Patterns of treatment and *BRAF* testing with immune checkpoint inhibitors and targeted therapy in patients with metastatic melanoma presumed to be *BRAF* positive

Sameer Ghate[a], Raluca Ionescu-Ittu[c], Rebecca Burne[c], Briana Ndife[a], François Laliberté[c], Antonio Nakasato[a] and Mei Sheng Duh[b]

Patients with *BRAF* V600 (*BRAF*) mutated metastatic melanoma are eligible for therapy with both immune checkpoint inhibitors and targeted therapies, making treatment choice a complex decision. The present study aimed to describe patterns of treatment with immunotherapy and targeted therapy and *BRAF* testing in patients with metastatic melanoma presumed to have *BRAF* mutations (*BRAF*+) in the years following the approval of the newer generation of immune checkpoint inhibitors and targeted therapies (2014–2016). Two large US commercial claims databases [Truven Health Analytics MarketScan and IQVIA Real-World Data Adjudicated Claims – USA (IQVIA RWD Adjudicated Claims – USA)] were used. Patients were presumed *BRAF*+ if they received at least 2 lines of therapy of which at least 1 included targeted therapy. Sequence of lines of therapy and regimens used in first (1L), second (2L), and third (3L), as well as timing of *BRAF* testing by sequence of therapy were described. In the Truven sample (*n* = 162), targeted therapy was used by 66% in 1L and by 54% in 2L, and 62% had a *BRAF* test; in the IQVIA RWD Adjudicated Claims – USA sample (*n* = 247), targeted therapy was used by 62% in 1L and by 50% in 2L, and 68% had a *BRAF* test. Among those with a claim for a *BRAF* test prior to 1L, over two-thirds were initiated on targeted therapy. These findings suggest that the rate of *BRAF* testing remained low in the years following the approval of *BRAF*-targeted regimens for metastatic disease. Given the recently approved adjuvant treatment options for stage III melanoma, improving the rates of *BRAF* testing becomes increasingly important. *Melanoma Res* 29:301–310 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

[a]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, [b]Analysis Group Inc., Boston, Massachusetts, USA and [c]Groupe d'analyse, Ltée, Montréal, Québec, Canada

Correspondence to Mei Sheng Duh, MPH, ScD, Analysis Group Inc., 111 Huntington Avenue, 14th Floor, Boston, MA 02199, USA
Tel: + 1 617 425 8131; fax: + 1 617 425 8001;
e-mail: mei.duh@analysisgroup.com

Introduction

Melanoma – a type of skin cancer – constitutes a small proportion (< 5%) among different skin cancers, yet accounts for the vast majority of skin-cancer-related deaths [1]. An estimated 87 110 new cases of melanoma of the skin were diagnosed in the USA in 2017, with 9730 associated deaths [2]. While 5-year survival rates for localized melanoma are over 90%, metastatic melanoma generally has a poor prognosis, with a 5-year survival of 15–20% [1].

For a long time, therapeutic options for patients with metastatic melanoma were limited to cytotoxic chemotherapy despite lack of evidence for overall survival benefit [3]. Recent advances in molecular diagnostics have enabled identification of several oncogenes as important prognostic markers in metastatic melanoma. Mutation in the *BRAF* (V600) gene is the most commonly identified oncogene, present in ~50% of cutaneous melanoma cases (*BRAF*+ melanoma) [4], with the remaining patients having unmutated BRAF melanoma. The *BRAF* mutation leads to the activation of RAF/MEK/ERK cell-signaling pathways – the protein product of this oncogene can selectively target metastasized cells and clinically undetected cells that harbor the *BRAF* mutation. *BRAF* gene mutation is an important tool for diagnosis, treatment, and predicting patient outcomes, and may have an impact on prognosis [5,6]. The NCCN clinical practice guidelines recommend *BRAF* mutation testing in patients with unresectable or metastatic melanoma to guide treatment decisions as patients harboring a *BRAF* mutation may have different treatment options [7–9].

Molecularly targeted agents have been developed to specifically target *BRAF*-mutated melanoma. Tyrosine kinase inhibitors, vemurafenib, and subsequently, dabrafenib and trametinib monotherapy demonstrated remarkable clinical benefits for patients with advanced or

metastatic *BRAF*-mutated melanoma [3,10,11], although response durability was variable due to drug resistance [12, 13]. However, using a combination of *BRAF* and *MEK* inhibitors has led to prolonged response and decreased incidence of secondary skin malignancies compared with *BRAF* monotherapies [11,14]. In particular, combination therapy with dabrafenib and trametinib has shown durable long-term overall and progression-free survival in patients with *BRAF*-mutated metastatic melanoma [15].

In parallel, advances in immune-oncology, notably the discovery of immune-checkpoints- molecules responsible for dampening immune response, including programmed cell-death protein 1 (PD-1), and cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors, have offered more treatment options for patients with *BRAF*-mutated metastatic melanoma and other melanoma subtypes [16,17]. CTLA-4 inhibitors, ipilimumab and tremelimumab, and PD-1 inhibitors, nivolumab and pembrolizumab, have shown survival benefit for advanced or metastatic melanoma regardless of *BRAF* mutation status [18,19]. Despite slower initial response and higher risk for severe auto-immune toxicity compared with targeted therapies, some immunotherapies can result in durable long-term survival in patients with metastatic melanoma [20,21]. Combination therapy with ipilimumab and nivolumab has shown more rapid response rates and longer overall survival compared with monotherapy [22].

With the current repertoire of mono and combination targeted therapies and immune checkpoint inhibitors options for metastatic *BRAF*-mutated melanoma, choosing the appropriate therapy is a complex decision. Current considerations that may influence treatment decisions include various clinical and patient considerations including disease-related symptom burden, performance status, presence of brain metastases, possible adverse events of different agents, or patient preference for oral vs. intravenous medications [23,24]. However, in the absence of head-to-head comparisons between immune checkpoint inhibitors and targeted therapies many questions remain unanswered with respect to the optimal treatment sequence in metastatic melanoma [23]. A better understanding of treatment patterns and *BRAF* testing in real-world practice is needed to identify unmet needs in this patient population. However, data regarding real-world treatment practices and patterns of *BRAF* testing remain scarce. Using two large commercial claims databases in the USA, this study aimed to describe patterns of *BRAF* testing and treatment with immune checkpoint inhibitors and targeted therapy in patients with metastatic melanoma presumed to have *BRAF* mutations (*BRAF +*) in the years following the approval of the newer generation of immune checkpoint inhibitors and targeted therapies (2014–2016).

Methods
Data sources
The study used data from two large commercial pharmacy and medical claims databases in the USA: the Truven Health Analytics MarketScan (Truven, Ann Arbor, Michigan, USA) and IQVIA (Danbury, Connecticut, USA) Real-World Data Adjudicated Claims – USA database (IQVIA RWD Adjudicated Claims – USA). As the two databases cannot be combined, analyses were performed separately on the two samples.

Truven database contains health services claims for more than 230 million individuals from ~100 employers and several health plans. IQVIA RWD Adjudicated Claims – US contains health services claims for more than 87 million members from over 100 health plans across the US. Both databases include demographic characteristics, enrollment history, and claims for medical (provider and institutional) and pharmacy services. Truven data are representative of all census regions, predominantly the South and North Central (Midwest) regions. IQVIA RWD Adjudicated Claims – USA database is representative of the national commercially insured population. Both databases contain data from large employers that tend to have generous coverage, especially for new agents. The databases are fully compliant with the Health Insurance Portability and Accountability Act, and thus, no ethics board review was required [25].

Study design
A retrospective cohort design was employed. In both samples, patients were assigned an index date corresponding to the date of initiation of the first immune checkpoint inhibitor(s) or targeted therapy for metastatic melanoma after a diagnosis of melanoma. The baseline period was the 6 months prior to the index date and was extended until the earliest of the end of eligibility (due to disenrollment or death), or the end of data availability (30 June 2016 for Truven and 30 September 2016 for IQVIA RWD Adjudicated Claims – USA).

Study sample
Both samples (Truven and IQVIA RWD Adjudicated Claims – USA) included patients with metastatic melanoma as identified by claims for melanoma after 1 January 2014, and a systemic therapy with immune checkpoint inhibitors or targeted therapy for metastatic melanoma. Patients were included in the study if they (a) were at least 18 years old on the index date; (b) had at least one diagnosis of melanoma (International Classification of Disease, 9th ed., clinical modification code 172.xx), from 1 January 2008 to end of data availability specific to each database; (c) had initiated at least one immune checkpoint inhibitor (ipilimumab, pembrolizumab, nivolumab) or targeted therapy (vemurafenib, dabrafenib, trametinib), on or after 1 January 2014 either as monotherapy or as combination regimens;

(d) had a first diagnosis of melanoma before or on the index date; (e) had continuous healthcare plan eligibility (including drug coverage) during the baseline period and at least 1 month after the index date; (f) were not enrolled in a clinical trial at any time after the melanoma diagnosis date; and (g) received two or more lines of therapy after the index date, of which at least one line included targeted therapy (i.e. patients were presumed to be *BRAF* +). At least two lines of treatment were required for all patients as those treated with immune checkpoint inhibitors in 1L had to have two or more lines of therapy to be identified as presumed *BRAF* + . A small number of patients who received combined immune checkpoint inhibitors and targeted therapy in first line (< 1%) were excluded (Supplementary Fig. 1A and 1B, Supplemental digital content 1, *http://links.lww.com/MR/A65*).

Study measures and statistical analyses

All analyses were descriptive. Frequencies and proportions were reported for categorical variables, and means (SD), medians, and ranges were reported for continuous variables. For each of the two samples, reported treatment patterns post-index date included sequence of lines of therapies as well as all treatment regimens used in first (1L), second (2L), and third (3L) lines post-index date. Identification of lines of pharmacological therapy was adapted from previously published algorithms [26–28]. All agents – single or combination of multiple agents – received during the first 28 days of the line of therapy start constituted the treatment regimen. For regimens with immune check-point inhibitors (intravenous) the length of a cycle was assumed to be 21 days, while for targeted agents (oral) duration of treatment was based on the days' supply. In both cases, gaps of more than 45 days were allowed between consecutive treatments with the same regimen. Thus, a line of therapy was considered to be discontinued if there was a gap of more than 45 consecutive days without treatment or if a new agent (i.e. new line of therapy) was initiated. In the case of immune check-point inhibitors, gaps up to 180 days were allowed if the patient received steroids. Lines of therapy were censored if the patient was still on treatment at the end of the study follow-up.

The proportion of patients presumed *BRAF* + for whom *BRAF* testing was performed from the date of first melanoma diagnosis to 2L start, and the timing of *BRAF* testing by sequence of therapy were described. Identification of *BRAF* testing was based on procedure codes for *BRAF*-specific and sequencing tests [i.e. *BRAF* gene analysis and other multigene sequencing tests did not include immunohistochemistry (IHC)]. Procedure codes for *BRAF*-specific testing also captured other methods of *BRAF* testing including the Droplet Digital PCR test (Bio-Rad, Hercules, California, USA) and Idylla *BRAF* Mutation Test (Biocartis, Mechelen, Belgium). Patient characteristics during the baseline period, including demographic characteristics, underlying tumor burden, comorbidities, and healthcare utilization and costs were outlined by the type of therapy received in 1L in patients with and without a BRAF test claim before 1L initiation.

Results

A total of 2231 and 2632 patients with at least one diagnosis of melanoma and at least one immune checkpoint inhibitor administration or dispensing of targeted therapy on or after the index date were identified from the Truven database and IQVIA RWD Adjudicated Claims – USA database, respectively. From these, 162 patients from the Truven database, and 247 patients from the IQVIA RWD Adjudicated Claims – USA database with metastatic melanoma and presumed *BRAF* + met the inclusion criteria and were included in the study (Supplementary Fig. 1A and 1B, Supplemental digital content 1, *http://links.lww.com/MR/A65*). In the Truven sample, mean age was 56 years and ∼ 60% of the patients were men. In the IQVIA RWD Adjudicated Claims – USA sample, mean age was 53 years and ∼ 62% were men.

Treatment patterns

In the Truven sample, 107 (66%) of presumed *BRAF* + patients were initiated in 1L on targeted therapies and 55 (34%) were initiated on immune checkpoint inhibitors (Fig. 1a). In 2L, 86 (55%) and 61 (38%) received targeted therapy and immune checkpoint inhibitors, respectively; seven (4%) were treated with combination targeted therapies and immune checkpoint inhibitors in 2L. Fifty percent of patients treated with targeted therapy in 1L switched to immune checkpoint inhibitors in 2L and 78% of patients receiving immune checkpoint inhibitors in 1L switched to targeted therapy in 2L (Fig. 1a). In the IQVIA RWD Adjudicated Claims – USA sample, 152 (62%) of presumed *BRAF* + patients were initiated on targeted therapy and 95 (38%) were initiated on immune checkpoint inhibitors (Fig. 1b). In 2L, 124 (50%) and 77 (31%) received targeted therapy and immune checkpoint inhibitors, respectively; 29 (12%) were treated with combination targeted therapies and immune checkpoint inhibitors in 2L. Forty-two percent of patients treated with targeted therapy in 1L switched to immune checkpoint inhibitors in 2L and 73% of patients receiving immune checkpoint inhibitors in 1L switched to targeted therapy in 2L (Fig. 1b).

Figure 2 depicts the distribution of specific treatment regimens by line of therapy. In both Truven and IQVIA RWD Adjudicated Claims – USA samples, during the 2014–2016 study period, the most common immune checkpoint inhibitor regimen used in 1L and 2L was ipilimumab monotherapy, while pembrolizumab monotherapy was the most common immune checkpoint inhibitor regimen in 3L. Dabrafenib and trametinib

Fig. 1
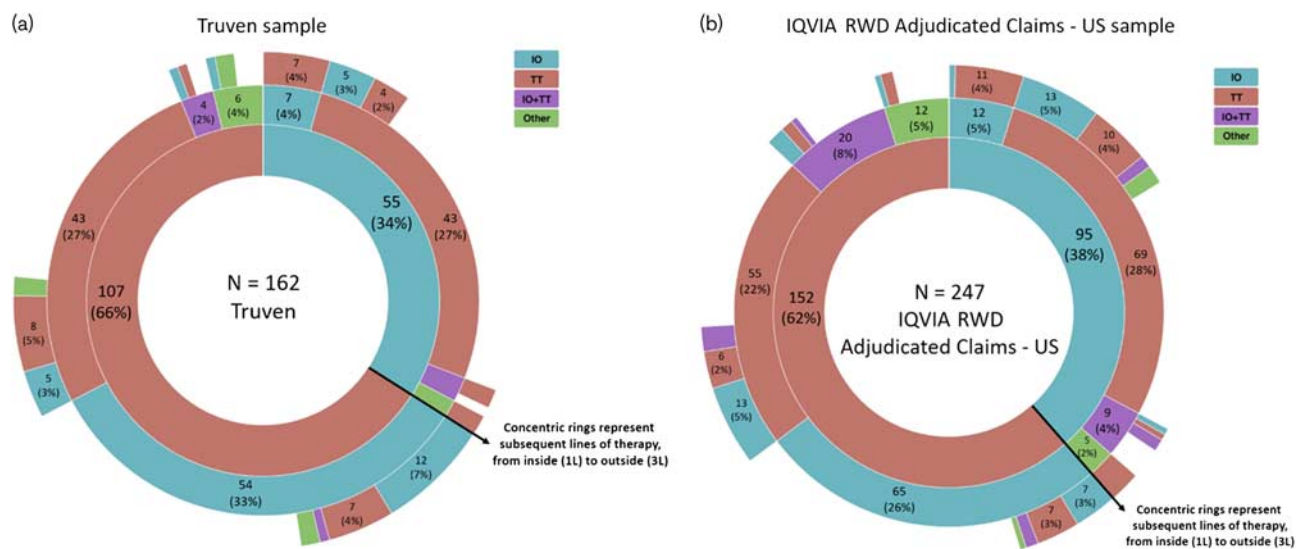
Sequences of lines of pharmacological therapies post-index date: (a) Truven sample, (b) IQVIA RWD Adjudicated Claims – USA sample. I-O, immune check-point inhibitors; other, include: combinations of I-O or TT drugs with other antineoplastic agents, or other antineoplastic agents (by design not in 1L). 1L, first line of therapy post-index; 3L, third line of therapy post-index; TT, targeted therapy.

combination therapy was the most commonly prescribed targeted therapy in 1L, 2L, and 3L (Fig. 2a and b).

BRAF testing
In the Truven sample, 100 of 162 (62%) of presumed *BRAF* + patients had a *BRAF* test claim between melanoma diagnosis and 2L, including 57% of patients who initiated targeted therapy and 56% who initiated immune checkpoint inhibitors. The majority of those with a *BRAF* test claim (92%) had the test between the first melanoma diagnosis and 1L initiation (Table 1). In the IQVIA RWD Adjudicated Claims – USA sample, 168 of 247 (68%) of presumed *BRAF* + patients had a *BRAF* test claim between melanoma diagnosis and 2L, inclusive of 65% of patients who initiated targeted therapy and 61% who initiated immune checkpoint inhibitors; 94% were tested between first melanoma diagnosis and 1L initiation (Table 1).

Table 2 describes the characteristics of patients presumed to be *BRAF* + with and without a *BRAF* test claim before 1L initiation stratified by type of therapy received in 1L, in the Truven and IQVIA RWD Adjudicated Claims – USA samples, respectively. In the Truven sample, among those with claim(s) for *BRAF* test, the proportion of patients with emergency department visits and renal disease during the baseline period was significantly higher in patients who initiated targeted therapy compared with those who initiated immune checkpoint inhibitors ($P < 0.05$). Likewise, in the IQVIA RWD Adjudicated Claims – USA sample, among those with claim(s) for *BRAF* test, the proportion of patients

with inpatient admissions was significantly higher among patients who initiated targeted therapy compared with those who initiated immune checkpoint inhibitors ($P < 0.05$). No statistically significant differences were observed between patients treated in 1L with immune checkpoint inhibitors versus targeted therapies among those without a *BRAF* test claim prior to 1L.

Even though not statistically significant, a tendency towards more patients with brain metastases, anemia, immune diseases, and liver disease was observed among patients treated with targeted therapies in 1L as compared with patients treated with immune checkpoint inhibitors in 1L, especially in the Truven sample. At the same time, there were numerically more patients with cardiovascular diseases among those treated with immune checkpoint inhibitors than those treated with targeted therapies. In both samples, more than half of the patients who did not have a claim for *BRAF* test before 1L initiation had claim(s) for IHC test in the same period.

Overall, in the Truven sample, patients with a *BRAF* test claim prior to 1L initiation had more brain metastases, a higher number of metastatic sites, and higher Charlson comorbidity score than patients who did not have a claim for *BRAF* test prior to 1L initiation (Supplementary Table 1A, Supplemental digital content 1, *http://links. lww.com/MR/A65*). They also had higher all-cause cost during the baseline period, and more IHC tests before 1L initiation. In the IQVIA RWD Adjudicated Claims – USA sample, patients with a *BRAF* test claim prior to 1L initiation had more surgeries, a higher number of metastatic sites, and more IHC tests before 1L than
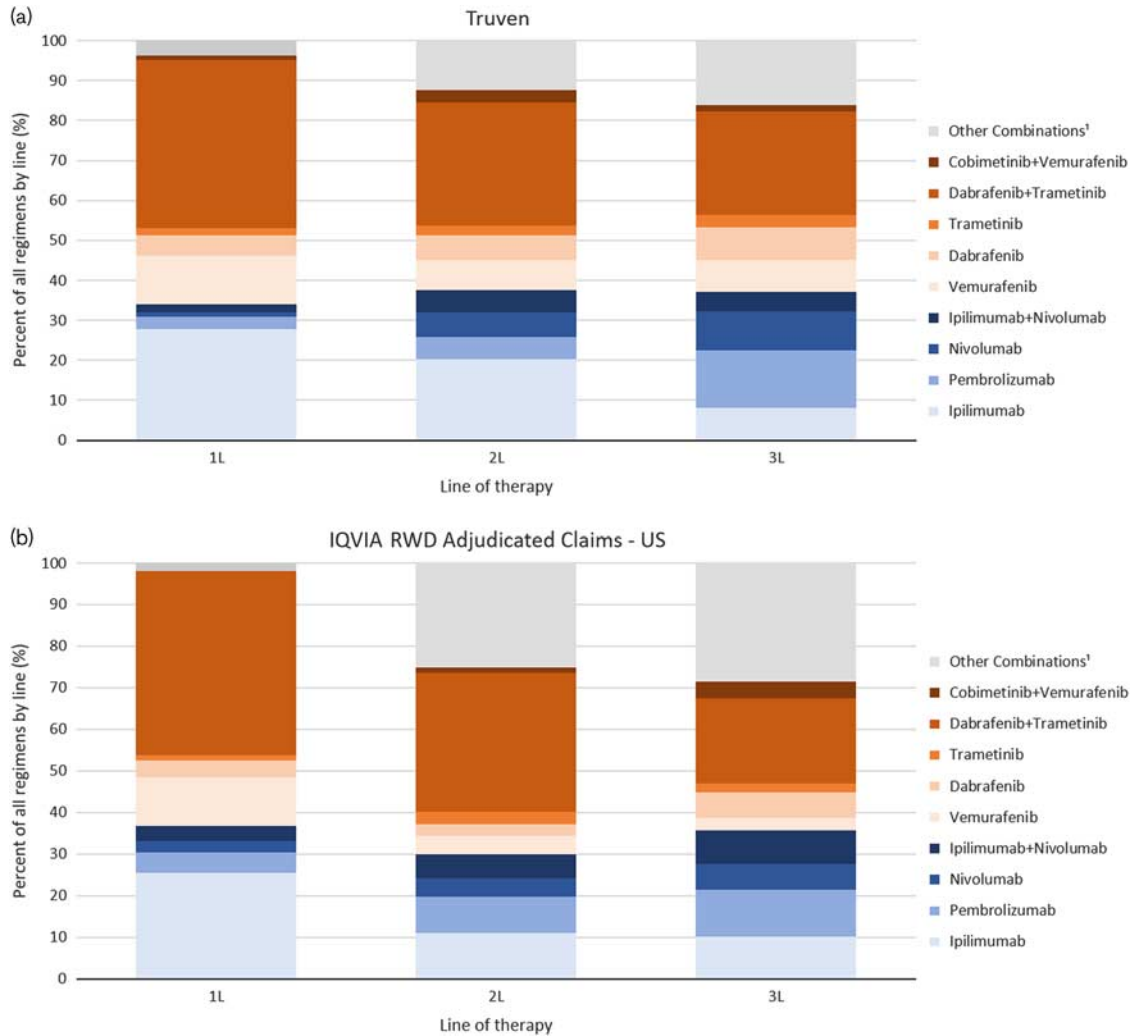
Distribution of immune checkpoint inhibitors (I-O), targeted therapy (TT), and other regimens by line of therapy: (a) Truven sample, (b) IQVIA Real-World Data Adjudicated Claims – USA sample. Other combinations include: nonstandard combinations of I-O or TT drugs, combinations of I-O or TT drugs with other antineoplastic agents, I-O in combination with TT (not in 1L by design), or other antineoplastic agents (not in 1L by design) [1]. 1L, first line of therapy post-index; 2L, second line of therapy post-index; 3L, third line of therapy post-index.

patients who did not have a claim for *BRAF* test prior to 1L initiation (Supplementary Table 1B, Supplemental digital content 1, *http://links.lww.com/MR/A65*). They also had a tendency towards having more brain metastases, although this was not statistically significant.

Discussion

This study documents patterns of treatment and *BRAF* testing among patients diagnosed with melanoma and presumed *BRAF +* in a real-world clinical setting. A higher proportion of patients presumed to be *BRAF +* were treated with targeted therapy than immune checkpoint inhibitors in 1L and subsequent lines. Approximately two-thirds of presumed *BRAF +* patients received targeted

therapy in 1L and half received targeted therapy in 2L. Although recently approved targeted therapies and immune checkpoint inhibitors were commonly used; surprisingly, older agents particularly ipilimumab mono-therapy, continued to be used for some patients during the study period. Only two-thirds of patients presumed to be *BRAF +* had a *BRAF*-specific or sequencing test between melanoma diagnosis and 2L, although many of those without a *BRAF*-specific or sequencing test had an IHC test. Among patients who had a claim for a *BRAF* test, over two-thirds received targeted therapy in 1L.

Studies of treatment patterns specifically among patients with *BRAF*-mutant metastatic melanoma in real-world settings remain scare. To our knowledge, no study to

Table 1 Timing of *BRAF* testing by treatment sequence

1L→2L sequence	1L→2L sequence (*N*)	Newly tested during period [*n* (%)]		
		From melanoma diagnosis to start 1L	During 1L	From end 1L to end 2L
Truven sample				
I-O→I-O	7	3 (43)	0 (0)	0 (0)
I-O→TT	43	24 (56)	2 (5)	0 (0)
I-O→I-O + TT	3	3 (100)	0 (0)	0 (0)
I-O→other	2	1 (50)	0 (0)	1 (50)
TT→I-O	54	31 (57)	2 (4)	0 (0)
TT→TT	43	24 (56)	2 (5)	0 (0)
TT→I-O + TT	4	2 (50)	0 (0)	1 (25)
TT→other	6	4 (67)	0 (0)	0 (0)
IQVIA Real-World Data Adjudicated Claims – USA sample				
I-O→I-O	12	6 (50)	2 (17)	0 (0)
I-O→TT	69	44 (64)	3 (4)	0 (0)
I-O→I-O + TT	9	5 (56)	1 (11)	0 (0)
I-O→other	5	3 (60)	0 (0)	1 (20)
TT→I-O	65	43 (66)	2 (3)	1 (2)
TT→TT	55	39 (71)	0 (0)	0 (0)
TT→I-O + TT	20	12 (60)	0 (0)	0 (0)
TT→other	12	6 (50)	0 (0)	0 (0)

Other includes: combinations of I-O or TT drugs with other antineoplastic agents, or other antineoplastic agents (by design not in 1L).
I-O, immune check-point inhibitors; 1L, first line of therapy post-index; 2L, second line of therapy post-index; TT, targeted therapy.

date has examined patterns of *BRAF* testing among patients with metastatic melanoma in real-world settings, with the exception of one study that investigated treatment patterns and outcomes in *BRAF*-mutant melanoma patients with brain metastases receiving vemurafenib, a subgroup of patients that is likely not representative to all patients with metastatic melanoma [29]. Furthermore, there are no head-to-head comparisons between targeted therapies and immune checkpoint inhibitors in metastatic melanoma [23], even though there is evidence showing efficacy of both targeted therapy and immune checkpoint inhibitors relative to older therapies in 1L [19,30,31]. Therefore, past studies are of limited relevance to the present study that describes treatment patterns in a broader population of melanoma patients presumed *BRAF* + -treated with a wide range of targeted or immune checkpoint inhibitors regimens in real clinical practice.

In the absence of hard evidence of optimal treatment sequence, it remains unclear how physicians select 1L and subsequent treatments in real-world settings and which treatments are favored by the physicians at present [23]. The results of the current study suggest approximately two-thirds of patients presumed to be *BRAF* + receive targeted therapy in 1L and subsequent lines of therapy, while approximately one-third receive immune checkpoint inhibitors. Furthermore, some patients appear to continue to be treated with older therapies (i.e. ipilimumab, targeted agents in monotherapy) even after the approval of the new generation of immune checkpoint inhibitors and targeted therapies. A proportion of patients treated with targeted therapy in 1L continued on

targeted therapy in 2L. The reasons for discontinuing or restarting a treatment regimen are not known in claims data and our study algorithm counts as a different line of therapy if the patient restarts one or more agents from the initial regimen after a gap of more than 45 days without treatment (in Truven this pattern was observed for 53.5% of patients who received targeted therapy in both 1L and 2L; in IQVIA RWD Adjudicated Claims – USA sample the pattern was observed for 30.9%). For the remaining patients in both samples, 2L included at least one new agent (i.e. either an add-on to the regimen used in 1L or a switch to a completely new regimen; for 18.6 and 30.9%, respectively, the change was from vemurafenib monotherapy in 1L to regimens with newer agents in 2L).

The choice of treatment in this patient population is likely influenced by numerous patient-specific and treatment-specific factors such as patient's tumor and comorbidity profile, treatment adverse effects profile, as well as physician preference. The present study suggests that targeted therapy may be channeled towards more frail patients with higher comorbidity burden including those with brain metastases. Patients receiving targeted therapy had a higher comorbidity burden compared with those receiving immunotherapy in the IQVIA RWD Adjudicated Claims – USA sample; in the Truven sample, the proportion of patients with brain metastases was numerically higher among patients receiving targeted therapy compared with those receiving immune checkpoint inhibitors (all patients regardless of *BRAF* testing: 39 vs. 22%, $P = 0.02$). Healthcare utilization [emergency department visits (Truven sample) and inpatient admissions (IQVIA RWD Adjudicated Claims – USA sample)] during the baseline period, which may be indicative of higher comorbidity burden, was also higher among patients who were treated with targeted therapy compared with those who received immune checkpoint inhibitors. Previous studies also suggested that the underlying comorbidity and tumor burden are important clinical factors influencing treatment choice. For example, in cases of extensive or rapidly progressing visceral metastases or high disease-related symptom burden, targeted therapy may be favored to achieve rapid response and disease stabilization [32]. Similarly, in the setting of brain metastases, targeted therapy may be favored over immune checkpoint inhibitors based on the numerous studies supporting its use in this patient population [33–35]. However, immune checkpoint inhibitors were also shown to have activity in this setting [36], which may partly explain why some patients with brain metastases in this study received immune checkpoint inhibitors.

In the absence of head-to-head randomized clinical trials comparing targeted therapies and immune checkpoint inhibitors, physician preference likely plays a role. It is possible that physician's choice of immune checkpoint inhibitors instead of targeted therapy in treating *BRAF* +

Table 2 Patient characteristics stratified by *BRAF* testing and treatment used in 1L

Truven sample	With claim for *BRAF* test before 1L			Without a *BRAF* claim before 1L		
	I-O in 1L (N=31)	TT in 1L (N=61)	P value[a]	I-O in 1L (N=24)	TT in 1L (N=46)	P value[a]
Demographics (at index date)						
Age						
Mean ± SD	55.1 ± 10.1	55.0 ± 14.1	0.955	55.8 ± 9.6	59.2 ± 12.5	0.254
Median (IQR)	57.0 (47.0–62.0)	57.0 (47.0–62.0)		56.5 (48.0–61.0)	59.0 (50.0–67.0)	
Male [N (%)]	15 (48.4)	40 (65.6)	0.112	14 (58.3)	29 (63.0)	0.701
Underlying tumor burden (between first melanoma diagnosis and line start)						
Prior cancer-directed therapies [N (%)]						
Pharmacological	5 (16.1)	13 (21.3)	0.554	5 (20.8)	5 (10.9)	0.258
Radiation therapy	11 (35.5)	32 (52.5)	0.123	9 (37.5)	18 (39.1)	0.894
Surgery (patients can have > 1 type of surgery) [N (%)]						
Skin biopsy	16 (51.6)	34 (55.7)	0.707	13 (54.2)	17 (37.0)	0.167
Excision of skin tumor	16 (51.6)	34 (55.7)	0.707	12 (50.0)	30 (65.2)	0.217
Lymph node dissection	19 (61.3)	30 (49.2)	0.271	13 (54.2)	20 (43.5)	0.395
Brain metastases	9 (29.0)	28 (45.9)	0.119	3 (12.5)	14 (30.4)	0.097
Number of metastatic sites (maximum = 6; listed above)						
Mean ± SD	2.4 ± 1.2	2.6 ± 1.4	0.375	1.8 ± 0.9	2.2 ± 1.2	0.152
Median (IQR)	2.0 (1.0–3.0)	2.0 (2.0–3.0)		2.0 (1.0–2.0)	2.0 (1.0–3.0)	
Comorbidities (during baseline period)						
Charlson comorbidity score (CCI)[b]						
Mean ± SD	6.8 ± 1.5	7.2 ± 1.3	0.158	6.5 ± 1.0	6.6 ± 1.0	0.561
Median (IQR)	6.0 (6.0–7.0)	7.0 (6.0–8.0)		6.0 (6.0–6.0)	6.0 (6.0–7.0)	
Specific comorbidities [N (%)]						
Anemia	4 (12.9)	18 (29.5)	0.078	4 (16.7)	7 (15.2)	0.874
Cardiovascular disease[c]	17 (54.8)	28 (45.9)	0.418	11 (45.8)	22 (47.8)	0.874
Diabetes (type I or II)	4 (12.9)	9 (14.8)	0.810	2 (8.3)	6 (13.0)	0.557
Hemiplegia	3 (9.7)	5 (8.2)	0.812	1 (4.2)	1 (2.2)	0.635
Immune diseases[d]	0 (0.0)	6 (9.8)	0.071	3 (12.5)	5 (10.9)	0.839
Liver disease	4 (12.9)	16 (26.2)	0.143	4 (16.7)	9 (19.6)	0.767
Renal disease	0 (0.0)	8 (13.1)	0.035*	0 (0.0)	1 (2.2)	0.467
Healthcare resource utilization (during baseline period)						
Inpatient admission(s) [N (%)]	13 (41.9)	31 (50.8)	0.420	10 (41.7)	19 (41.3)	0.977
Emergency department visit(s) [N (%)]	5 (16.1)	22 (36.1)	0.047*	5 (20.8)	14 (30.4)	0.391
Healthcare cost (during baseline period)						
All-cause cost (per patient per month)						
Mean ± SD	9,858 ± 10,075	14,643 ± 17,338	0.098	7,082 ± 6,300	9,255 ± 12,963	0.349
Median (IQR)	6,293 (2,533–10,486)	9,623 (2,935–17,733)		5,634 (2,195–9,788)	5,724 (1,645–11,243)	
Immunohistochemistry testing (from first melanoma diagnosis to 1L start)						
IHC test before 1L [N (%)]	26 (83.9)	55 (90.2)	0.379	18 (75.0)	35 (76.1)	0.920

IQVIA RWD Adjudicated Claims – USA	With claim for *BRAF* test before 1L			Without a *BRAF* claim before 1L		
	I-O in 1L (N=58)	TT in 1L (N=100)	P value[a]	I-O in 1L (N=37)	TT in 1L (N=52)	P value[a]
Demographics (at index date)						
Age						
Mean ± SD	50.0 ± 9.5	52.1 ± 10.6	0.211	54.8 ± 11.0	54.7 ± 10.9	0.947
Median (IQR)	51.5 (43.0–57.0)	54.0 (45.5–60.0)		57.0 (46.0–62.0)	55.5 (50.5–62.5)	
Males [N (%)]	29 (50.0)	63 (63.0)	0.110	22 (59.5)	39 (75.0)	0.120
Underlying tumor burden (between first melanoma diagnosis and line start)						
Prior cancer-directed therapies [N (%)]						
Pharmacological	9 (15.5)	14 (14.0)	0.794	4 (10.8)	7 (13.5)	0.708
Radiation therapy	22 (37.9)	45 (45.0)	0.386	10 (27.0)	20 (38.5)	0.261
Surgery (patients can have > 1 type of surgery) [N (%)]						
Skin biopsy	24 (41.4)	45 (45.0)	0.658	11 (29.7)	17 (32.7)	0.767
Excision of skin tumor	36 (62.1)	61 (61.0)	0.894	18 (48.6)	20 (38.5)	0.338
Lymph node dissection	35 (60.3)	54 (54.0)	0.438	17 (45.9)	21 (40.4)	0.601
Brain metastases [N (%)]	18 (31.0)	35 (35.0)	0.611	8 (21.6)	12 (23.1)	0.871
Number of metastatic sites (maximum = 6; listed above)						
Mean ± SD	2.6 ± 1.3	2.7 ± 1.4	0.459	2.1 ± 1.4	2.4 ± 1.2	0.264
Median (IQR)	2.0 (2.0–3.0)	3.0 (2.0–4.0)		2.0 (1.0–3.0)	2.0 (1.5–3.0)	
Comorbidities (during baseline period)						
Charlson comorbidity score (CCI)[b]						
Mean ± SD	6.6 ± 1.1	6.9 ± 1.2	0.071	6.6 ± 0.9	7.2 ± 1.2	0.018*
Median (IQR)	6.0 (6.0–7.0)	6.0 (6.0–8.0)		6.0 (6.0–7.0)	7.0 (6.0–8.0)	
Specific comorbidities [N (%)]						
Anemia	13 (22.4)	24 (24.0)	0.820	4 (10.8)	12 (23.1)	0.137
Cardiovascular disease[c]	18 (31.0)	26 (26.0)	0.496	8 (21.6)	27 (51.9)	0.004*
Diabetes (type I or II)	6 (10.3)	7 (7.0)	0.461	6 (16.2)	8 (15.4)	0.915
Hemiplegia	2 (3.4)	5 (5.0)	0.648	0 (0.0)	2 (3.8)	0.228
Immune diseases[d]	4 (6.9)	9 (9.0)	0.643	5 (13.5)	4 (7.7)	0.369
Liver disease	11 (19.0)	27 (27.0)	0.255	8 (21.6)	18 (34.6)	0.184
Renal disease	1 (1.7)	8 (8.0)	0.101	2 (5.4)	9 (17.3)	0.093

Table 2 (*continued*)

IQVIA RWD Adjudicated Claims – USA	With claim for *BRAF* test before 1L			Without a *BRAF* claim before 1L		
	I-O in 1L (*N* = 58)	TT in 1L (*N* = 100)	*P* value[a]	I-O in 1L (*N* = 37)	TT in 1L (*N* = 52)	*P* value[a]
Healthcare resource utilization (during baseline period)						
Inpatient admission(s) [*N* (%)]	17 (29.3)	47 (47.0)	0.029*	12 (32.4)	27 (51.9)	0.068
Emergency department visit(s) [*N* (%)]	21 (36.2)	27 (27.0)	0.225	11 (29.7)	20 (38.5)	0.394
Healthcare cost (during baseline period)						
All-cause cost (per patient per month)						
Mean ± SD	8,669 ± 8,874	14,034 ± 22,673	0.037*	9,005 ± 17,021	15,104 ± 21,861	0.160
Median (IQR)	6,200	8,212		3,575	6,990	
	(3,113–10,056)	(3,507–16,332)		(1,436–8,427)	(2,351–17,114)	
Immunohistochemistry testing (from first melanoma diagnosis to 1L start)						
IHC test before 1L [*N* (%)]	47 (81.0)	84 (84.0)	0.633	20 (54.1)	27 (51.9)	0.843

IHC, immunohistochemistry; I-O, immune check-point inhibitors; IQR, interquartile range; 1L, first line of therapy post-index; 2L, second line of therapy post-index; TT, targeted therapy.
[a]χ^2-Tests and *t*-tests were conducted to assess whether there are any statistically significant differences between cohorts.
[b]All patients received six points in the CCI score for the metastatic disease [43].
[c]Any of the following: cerebrovascular disease, congestive heart failure, myocardial infarction, peripheral vascular disease.
[d]Any of the following: ankylosing spondylitis; thyroiditis; Graves' disease; inflammatory bowel disease (including Crohn's disease and ulcerative colitis), multiple sclerosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, systemic lupus erythematosus, or vitiligo.
*Statistically significant at a 5% significance level.

metastatic melanoma is based on evidence of long-term disease control achieved with immune checkpoint inhibitors in some patients. Physicians may deem the benefit of achieving durable response with immune checkpoint inhibitors to outweigh risk of severe immune-related adverse events. However, recent long-term clinical trial outcome data suggest that patients treated with first-line targeted therapy may also achieve durable disease control [37]. Moreover, resistance and toxicity observed with single agent targeted therapy have been overcome by combination of *BRAF* and *MEK* inhibition that has greatly improved the efficacy and safety profile of targeted therapies [11,30]. A recent meta-analysis that estimated relative efficacy and safety of systemic therapies for advanced treatment-naive *BRAF*-mutated melanoma found no significant difference in overall survival between PD-1 and *BRAF/MEK* inhibitors [8]. A significant advantage of *BRAF/MEK* inhibition compared with all other treatment strategies (i.e. targeted monotherapies, CTLA-4/GM-CSF, CTLA-4/chemo, MEK/chemo, chemo) was found for progression-free survival. Moreover, first-line use of combination *BRAF/MEK* targeted therapy was the most effective treatment regimen for patients with bulky or highly symptomatic disease [8]. It is unclear why older therapies continue to be used after the introduction of new treatments with improved efficacy and safety profiles. One possibility is the delayed uptake of newer treatments, particularly outside academic settings. This hypothesis is supported by the trends in use of immune checkpoint inhibitor and targeted therapy regimens in the period from 2014 to 2016 in our data. For immune checkpoint inhibitors, there was a gradual shift away from ipilimumab monotherapy (100% in 2014 to <10% in 2016) to treatment with newer immune checkpoint inhibitor regimens, in particular ipilimumab + nivolumab combination. Likewise, for targeted therapy regimens, there was a shift away from monotherapy with dabrafenib (~10% in 2014 to 0% in 2016) and vemurafenib (~25% in 2014 to <15% in 2016), to combination therapy with dabrafenib + trametinib (Supplementary Fig. 2A and 2B, Supplemental digital content 1, *http://links.lww.com/MR/A65*). Two-thirds of patients had a *BRAF* test claim between melanoma diagnosis and 2L, inclusive, with the majority tested prior to 1L. The remaining patients may have been tested later or may have had a *BRAF* test that was not reimbursed by a commercial insurer, and therefore not captured in the data. In addition, procedure codes used to identify *BRAF* + status in this study were restricted to *BRAF*-specific or sequencing tests. However, approximately half of patients presumed to be *BRAF* +, who did not have claims for *BRAF*-specific or sequencing tests, had claims for IHC tests prior to 1L. Given the high specificity of IHC [38], it is possible that in a subset of patients the choice of treatment was guided by IHC results. Although the NCCN guidelines state that positive VE1 (an anti-*BRAF* V600E monoclonal antibody) IHC results are sufficient for initiating targeted therapy, it is recommend that all VE1 IHC results should be confirmed by sequencing [7].

This study was subject to common limitations of studies based on healthcare claims data, such as occasional coding errors. However, potential inaccuracies are expected to affect all groups to a similar extent. The findings are only generalizable to the population and time period studied. Although the treatment landscape in metastatic melanoma is rapidly shifting, a lag of 6–9 months exists in the database and data were available only up to 30 June 2016 (Truven) and 30 September 2016 (IQVIA RWD Adjudicated Claims – USA). In addition, identification of *BRAF* testing based on procedure codes has limitations and *BRAF* testing that was not reimbursed by the patient's commercial insurer was not captured. Moreover,

barriers to pharmacogenetic testing may exist and reimbursement practices vary across providers that require different criteria for reimbursement of pharmacogenetic tests [39–41]. In some cases the insurer or the hospital may cover the cost of testing, and in some cases patients may pay out of their pocket [42]. Accessibility to pharmacogenetic tests, particularly multigene tests, is made challenging by the complex and time-consuming process of ordering these tests [40,42]. As it was not possible to distinguish between *BRAF*+ and *BRAF*− in the data, *BRAF*+ was defined based on the use of targeted therapy in at least one line of treatment. Given that only patients who received two or more lines of therapy were included, those who stopped treatment after 1L due to either death or adequate response to treatment were not observed, and therefore findings apply only to patients who receive two or more lines of therapy. As *BRAF*+ patients who experience progression or relapse during or after treatment with immune checkpoint inhibitors in 1L are likely to receive targeted therapy in 2L [7], this is a reasonable method of identifying *BRAF*+ patients.

Given the rapidly evolving therapeutic landscape of metastatic melanoma, it is important to understand treatment patterns and factors that influence treatment decisions in real-world practice, before the introduction of newer agents. This study provides real-world insight into treatment patterns in patients with metastatic melanoma that reflect the diversity of therapeutic agents used in real-world clinical practice. The multitude of effective targeted therapy and immune checkpoint inhibitors options available to patients with *BRAF*+ metastatic melanoma, and the complexity of the disease, may lead to variable treatment patterns and lack of consensus regarding the optimal treatment of patients with *BRAF*+ metastatic melanoma in real-world practice. Further studies are needed to clarify the prognostic importance of *BRAF* mutation status in the metastatic melanoma setting.

Acknowledgements

Conflicts of interest

References

1 National Cancer Institute Surveillance Epidemiology and End Results Program. Cancer Statistics Cancer Stat Facts: Melanoma of the Skin. 2014. Available at: *https://seer.cancer.gov/statfacts/html/melan.htm.l.* [Accessed March 2018].

2 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017; **67**:7–30.

3 Chapman PB, Einhorn LH, Meyers ML, Saxman S, Destro AN, Panageas KS, *et al.* Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *J Clin Oncol* 1999; **17**:2745–2751.

4 Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, *et al.* Mutations of the BRAF gene in human cancer. *Nature* 2002; **417**:949–954.

5 Ekedahl H, Cirenajwis H, Harbst K, Carneiro A, Nielsen K, Olsson H, *et al.* The clinical significance of BRAF and NRAS mutations in a clinic-based metastatic melanoma cohort. *Br J Dermatol* 2013; **169**:1049–1055.

6 Long GV, Menzies AM, Nagrial AM, Haydu LE, Hamilton AL, Mann GJ, *et al.* Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol* 2011; **29**:1239–1246.

7 Coit DG, Thompson JA, Albertini MR, Algazi A, Andtbacka R, Bichakjian CK, *et al.* Melanoma, version 1.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2017; **14**:450–473.

8 Devji T, Levine O, Neupane B, Beyene J, Xie F. Systemic therapy for previously untreated advanced BRAF-mutated melanoma: a systematic review and network meta-analysis of randomized clinical trials. *JAMA Oncol* 2017; **3**:366–373.

9 Pracht M, Mogha A, Lespagnol A, Fautrel A, Mouchet N, Le Gall F, *et al.* Prognostic and predictive values of oncogenic BRAF, NRAS, c-KIT and MITF in cutaneous and mucous melanoma. *J Eur Acad Dermatol Venereol* 2015; **29**:1530–1538.

10 Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, *et al.* Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2012; **380**:358–365.

11 Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, *et al.* Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med* 2015; **372**:30–39.

12 Carlos G, Anforth R, Clements A, Menzies AM, Carlino MS, Chou S, *et al.* Cutaneous toxic effects of BRAF inhibitors alone and in combination with MEK inhibitors for metastatic melanoma. *JAMA Dermatol* 2015; **151**:1103–1109.

13 Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, *et al.* Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; **364**:2507–2516.

14 Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, *et al.* Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med* 2012; **367**:1694–1703.

15 Long GV, Eroglu Z, Infante J, Patel S, Daud A, Johnson DB, *et al.* Long-term outcomes in patients with BRAF V600-mutant metastatic melanoma who received dabrafenib combined with trametinib. *J Clin Oncol* 2018; **36**:667–673.

16 O'Day SJ, Hamid O, Urba WJ. Targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4): a novel strategy for the treatment of melanoma and other malignancies. *Cancer* 2007; **110**:2614–2627.

17 Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, *et al.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; **366**:2443–2454.

18 Larkin J, Lao CD, Urba WJ, McDermott DF, Horak C, Jiang J, *et al.* Efficacy and safety of nivolumab in patients with BRAF V600 mutant and BRAF wild-type advanced melanoma: a pooled analysis of 4 clinical trials. *JAMA Oncol* 2015; **1**:433–440.

19 Shahabi V, Whitney G, Hamid O, Schmidt H, Chasalow SD, Alaparthy S, *et al.* Assessment of association between BRAF-V600E mutation status in melanomas and clinical response to ipilimumab. *Cancer Immunol Immunother* 2012; **61**:733–737.

20 Fecher LA, Agarwala SS, Hodi FS, Weber JS. Ipilimumab and its toxicities: a multidisciplinary approach. *Oncologist* 2013; **18**:733–743.

21 Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, *et al.* Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. *J Clin Oncol* 2015; **33**:1889–1894.

22 Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, *et al.* Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2017; **377**:1345–1356.

23 Levine O, Devji T, Xie F. Systemic therapy for previously untreated advanced BRAF-mutated melanoma: navigating a shifting landscape. *Immunotherapy* 2017; **9**:375–378.

24 Rauschenberg R, Garzarolli M, Dietrich U, Beissert S, Meier F. Systemic therapy of metastatic melanoma. *J Dtsch Dermatol Ges* 2015; **13**:1223–1235; [quiz 1236–1227].

25 Hansen LG, Chang S. White paper: Health research data for the real world: the marketscan databases. 2011. Available at: *http://truvenhealth.com/portals/0/assets/PH_11238_0612_TEMP_MarketScan_WP_FINAL.pdf.* [Accessed March 2018].

26 Hurvitz S, Guerin A, Brammer M, Guardino E, Zhou ZY, Latremouille Viau D, *et al.* Investigation of adverse-event-related costs for patients with metastatic breast cancer in a real-world setting. *Oncologist* 2014; **19**:901–908.

27 Ramsey S, Henk H, Smith G, Sollano J, Chen C. First-, second- and third-line lung cancer treatment patterns and associated costs in a US healthcare claims database. *Lung Cancer Manag Future Med* 2015; **1**:131–143.

28 Seal BS, Sullivan SD, Ramsey S, Shermock KM, Ren J, Kreilick C, *et al.* Medical costs associated with use of systemic therapy in adults with colorectal cancer. *J Manag Care Pharm* 2013; **19**:461–467.

29 Gibney GT, Gauthier G, Ayas C, Galebach P, Wu EQ, Abhyankar S, *et al.* Treatment patterns and outcomes in BRAF V600E-mutant melanoma patients with brain metastases receiving vemurafenib in the real-world setting. *Cancer Med* 2015; **4**:1205–1213.

30 Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, *et al.* Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med* 2015; **373**:23–34.

31 Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, *et al.* Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med* 2015; **372**:2006–2017.

32 Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G, Keilholz U. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26** (**Suppl 5**):v126–v132.

33 Dummer R, Goldinger SM, Turtschi CP, Eggmann NB, Michielin O, Mitchell L, *et al.* Vemurafenib in patients with BRAF(V600) mutation-positive melanoma with symptomatic brain metastases: final results of an open-label pilot study. *Eur J Cancer* 2014; **50**:611–621.

34 Frederick DT, Piris A, Cogdill AP, Cooper ZA, Lezcano C, Ferrone CR, *et al.* BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. *Clin Cancer Res* 2013; **19**:1225–1231.

35 Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, *et al.* Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; **13**:1087–1095.

36 Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, *et al.* Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol* 2012; **13**:459–465.

37 Long GV, Weber JS, Infante JR, Kim KB, Daud A, Gonzalez R, *et al.* Overall survival and durable responses in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib combined with trametinib. *J Clin Oncol* 2016; **34**:871–878.

38 Pearlstein MV, Zedek DC, Ollila DW, Treece A, Gulley ML, Groben PA, *et al.* Validation of the VE1 immunostain for the BRAF V600E mutation in melanoma. *J Cutan Pathol* 2014; **41**:724–732.

39 Lu CY, Loomer S, Ceccarelli R, Mazor KM, Sabin J, Clayton EW, *et al.* Insurance coverage policies for pharmacogenomic and multi-gene testing for cancer. *J Pers Med* 2018; **8**:E19.

40 Phillips KA. Evolving payer coverage policies on genomic sequencing tests: beginning of the end or end of the beginning? *JAMA* 2018; **319**:2379–2380.

41 Torre K, Jhorar P, Wu R, Pfeifer J, Elaba Z, Murphy M. Molecular testing practices and perceptions among dermatopathologists. *J Cutan Pathol* 2018; **45**:387–394.

42 Wu AC, Mazor KM, Ceccarelli R, Loomer S, Lu CY. Access to guideline-recommended pharmacogenomic tests for cancer treatments: experience of providers and patients. *J Pers Med* 2017; **7**:E17.

43 Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; **45**:613–619.