Real-world use and outcomes of targeted therapy and immunotherapy for adjuvant treatment of *BRAF*-mutated melanoma patients in the United States

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Using a customized, harmonized US electronic health record database, real-world prescription patterns of first-line adjuvant immunotherapy and targeted therapy were retrospectively assessed for *BRAF*V600-mutated melanoma. Adults with *BRAF*V600 mutation-positive stage IIIA-D cutaneous melanoma who received first-line adjuvant immunotherapy (nivolumab or pembrolizumab) or targeted therapy (dabrafenib plus trametinib) between 1 January 2014 and 30 August 2020 in the NOBLE database were included. Patients were followed from first-line adjuvant therapy initiation for at least 6 months, until death, progression, follow-up loss, or data cutoff. Primary endpoints were proportion of patients receiving either therapy in first-line and second-line, treatment switching, treatment timing, and status at the end of first-line therapy. Secondary endpoints included discontinuation rates, recurrence-free survival (RFS), and overall survival (OS). Of 318 patients evaluated, 67.6% received nivolumab, 14.2% pembrolizumab, and 18.2% targeted therapy as first-line adjuvant therapy. Median treatment duration was longest for nivolumab (292 days) and shortest for targeted therapy (115 days). Reason for discontinuation was recorded for 195 of 274 patients who discontinued first-line therapy; most common reasons were treatment completion and treatment-related toxicity [87/158 (55.0%) and 29/158 (18.4%), respectively, in immunotherapy-treated patients; 9/37 (24.3%) and 21/37 (56.8%) in targeted therapy-treated patients]. Median RFS and OS for targeted therapy and nivolumab were not reached and were 34.6 and 38.1 months, respectively, for pembrolizumab. These results inform on prescription preferences and clinical outcomes for *BRAF*V600-mutated melanoma patients in the first-line adjuvant setting.

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Introduction

Despite recent mortality declines, the incidence of cutaneous melanoma continues to rise as it remains the most common and fatal skin cancer [1]. *BRAF* mutations are detected in up to approximately 40–50% of patients with cutaneous melanoma [2–5]. The most common *BRAF* mutations occur on exon 15 as single nucleotide substitutions at codon 600 (valine) to glutamic acid (*BRAF*V600E, most common), lysine (*BRAF*V600K), or arginine (*BRAF*V600R, least common) [4–6]. The role of *BRAF* mutations in melanogenesis has been widely described and largely attributed to the resulting deregulated activation of downstream MEK/ERK effectors within the mitogen-activated protein kinase (MAPK) pathway, thereby driving cell proliferation, survival, and malignant growth [7].

The melanoma therapeutic landscape continues to evolve with the investigation and approval of multiple adjuvant therapies for treatment of melanoma patients at high risk for recurrence (stages III/IV). Selection of systemic adjuvant therapy considers multiple factors, including the risk of recurrence, stage at diagnosis, specific tumor and patient characteristics (e.g. *BRAF* mutation status, age, comorbidities), treatment-associated risks, and the patient's ability to tolerate therapy [8,9]. Ipilimumab is the first US Food and Drug Administration (FDA)-approved immune checkpoint inhibitor for cancer therapy and was approved in 2015 for the adjuvant therapy of cutaneous melanoma [10]. Although it was a preferred first-line adjuvant therapy option for some time, the approval of other anti-PD-1 and *BRAF*-targeted therapies with better efficacy and safety profiles shifted the treatment algorithm, with those therapies becoming the preferred treatments [11]. Presently, both immunotherapy with nivolumab (FDA approved December 2017

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[12]) or pembrolizumab (FDA approved February 2019 [13]), both of which target programmed cell death-1, and *BRAF*V600-targeted therapy with a combination of dabrafenib plus trametinib (FDA approved April 2018 [14,15]) for *BRAF* mutation-positive melanoma are preferred adjuvant systemic therapies for the management of cutaneous melanoma [9,16]. Currently, dabrafenib plus trametinib is the only approved targeted therapy for adjuvant use in melanoma.

Although randomized controlled phase III clinical trials have shown a significant improvement in recurrence-free survival (RFS) with adjuvant nivolumab, pembrolizumab, or dabrafenib plus trametinib for melanoma [17–19], data on physicians' prescription preferences, patterns of use and sequencing of immunotherapy and targeted therapy, and corresponding patient outcomes in real-world clinical practice are limited. Current evidence from real-world analyses demonstrates increased utilization of immunotherapy over targeted therapy as adjuvant treatment for *BRAF*-mutated melanoma [20,21]. In the absence of head-to-head comparison or other prospective clinical data demonstrating a stage-dependent benefit from either approved immunotherapy over targeted therapy, these patterns suggest that physician preferences, local guidelines, patient perceptions, or a combination of these, influence and drive decisions on choice of therapy.

To help address the paucity of data regarding adjuvant therapy choice, we developed a customized oncology-specific electronic health record (EHR) database by which to assess real-world use of nivolumab or pembrolizumab immunotherapy and dabrafenib plus trametinib targeted therapy as a first-line adjuvant melanoma treatment among *BRAF* mutation-positive patients in the USA. Our study will further expand our understanding of optimal treatment strategies, prescription preferences, and patient outcomes in clinical practice for stage III melanoma patients in the first-line adjuvant setting.

Patients and methods

Study design and study period

This retrospective longitudinal observational study used the Novartis *BRAF* mutation-positive meLanoma patients ObsErvational (NOBLE) database to assess real-world data on the use of immunotherapy and targeted therapy as a first-line adjuvant treatment for melanoma. Any patient with *BRAF*V600 mutation-positive stage III melanoma who had first-line adjuvant immunotherapy with nivolumab or pembrolizumab or targeted therapy with dabrafenib plus trametinib (index date) between 1 January 2014 and 30 August 2020 were assessed. Patients must have been diagnosed with stage IIIA to IIID melanoma and have evidence of resection (data start: 1 January 2011) prior to the index date. Patients were followed from first-line adjuvant therapy initiation until death, disease progression, loss of follow-up, or data cutoff date (30 August 2020), whichever occurred first (Supplementary Fig. S1, Supplemental Digital Content 1, *http://links.lww.com/MR/A399*). Start and end dates were supplied by the data providers and were collected based on pharmacy prescription records (for oral therapies) and on medical procedure records collected (for immunotherapy therapies). Treatment duration is calculated as the time from start of index date to first-line therapy until the last date as indicated on patient records. Although the first systemic therapy approved for use in the adjuvant melanoma setting occurred in 2015 [10], the study period of interest begins on 1 January 2014, including any potential off-label use of these therapies as adjuvant therapies.

Data sources

The NOBLE database was built specifically for melanoma-related research. The NOBLE dataset used here includes harmonized, customized data from patients with *BRAF*V600-mutated melanoma treated at oncology practices across the USA from the Flatiron Health and the Concerto Custom Patient360 oncology-specific EHR-derived databases. The nationwide EHR-derived de-identified Flatiron Health research database is a longitudinal retrospective database containing de-identified data from approximately 280 US cancer clinics (~800 sites of care) at the time of the study [22,23]. The majority of patients in the database originate from community oncology settings; relative community/academic proportions may vary depending on the study cohort. The Concerto Custom Patient360 EHR is an observational retrospective database derived from a repository of oncology EHR data, including from CancerLinQ-affiliated practices and curated research-grade data of ~50 000 cancer patients in the USA. Both the Flatiron Health and Concerto Custom Patient360 databases contain clinical, demographic, treatment, and mortality information for advanced melanoma.

Study population

Adults aged 18 years or older diagnosed with *BRAF*V600 mutation-positive stage IIIA-D (AJCC v8.0) cutaneous melanoma (ICD-9 172.x and ICD-10 C43.x or D03.x) who received first-line adjuvant nivolumab or pembrolizumab as immunotherapy or dabrafenib plus trametinib targeted therapy after successful tumor resection were included. Patients included in the analysis had at least 6 months of follow-up and a *BRAF*V600 mutation-positive test result prior to or up to 30 days after initiation of first-line adjuvant treatment. Patients were excluded if they received clinical trial treatment for cancer at any time on or after 1 January 2014. Patient demographic and clinical characteristics also assessed at baseline included age, gender, race, Eastern Cooperative Oncology Group performance status, Quan Charlson Comorbidity Index, disease stage (IIIA to IIID), lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase.

Endpoints

The primary objective of this study was to describe treatment patterns among patients treated with targeted therapy compared to immunotherapy. To do so, primary endpoints consisted of the proportion of patients receiving either type of treatment in first-line and second-line, the proportion of patients switching from first-line targeted therapy to second-line immunotherapy or switching from first-line immunotherapy to second-line targeted therapy, time from diagnosis to initiation of first-line therapy, treatment duration, and treatment status at the end of first-line therapy. Secondary endpoints included evaluation of discontinuation rates and reasons for first-line and subsequent lines of therapy among patients receiving immunotherapy or targeted therapy, as well as estimating the median, 1-year, and 2-year rates of RFS (time from initiation of first-line therapy until recurrence) and overall survival (OS; time from initiation of first-line therapy until death from any cause). Recurrence was defined as a clinician-documented instance of melanoma returning after treatment, such as regrowth of melanoma in close proximity to the anatomic site from which the primary tumor was excised, or a clinician-documented instance of clinical manifestation of small tumor emboli trapped within the dermal and subdermal lymphatics between the site of the primary tumor and regional lymph node drainage basin/s [24], and was included as a data element already abstracted into the databases.

Statistical analysis

Descriptive statistics were performed to summarize baseline characteristics and treatment patterns for all patients and stratified by class of treatment. Descriptive analyses were summarized using counts and percentages for dichotomous and categorical variables, whereas measures of means with standard deviations or medians with interquartile range (IQR) were used for continuous variables as appropriate. When deemed necessary, comparisons between groups were performed by nonparametric Mann–Whitney U test for continuous variables and Chi-square test for categorical variables. Kaplan–Meier survival curves with log-rank testing were used to describe RFS and OS, which were compared between targeted therapy and immunotherapy and between the three treatments dabrafenib plus trametinib, nivolumab, and pembrolizumab. Patients were censored due to risk of death or if they were lost to follow-up. A $P < 0.05$ was considered for statistical significance. The data were analyzed using SAS 9.4 software (SAS Institute Inc., Cary, North Carolina, USA).

Ethics

Data collection was fully compliant with the US patient confidentiality requirements (the Health Insurance Portability and Accountability Act of 1996); patients' data remained anonymous and de-identified to conform to the US Health Insurance Portability and Accountability Act requirements. Because this study only used de-identified data, approval of an institutional review board or ethics committee and informed consent were not required.

Results

Baseline characteristics

A total of 318 patients (Fig. 1) were included in this analysis, of which 215 (67.6%) received nivolumab as first-line adjuvant therapy, 58 (18.2%) received dabrafenib plus trametinib targeted therapy, and 45 (14.2%) received pembrolizumab (Table 1). The median age of the overall population was 60 years (IQR 49–69), which was similar across the three different treatment groups. More than half of the patients who received either targeted therapy or nivolumab monotherapy were male; overall, more patients started first-line therapy at disease stage IIIC ($n = 100$, 40.8%).

Treatment patterns

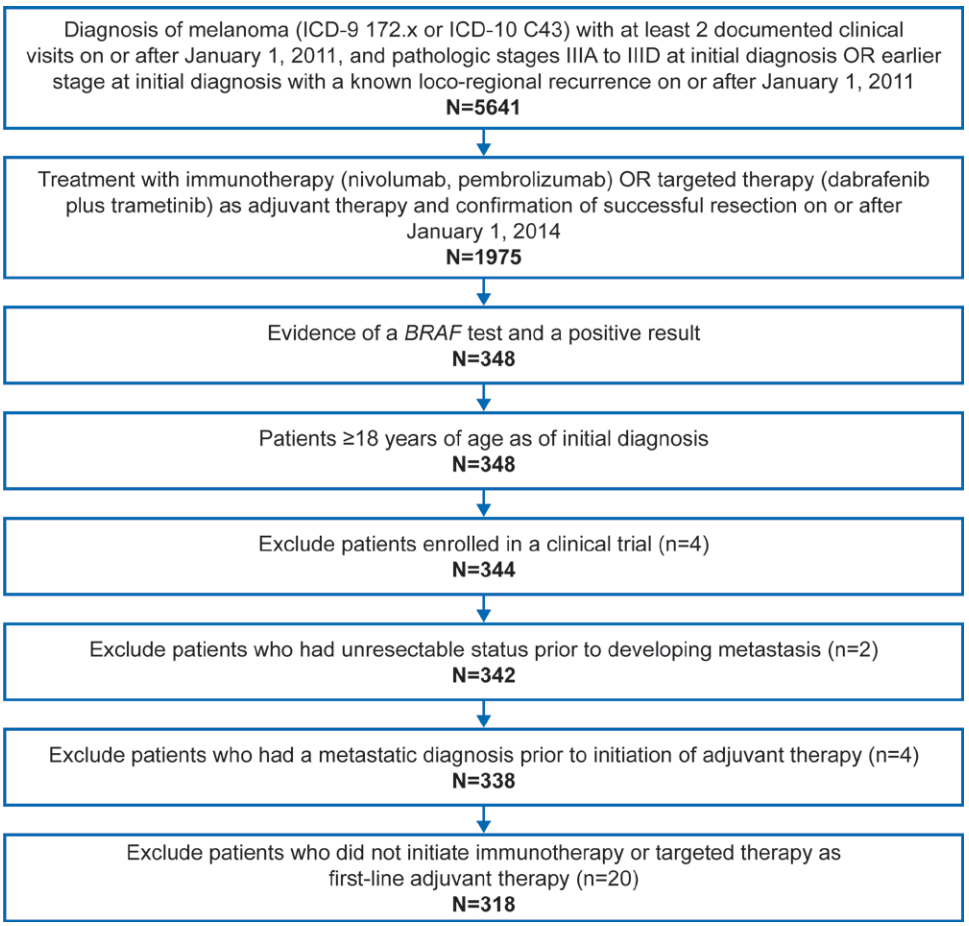
The median time from diagnosis to first-line therapy initiation was 93 days (IQR 66–130) for nivolumab, 115 days (IQR 61–172) for pembrolizumab, and 99 days (IQR 69–135) for targeted therapy. Median first-line treatment duration was 292 days (IQR 112–350) for nivolumab, 147 days (IQR 63–273) for pembrolizumab, and 115 days (IQR 57–290) for targeted therapy ($P < 0.001$). Of 11 (19.0%) patients who discontinued first-line adjuvant targeted therapy and started second-line therapy, 7 (63.6%) patients did so with nivolumab (Table 2). Of the 16 (7.4%) patients who discontinued first-line nivolumab and the 4 (8.9%) patients who discontinued first-line pembrolizumab, 11 (68.8%) and 3 (75.0%) moved on to second-line dabrafenib plus trametinib, respectively.

The most common reasons for discontinuing first-line adjuvant therapy (Table 3) in the overall population of this analysis were treatment completion ($n = 96$, 49.2%), followed by treatment-related toxicities ($n = 50$, 25.6%), and recurrence ($n = 30$, 15.4%). More patients in each immunotherapy group reported treatment completion as the reason for first-line discontinuation (nivolumab: $n = 79$, 57.2%; pembrolizumab: $n = 8$, 40.0%) than those in the targeted therapy group ($n = 9$, 24.3%). Conversely, recurrence was cited by a higher proportion of patients who received first-line nivolumab ($n = 24$, 17.4%) compared with pembrolizumab ($n = 3$, 15.0%) and targeted therapy ($n = 3$, 8.1%). Interestingly, a higher percentage of patients discontinued first-line therapy due to treatment-related toxicities in the targeted therapy ($n = 21$, 56.8%) group compared with the nivolumab ($n = 24$, 17.4%) and pembrolizumab ($n = 5$, 25.0%) groups.

Survival patterns

The 1- and 2-year rates of RFS and OS for each first-line therapy (Table 4) were all high. The 2-year RFS rates

Fig. 1



Sample selection from NOBLE database. NOBLE, Novartis *BRAF* mutation-positive meLanoma patients ObsErvational.

were 70.7, 68.6, and 66.2%, and the 2-year OS rates were 81.1, 70.0, and 76.6% for nivolumab, pembrolizumab, and targeted therapy, respectively.

Although the median RFS and OS for both targeted therapy and nivolumab groups were not yet reached, the median RFS and OS for pembrolizumab were 34.6 and 38.1 months, respectively. No significant differences in RFS ($P = 0.8003$; Fig. 2a) or OS ($P = 0.1140$; Fig. 2b) were observed among any of the three treatments.

Discussion

To the best of our knowledge, this is the most recent study to evaluate real-world use of systemic immunotherapy and targeted therapy as first-line adjuvant treatment of *BRAF*V600 mutation-positive patients with stage III melanoma in the USA. This retrospective analysis using the NOBLE database revealed that most patients were prescribed first-line adjuvant immunotherapy over targeted therapy despite their *BRAF*V600 mutation-positive status, there were no significant differences in median RFS or OS between the treatment groups. Moreover, the duration of treatment for patients who received first-line targeted therapy was less than half that of patients treated with first-line immunotherapy, yet 2-year RFS and OS rates were relatively similar between immunotherapy and targeted therapy groups, an observation that warrants further study.

The results suggest a preference for prescribing immunotherapy over targeted therapy as first-line adjuvant therapy in patients with *BRAF*V600-mutated melanoma in the USA, a finding similar to that reported by European centers [20,21]. The NOBLE database does not capture the reasons for physicians' or patients' therapeutic decision making.

The NOBLE dataset baseline indicators of comorbidities (Charlson Comorbidity Index, Eastern Cooperative Oncology Group performance status, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase) were low and/or in the normal range for most patients. As such, a limitation of this work is an inability to determine the effects, if any, that patient baseline characteristics had on the prescriptive preference in this US dataset.

A possible reason for first-line immunotherapy preference in the adjuvant setting is that immunotherapy

Table 1 Baseline demographics and clinical characteristics in the overall population and by first line of adjuvant therapy received

Baseline demographics	All patients $N=318$	Dabrafenib plus trametinib $N=58$	Nivolumab $N=215$	Pembrolizumab $N=45$	*P* value[a]
Age, years, median (IQR)	60 (49–69)	60 (50–67)	60 (49–69)	58 (49–73)	0.734
Male, *n* (%)	192 (60.4)	35 (60.3)	135 (62.8)	22 (48.9)	0.222
Race, *n* (% among tested)					0.129
White	255 (88.9)	47 (94.0)	172 (87.3)	36 (92.3)	
Other	31 (10.8)	3 (6.0)	25 (12.7)	3 (7.7)	
Disease stage provided, *n* (% among provided)	245 (77.0)	43 (74.1)	167 (77.7)	35 (77.8)	0.844
IIIA	52 (21.2)	12 (27.9)	35 (21.0)	5 (14.3)	
IIIB	64 (26.1)	9 (20.9)	48 (28.7)	7 (20.0)	
IIIC	100 (40.8)	17 (39.5)	63 (37.7)	20 (57.1)	
IIID	4 (1.6)	0	4 (2.4)	0	
III unspecified	25 (10.2)	5 (11.6)	17 (10.2)	3 (8.6)	
CCI (mean ± SD)	0.4 (0.8)	0.4 (0.7)	0.3 (0.8)	0.3 (0.7)	0.883
ECOG PS,[b] *n* (% among tested)					0.808
0	139 (69.5)	26 (72.2)	97 (69.8)	16 (64.0)	
1	56 (28.0)	10 (27.8)	37 (26.6)	9 (36.0)	
2	1 (0.5)	0	1 (0.7)	0	
3	4 (2.0)	0	4 (2.9)	0	
LDH value, *n* (% among tested)	179 (56.3)	30 (51.7)	125 (58.1)	24 (53.3)	0.622
Normal	131 (73.2)	23 (76.7)	90 (72.0)	18 (75.0)	0.393
Elevated	9 (5.0)	3 (10.0)	5 (4.0)	1 (4.2)	
AST value, *n* (% among tested)	233 (73.3)	41 (70.7)	160 (74.4)	32 (71.1)	0.799
Low	28 (12.0)	6 (14.6)	19 (11.9)	3 (9.4)	0.670
Normal	187 (80.3)	30 (73.2)	131 (81.9)	26 (81.3)	
Elevated	18 (7.7)	5 (12.2)	10 (6.3)	3 (9.4)	
ALT value, *n* (% among tested)	231 (72.6)	41 (70.7)	158 (73.5)	32 (71.1)	0.886
Low	95 (41.1)	9 (22.0)	69 (43.7)	17 (53.1)	0.020
Normal	109 (47.2)	23 (56.1)	75 (47.5)	11 (34.4)	
Elevated	27 (11.7)	9 (22.0)	14 (8.9)	4 (12.5)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; LDH, lactate dehydrogenase.
[a]Mann–Whitney U test was used to test for significance of continuous variables, and Chi-squared test was used to test for significance of categorial variable. A $P<0.05$ indicates a significant difference between the three patient cohorts.
[b]Nearest ECOG PS recorded prior to initiation of first line.

Table 2 Treatment status at end of first-line adjuvant therapy

Variable, *n* (%)	All patients $N=318$	Dabrafenib plus trametinib $N=58$	Nivolumab $N=215$	Pembrolizumab $N=45$	*P* value[a]
Treatment status					<0.001
Censored at first-line	44 (13.8)	18 (31.0)	19 (8.8)	7 (15.6)	
Discontinued first-line and received no second-line until cutoff	243 (76.4)	29 (50.0)	180 (83.7)	34 (75.6)	
Discontinued first-line and continued with second-line	31 (9.7)	11 (19.0)	16 (7.4)	4 (8.9)	
Among those continued with second-line					<0.001
Dabrafenib plus trametinib	14 (45.2)	0	11 (68.8)	3 (75.0)	
Nivolumab	7 (22.6)	7 (63.6)	0	0	
Pembrolizumab	0	0	0	0	
Dabrafenib plus trametinib plus pembrolizumab	7 (22.6)	4 (36.4)	2 (12.5)	1 (25.0)	
Other[b]	3 (9.7)	0	3 (18.8)	0	

[a]$P<0.05$ indicates a significant difference between the three patient cohorts.
[b]Other: three patients received nivolumab and pembrolizumab as interchanging therapy in the second-line.

provides meaningful benefit regardless of *BRAF* mutation status [17,19]. In unresectable *BRAF*V600 mutant melanoma, recent studies have shown that the sequence of immunotherapy and targeted therapy used may significantly affect survival. Data from both the SECOMBIT and DREAMseq trials on unresectable stage III/IV *BRAF*V600-mutated melanoma demonstrate that initiating first-line treatment with combination immunotherapy, instead of combination BRAF/MEK inhibitor targeted therapy, leads to longer OS [25,26]. In the adjuvant setting, however, our results suggest similar survival outcomes across immunotherapy and targeted therapy treatment groups in real-world clinical experiences. These data suggest that further studies are warranted assessing therapeutic sequencing in the adjuvant setting in *BRAF*V600-mutated melanoma. Further analysis of the effect of treatment sequence and combinations on survival from patients in the NOBLE database are necessary to confirm this trend in US clinical practice.

Risk of treatment-related toxicity, especially with respect to patient age and underlying comorbidities, is also a major consideration in selection of curative-intent first-line adjuvant therapy. Although both immunotherapy and targeted therapy are associated with relatively similar rates of grade ≥3 adverse events (AE) [26], discontinuation rates

Table 3 Reasons for treatment discontinuation in the first-line adjuvant treatment setting

Reason for discontinuation, *n* (%)	All patients *N* = 318	Dabrafenib plus trametinib *N* = 58	Nivolumab *N* = 215	Pembrolizumab *N* = 45	*P* value[a]
Among those with reasons provided	195 (61.3)	37 (63.8)	138 (64.2)	20 (44.4)	0.001
Recurrence	30 (15.4)	3 (8.1)	24 (17.4)	3 (15.0)	
Toxic effect of therapy	50 (25.6)	21 (56.8)	24 (17.4)	5 (25.0)	
Disease-related symptoms not due to therapy	3 (1.5)	1 (2.7)	1 (0.7)	1 (5.0)	
Patient requested	8 (4.1)	0	6 (4.3)	2 (10.0)	
Completed treatment	96 (49.2)	9 (24.3)	79 (57.2)	8 (40.0)	
No evidence of disease	3 (1.5)	1 (2.7)	1 (0.7)	1 (5.0)	
Financial	1 (0.5)	1 (2.7)	0	0	
Other[b]	3 (1.5)	1 (2.7)	2 (1.4)	0	
Unknown	1 (0.5)	0	1 (0.7)	0	

[a]A $P < 0.05$ indicates a significant difference between the three patient cohorts.
[b]Other: reasons other than those listed in the table.

Table 4 RFS and OS 1- and 2-year rates by first line of adjuvant therapy

Survival rate (%)	Dabrafenib plus trametinib *N* = 58	Nivolumab *N* = 215	Pembrolizumab *N* = 45
1-year RFS	87.5	80.2	86.2
2-year RFS	66.2	70.7	68.6
1-year OS	99.9	94.9	80.0
2-year OS	76.6	81.1	70.0

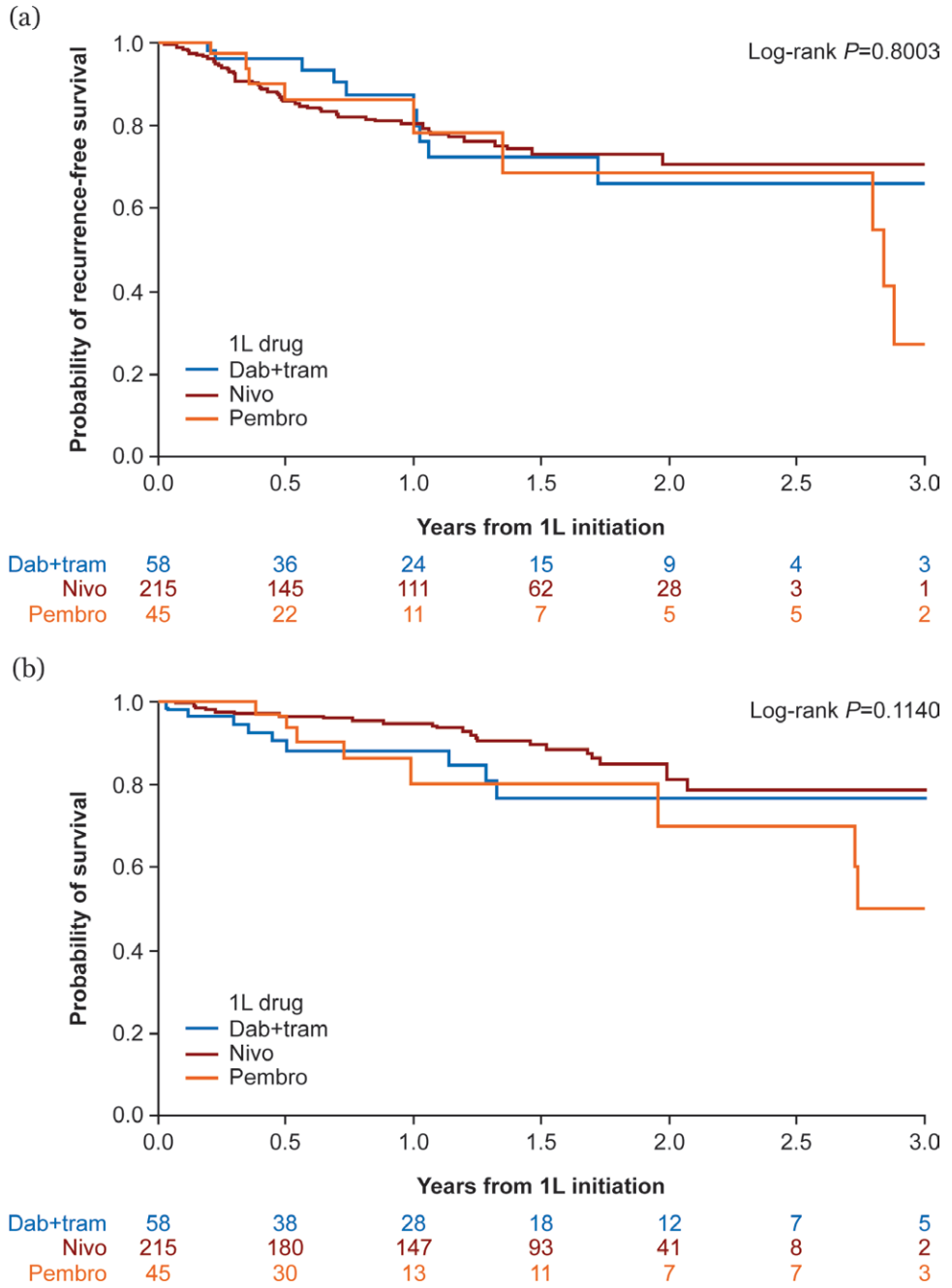
OS, overall survival; RFS, recurrence-free survival.

for targeted therapy have been reported as higher than immunotherapy in clinical trials (26% vs 10–14%) [17–19]. Similarly, a greater percentage of patients from the NOBLE dataset discontinued first-line targeted therapy due to treatment-related toxicities than those who received first-line immunotherapy. Although targeted therapy-related toxicities may occur more frequently, it should be noted that they are typically moderate and reversible [27]. Pyrexia is a common AE observed in ~50% of patients treated with the dabrafenib plus trametinib combination in clinical studies; exposure to the hydroxy-dabrafenib metabolite and, less likely, dabrafenib is associated with symptoms. Acute pyrexia events are generally managed with dose modifications, interruptions, or both, and resolved in 97% of patients [27,28]. In addition to pyrexia, other common AEs reported in patients treated with dabrafenib plus trametinib in a phase III clinical trial included fatigue (35%), headache (30%), nausea (30%), and chills (30%). Hyperproliferative events, such as cutaneous squamous cell carcinoma, are AEs of interest associated with *BRAF* inhibitors arising from the paradoxical activation of the MAPK pathway. However, these were abrogated when dabrafenib was combined with trametinib (cutaneous squamous cell carcinoma, all grade: 9% for dabrafenib vs 2% for dabrafenib plus trametinib; cutaneous hyperkeratoses, all grade: 32% for dabrafenib vs 3% for dabrafenib plus trametinib) [28]. In contrast, immunotherapy-related toxicities, which are caused by autoimmune activity, can affect any organ system and persist or develop even after therapy is discontinued [29,30]. Additionally, moderate to severe immune-related AEs can lead to decreased patient quality of life and increased mortality [30].

In our study, more males received targeted therapy (60.3%) or immunotherapy with nivolumab (62.8%) than females, in alignment with the higher incidence of cutaneous melanoma in males compared with females, particularly for those older than 40 years [31]. In the US, age-adjusted incidence rates (2017–2021) of cutaneous melanoma for males are 27.1/100 000 persons compared with 16.9/100 000 persons for women [32]. Conversely, immunotherapy with pembrolizumab was prescribed more evenly, with just slightly more women (51.1%) receiving this regimen than men, possibly representing a factor physicians considered when selecting therapy in our real-world cohort. Although greater benefit from immunotherapy has been shown in male versus female patients in some studies [33], what exact role sex hormone levels play, especially with respect to different types of immunotherapy, remains unknown [34].

Limitations of this retrospective EHR-derived dataset are the result of being captured from 2 different EHR systems (Flatiron Health and Concerto Custom Patient360) in which data originate from separate physician EHRs. Even with data being harmonized based on measurement, data are not entered into each source equally. If the underlying methods for data collection (e.g. prompts for information entry in the EHR) differ, data quality, quantity, and capture rate are highly affected. Both EHR systems had data of patients treated with targeted therapy and immunotherapy; therefore, this limitation affected both treatment groups. Other inherent limitations include some degree of missing data, pending on the completeness of data collection, and lack of granularity of certain clinical data, such as grade of toxicity that caused treatment discontinuation. The potential for bias could also be introduced regarding oral prescription records as they only indicate that the medication is dispensed, but not if the patient followed the prescription as instructed. Additional aspects not captured in the NOBLE database limiting interpretation of prescriptive preferences are related to cost (e.g. insurance coverage) and method of treatment delivery. Oral targeted therapy would be favorable to intravenous immunotherapy because patients would not be required to travel long distances for treatment and could opt to

Fig. 2



RFS (a) and OS (b) in *BRAF*V600 melanoma patients treated with first-line adjuvant immunotherapy or targeted therapy. A $P < 0.05$ indicates a significant difference between the three patient cohorts. Dab, dabrafenib; Nivo, nivolumab; OS, overall survival; Pembro, pembrolizumab; RFS, recurrence-free survival; Tram, trametinib.

commence therapy in the comfort of their home. Finally, although this study included the use of systemic adjuvant therapy prior to FDA approval, the proportion of patients who received off-label adjuvant therapy is not available. Although off-label use is not suggested in clinical practice, it is not uncommon in the field of oncology, particularly when current treatments may not provide the best support for patients [35].

Conclusion

This real-world study demonstrates a sample of current US patterns for first-line treatment of resected melanoma in *BRAF*V600-mutated patients. Most patients were given first-line adjuvant immunotherapy with nivolumab or pembrolizumab over targeted therapy combination of dabrafenib plus trametinib, and patients who received targeted therapy combination had the shortest duration

of therapy. Despite differences in the duration of therapy, 1- and 2-year RFS and OS rates remain high in all treatment groups. A further study assessing the relationship between patient/disease characteristics and the selection of adjuvant treatment would help better understand physician/patient prescription preferences in the USA.

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The datasets generated during and/or analyzed during the current study are not available.

Conflicts of interest

Y-L.L. declared to be employed by Novartis and holds stocks in Novartis. J.T. declared to be employed by Asclepius Analytics; received consulting fees, payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Novartis; institution received consultancy payment from Novartis. S.C. reports no conflicts of interest.

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