those included in randomized controlled trials in which patients are often

Table 4. Kaplan–Meier estimates of time (months) to next line of treatment, by line of therapy and treatment category.

Treatment category	First-line therapy	Second-line and later therapy	All lines
<b>Anti-PD-1 monotherapy</b>			
Total patients, N	301	255	556
Time (months) to next line, median (95% CI):	14.1 (10.2–NA)	7.4 (5.1–11.7)	10.9 (8.4–14.3)
– 1-year on the same line rate (95% CI)	53.93% (47.68–59.76%)	43.20% (36.53–49.67%)	49.05% (44.49–53.44%)
– 2-year on the same line rate (95% CI)	40.51% (29.20–51.52%)	33.37% (25.73–41.16%)	37.42% (31.01–43.82%)
<b>Anti-PD-1 combination therapy</b>			
Total patients, N	128	76	204
Time (months) to next line, median (95% CI):	11.3 (6.4–NA)	7.4 (5.4–11.0)	8.2 (6.6–11.6)
– 1-year on the same line rate (95% CI)	45.47% (35.61–54.80%)	29.66% (15.32–45.50%)	41.13% (32.90–49.17%)
<b>Regimen with ipilimumab</b>			
Total patients, N	387	60	447
Time (months) to next line, median (95% CI):	5.1 (4.4–5.8)	3.3 (2.9–4.0)	4.9 (4.3–5.5)
– 1-year on the same line rate (95% CI)	27.73% (23.10–32.53%)	13.95% (5.51–26.22%)	26.05% (21.79–30.49%)
– 2-year on the same line rate (95% CI)	17.95% (13.74–22.64%)	9.30% (2.28–22.49%)	16.91% (13.04–21.23%)
<b>BRAF inhibitor monotherapy</b>			
Total patients, N	70	23	93
Time (months) to next line, median (95% CI):	5.2 (4.3–8.3)	3.4 (1.5–5.3)	4.7 (3.9–6.5)
– 1-year on the same line rate (95% CI)	27.32% (16.90–38.80%)	20.50% (6.42–40.06%)	25.25% (16.27–35.23%)
– 2-year on the same line rate (95% CI)	15.11% (7.10–25.91%)	NA	12.96% (6.14–22.40%)
<b>BRAF inhibitor combination therapy</b>			
Total patients, N	155	91	246
Time (months) to next line, median (95% CI):	6.8 (5.8–9.1)	6.6 (5.5–9.0)	6.8 (6.0–7.9)
– 1-year on the same line rate (95% CI)	32.44% (24.69–40.42%)	28.79% (18.87–39.47%)	31.27% (25.07–37.65%)
– 2-year on the same line rate (95% CI)	10.98% (4.99–19.64%)	10.52% (3.45–22.18%)	10.57% (5.58–17.40%)
<b>Other</b>			
Total patients, N	99	63	162
Time (months) to next line, median (95% CI):	6.0 (4.3–9.7)	3.2 (2.2–4.2)	4.5 (3.8–6.0)
– 1-year on the same line rate (95% CI)	38.62% (28.60–48.53%)	7.22% (1.91–17.46%)	27.78% (20.43–35.59%)
– 2-year on the same line rate (95% CI)	29.70% (19.77–40.28%)	NA	19.44% (12.60–27.40%)

NA: Not available.

excluded if they have an ECOG PS of  $\geq 2$  (17% of patients in our study) or active brain metastases (9% of patients in our study had a history of brain metastases) [31].

This study has several other limitations. Some of the data needed to characterize the patients' clinical and disease characteristics were incomplete, usually because the oncology clinic did not collect the information. For example, LDH level data at the index date were available for only 56% and ECOG PS data for only 48% of patients. We do not know why LDH was not assessed for all patients, but, as a result, we were unable to conduct multivariable analyses of OS and time to next treatment line because these key variables were missing. Moreover, not all prescribing information for oral antineoplastic agents (e.g., trametinib, vemurafenib and dabrafenib) was available because of inconsistent recording in the medical record; thus, we made assumptions about prescription durations. For patients with multiple prescriptions of an oral drug, for example, trametinib, vemurafenib and dabrafenib, we calculated days' supply as the number of days between first and last prescriptions plus 30 days. For patients with only one prescription of an oral drug, we assumed 30 days' supply for those without such information. Moreover, while we were able to capture the variety of regimens prescribed in clinical practice, prescribing patterns may not be representative of those at different types of clinical practices, such as at academic medical centers, which are in the minority of practices participating with Flatiron. Detailed information regarding the management of brain metastases was not planned for this study. Future studies can potentially include this information for consideration, pending assessment of feasibility provided in real-world detailed documentation.

Our findings suggest that NCCN guidelines for malignant melanoma are generally followed in community oncology practice [35]. Most patients with *BRAF*-mutant melanoma received targeted therapy with a *BRAF* inhibitor. Our findings also suggest that clinical practice is responsive to data presentation, inclusion in NCCN compendia, and label updates, as prescribing trends showed a drop in use of *BRAF* inhibitor monotherapy in favor of combination therapy and are now favoring the use of the anti-PD-1 agents, irrespective of *BRAF* mutation status, with decreasing use of *BRAF* inhibitors and ipilimumab. There are more treatment choices for patients with *BRAF*-mutant melanoma. Nonetheless, an unexpected finding was that *BRAF* inhibitor monotherapy was prescribed even after combination therapy was approved, perhaps because they are oral medications and associated in the US with higher out-of-pocket costs [49]. We can speculate that these changes are occurring because of perceived greater effectiveness of the anti-PD-1 agents, as evidenced in head-to-head clinical trials [20,31,32], coupled with the known frequent adverse effects associated with ipilimumab therapy [28,45,50,51].

More information is needed about the relationship between these changes and population-based outcomes such as contemporary survival estimates for AMel and patient experiences associated with these new therapies. Moreover, response patterns to immuno-oncology agents may differ from those to chemotherapy [52,53], underscoring the need for training to manage pseudoprogression and potential side effects from immunotherapy. Further studies are needed that include patients with all stages of melanoma and incorporate all treatment choices (e.g., surgery) into treatment patterns analysis to have a more complete understanding of the trajectory of clinical care over time.

## Conclusion

The results of this study vividly illustrate the changing paradigms of therapy for AMel in US community oncology practices, with the increasing use of anti-PD-1 agents, regardless of *BRAF* mutation status. The time to next treatment line and OS findings provide a preliminary, descriptive assessment of real-world treatment outcomes but should be interpreted with caution because of the observational study design.

## Future perspective

The treatment patterns for AMel in the real-world setting of US oncology clinical practices will likely continue to evolve with newer therapies available, and some of these therapies have now been approved for use in the adjuvant setting. In response to this trend, patient outcomes (e.g., OS) will likely continue to improve for patients with AMel.

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## Authors' contributions

Conception and design of the study: ED Whitman, FX Liu, AP Abernethy. Data analysis: X Cao. Interpretation of findings, critical review and revision of the manuscript: ED Whitman, FX Liu, X Cao, SJ Diede, A Haiderali, AP Abernethy. All authors read and approved the final manuscript.

## Financial & competing interests disclosure

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### Ethical conduct of research

The de-identified dataset supporting the conclusions of this article was provided by Flatiron Health. Institutional review board (IRB) approval of the study protocol was obtained through Flatiron procedure and approved by Copernicus Group IRB before study conduct and included a waiver of informed consent. Provisions were in place to prevent re-identification of de-identified data in order to protect patients' confidentiality.

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### Summary points

- The last 8 years have seen incredible growth in the number of systemic therapies available for advanced melanoma (AMel). However, limited information exists on how these trends and associated patient outcomes are manifesting in a real-world setting.
- This study aimed to understand the evolution of treatment patterns, time to next treatment line and associated overall survival for patients with AMel in US real-world oncology clinical practices.
- In total, 1140 patients with AMel from a longitudinal and geographically diverse electronic health record database were included for this analysis.
- The most common first-line regimens were ipilimumab-based therapies (34%), followed by anti-PD-1 monotherapy (26%) and regimens including a BRAF inhibitor (20%).
- Since the third quarter of 2014, when the US FDA first approved an anti-PD-1 agent for systemic therapy of AMel, the treatment regimens have changed rapidly, with decreased first-line prescribing of ipilimumab-based and BRAF inhibitor regimens, and by the second quarter of 2016, 55 and 91% of *BRAF*-mutant and *BRAF* wild-type cohorts, respectively, received a first-line anti-PD-1 regimen.
- The median time to next treatment across all treatment lines was 4.9 months for ipilimumab-based regimens, 10.9 and 8.2 months for anti-PD-1 monotherapy and combination therapy, respectively, and 4.7 and 6.8 months for BRAF inhibitor monotherapy and BRAF/MEK inhibitor combination therapy, respectively.
- The 1-year estimated survival rate by first-line regimen type was 62.0% for ipilimumab-based, 67.5% for anti-PD-1 monotherapy, 61.5% for anti-PD-1 combination therapy, 58.2% for BRAF inhibitor monotherapy and 48.9% for BRAF/MEK inhibitor combination therapy. The median OS from initiation of first-line therapy for all patients was 18.8 months (95% CI: 16.3–23.3).
- The study results illustrate the rapidly changing paradigms of systemic therapy for AMel in US clinical oncology practices, with increasing use of anti-PD-1 agents, regardless of *BRAF* mutation status.
- The findings on time to next treatment line and overall survival provide a preliminary, descriptive assessment of real-world treatment outcomes for patients with AMel, and further research should be conducted to confirm these results.

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