Research Article

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Targeted agents or immuno-oncology therapies as first-line therapy for BRAF-mutated metastatic melanoma: a real-world study

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Aim: Targeted therapy (TT) and immuno-oncology (IO) drugs are approved for patients with BRAF mutant metastatic melanoma (MM). We compared real-world outcomes for first-line (1L) TT versus 1L IO to evaluate optimal sequencing. **Materials & methods:** Physicians-identified BRAF mutant MM patients initiating 1L TT or IO therapies and extracted treatment, disease and clinical outcomes including disease response which were compared between TT and IO and individual regimens. **Results:** 440 MM patients (TT = 283, IO = 157) were identified. A higher proportion of TT patients had liver metastases (46.3 vs 35.0%) and abnormal lactate dehydrogenase (61.1 vs 42.7%). IO-treated had a RECIST-determined response rate of 45.9 versus 60.1% for TT and time on treatment of 7.2 versus 11.4 months, respectively. There was no survival difference between cohorts. **Conclusion:** Despite higher risk patients, 1L TT resulted in higher response rate and longer treatment duration suggesting a preferred 1L sequence.

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In just 4 years, seven drugs received US FDA approval and labeling for the treatment of patients with BRAF mutant metastatic melanoma (MM) and within two years all had a first-line (1L) indication. Since the approval of the BRAF inhibitor dabrafenib (D) and the MEK inhibitor trametinib (T) the National Comprehensive Cancer Network (NCCN) has given a category 1 recommendation for 1L BRAF/MEK combination therapy [1] with D+T [2,3] or vemurafenib plus cobimetinib (V+C) [4]. Additionally, the NCCN recommends immuno-oncology (IO) therapies including single-agent programmed cell death protein 1 (PD-1) treatment with nivolumab (nivo) [5], pembrolizumab (pembro) [6], or the combination of ipilimumab, a CTLA-4 inhibitor, plus nivo (ipi/nivo) [5]. In June 2018, an additional combination targeted therapy (TT), encorafenib plus binimetinib was approved for the treatment of BRAF mutant MM [7].

No head-to-head randomized controlled trials (RCTs) comparing TT and IO for BRAF mutant MM have been conducted. As such, there is no consensus on the optimal sequencing of 1L and subsequent treatment for these patients, nor is it known how patients outside of the RCT setting have responded to these novel agents [8]. Treatment comparisons via prospective trials, such as the ongoing ECOG-ACRIN trial NCT02224781 (randomization to 1L D+T or ipi/nivo followed by a switch to the other combination at progression), may be robust tools for comparing efficacy; but these approaches also have limitations in their ability to evaluate outcomes across heterogeneous patient and treatment populations or in being contemporaneous with evolving treatment patterns. Real-world observational research is one methodological approach for addressing these gaps; however, at the time of this writing, few real-world studies had compared outcomes between TT and IO for BRAF mutant MM patients since the introduction of PD-1 treatments [9–14]. The aims of this research were to describe characteristics of real-world BRAF mutant

MM patients prescribed 1L TT or IO, as well as the duration of 1L therapy, time between discontinuation of 1L to initiation of second-line (2L) therapy, disease response and overall survival (OS).

Materials & methods

Study design

This was a retrospective, observational study of BRAF mutant MM patients treated with 1L TT or IO therapy conducted using a chart review methodology. The preplanned study sample size was 600 patients. Providers selected a convenience sample of patients meeting the following inclusion criteria: confirmed BRAF V600 activating mutation; initiated 1L therapy after 1 January 2014 and before 30 June 2017; received 1L therapy with D+T, V+C, ipi, ipi/nivo, nivo or pembro; completed at least one cycle of 1L therapy; and followed for at least 6 months from the date of treatment initiation (or until death). Patients <18 years of age at the initiation of 1L therapy, who received 1L therapy as part of a clinical trial, or who were diagnosed with a second primary cancer following initiation of 1L therapy, were not eligible.

Data collection

Data were collected through a chart review by providers in the Cardinal Health Oncology Provider Extended Network (OPEN), an informal community of over 7000 oncologists from across the USA. Providers identified patients meeting the selection criteria and abstracted data in an anonymized electronic case report form (eCRF). For all data points providers were given the option to select 'unknown' or 'data not collected' if the data were unavailable in the patient's record. Data collection completed on 1 October 2018. The study protocol and data capture tool were reviewed by a central institutional review board who provided a waiver of obtaining informed consent from patients. Data from a random selection of 10% of cases were verified by requiring physicians to re-enter select data points at a later date.

Analyses

The primary study cohorts for analysis were patients treated in 1L with any combination TT (D+T or V+C) versus any 1L IO therapy (ipi/nivo, nivo, pembro). Additionally, subgroup comparisons were made by treatment regimen (D+T vs ipi/nivo; D+T vs PD-1 monotherapy), in an attempt to further understand comparative effectiveness between TT and IO therapies. The PD-1 monotherapy group included any patients treated with either single-agent nivo or pembro. Comparisons of the V+C arm to IO therapies were not made owing to the similarities in mechanism of action to D+T and the comparatively smaller sample size.

Treatment sequences in 1L and 2L, time on 1L (TOnT), time from discontinuing 1L to initiating 2L (time off treatment [ToffT]), disease response and OS were measured. TOnT was the interval from initiation of 1L until discontinuation of 1L due to any reason. ToffT was the interval from discontinuation of 1L treatment until initiation of 2L treatment. Patients on 1L treatment at the end of the study period were censored on the last date of known treatment. Disease response was assessed in two ways: provide reported-using the response description in the medical record; and retrospectively calculated based on RECIST v1.1 guidelines using lesion measurements provided by abstractors [15]. Provider-reported disease response was based on language used within the medical record narrative; providers were asked to indicate the patients' best response to 1L therapy as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). Retrospectively calculated response according to RECIST guidelines was performed by having providers abstract lesion measurements from CT, PET and/or other imaging at initiation of 1L treatment and at time of best response to 1L. Using these lesion measurements (to determine target lesions) as reported by the provider (and asking providers to report whether new lesions had appeared), disease response (CR, PR, SD or PD) was calculated based on RECIST v1.1 guidelines. No independent or central review of radiology images was conducted. The objective response rate (ORR) was taken as the sum of CRs and PRs. Rates of response in the retrospective calculation are based on the total patient sample, including those patients for which response could not be assessed (best response not yet occurred or unavailability of measurements of baseline lesions at best response). OS was defined as the interval from the initiation of 1L therapy until death due to any cause. Patients alive at the end of study period were censored on the last known date of follow-up.

Descriptive statistics were performed, and univariate comparisons of categorical and continuous variables were made using χ^2 tests and t-tests. Unknown or missing data are shown as occurred; for continuous measures only patients with known values were considered. TOnT, ToffT and OS were estimated using the Kaplan–Meier technique

with statistical comparison via the log-rank test, as not all patients had completed 1L treatment (right-censored). A hierarchical logistic regression model was used to examine likelihood of an objective disease response via RECIST v1.1, comparing cohorts and subgroups, including patients with unknown/not evaluable best disease response tumor measurements accounting for nesting of patients among providers [16]. Multivariate Cox-proportional hazards models were used to compare the risk of treatment discontinuation (from the TOnT estimates) between cohorts and subgroups. The risk of treatment discontinuation was the likelihood of the patient discontinuing 1L treatment for any reason (e.g., progression, death, toxicity, patient choice, etc.) over the interval. Both the logistic regression model and the Cox models were adjusted for age (<65 , ≥ 65), sex, presence of brain metastases, presence of liver metastases, total number of distant metastatic sites (1-3, ≥ 4) ECOG-PS (0/1 or ≥ 2) and lactate dehydrogenase (LDH; normal or abnormal). Actual LDH values were not collected in the eCRF; providers indicated whether the patient's LDH was normal, abnormal and $<$ two-times the upper limit of normal, or abnormal and $\geq$ two-times the upper limit of normal based upon charted lab reference range.

Results

Patients' cohorts & selection of 1L treatment

A total of 53 providers (60.3% practicing in the northeast, 15.1% midwest, 13.2% south and 11.3% west) participated in the study and contributed data on 440 patients with BRAF mutant MM who met the inclusion criteria. Recruitment was stopped at 440 out of the planned 600, as providers reported no further patients could be identified. The final analytical cohort consisted of 283 patients treated in 1L with TT (61.5%) and 157 patients treated with IO (34.1%). By individual treatment regimens received in 1L, there were: D+T = 188, V+C = 95, ipi/nivo = 81, PD-1 mono = 76.

Demographic and clinical characteristics of the TT and IO cohorts and the subgroups are summarized in Table 1. Both TT- and IO-treated patients were predominantly male (59.4% vs 58.6%) and covered by commercial/employer sponsored insurance (52.7% vs 46.5%). The median age at 1L treatment initiation was 61 years in both cohorts. Regarding disease characteristics, the TT cohort had significantly higher proportions of patients with liver metastases (46.3 vs 35.0%; $p = 0.02$) and abnormal LDH (61.1 vs 42.7%; $p < 0.01$) and significantly lower proportion of patients with any comorbidities (37.0 vs 48.0%; $p = 0.03$). Between the subgroups, patients treated with 1L D+T were significantly older (60.8 vs 56.5; $p = 0.01$) than those treated with 1L ipi/nivo, but significantly younger than those treated with PD-1 monotherapy (60.8 vs 66.3; $p < 0.01$) (Table 1). Patients treated with 1L D+T also had less favorable distributions with respect to total number of distant metastatic sites and LDH levels, relative to those treated with 1L PD-1 monotherapy. At end of follow-up, 17.3% ($n = 49$) of patients in the TT cohort and 15.9% ($n = 25$) of patients in the IO cohort were deceased, with an additional 1.8% and 5.1%, respectively, actively receiving hospice care. No statistically significant differences in number of lines of therapy, deaths or length of follow-up were noted between the main cohorts and the subgroups.

Treatment sequences are displayed in Table 2. Among the 97 patients receiving D+T in 1L and receiving a 2L treatment, 59.8% received PD-1 monotherapy as 2L. Among the 50 patients receiving ipi/nivo and 43 patients receiving PD-1 monotherapy in 1L and receiving 2L treatment, 62.0% and 44.2%, respectively, received 2L D+T.

Time on treatment, time off treatment & OS

TOnT was significantly longer for patients treated with TT in 1L compared with those treated with IO in 1L (11.4 vs 7.2 months; Figure 1A – TOnT), driven by the short duration for patients treated with ipi/nivo (4.6 months; Figure 1B – TOnT). No difference in TOnT was noted between D+T and PD-1 monotherapy ($p = 0.25$, Figure 1C – TOnT). ToffT was significantly longer for patients treated with IO (1.5 vs 0.6 months; Figure 1A – ToffT), driven by long ToffT of patients treated with ipi/nivo (4.6 months; Figure 1B – ToffT). The risk of treatment discontinuation was significantly higher among patients treated with IO therapy compared with TT (HR = 1.64; 95% CI: 1.25–2.14; $p < 0.001$) and was three times higher comparing ipi/nivo to D+T (HR = 3.24; 95% CI: 2.26–4.64; $p < 0.001$). There was no significant difference in the risk of discontinuation between D+T and PD-1 monotherapy (HR = 1.00; 95% CI: 0.68–1.49; $p = 0.99$). Median OS from 1L initiation of TT was 33.1 months (95% CI: 26.1–37.1 months) and was not reached in the IO-treated cohort. Median OS was not significantly different between the cohorts ($p = 0.664$).

Table 1. Demographics and clinical characteristics.

Demographics	TT (n = 283)	IO (n = 157)	D+T (n = 188)	ipi/nivo (n = 86)	PD-1 mono (n = 71)
Male	168 (59.4%)	92 (58.6%)	115 (61.2%)	53 (61.6%)	39 (54.9%)
Mean age at treatment initiation (median)	60.2 (61%)	60.9 (61%)	60.8 (61%)	56.5 (55.5%)	66.3 (69%)
Payer†:					
– Medicare	55 (19.4%)	39 (24.9%)	42 (22.3%)	12 (14.0%)	27 (38.0%)
– Medicare advantage/supplemental	60 (21.2%)	36 (22.9%)	38 (20.2%)	15 (17.4%)	21 (29.6%)
– Medicaid	25 (8.8%)	13 (8.3%)	17 (9.0%)	11 (12.8%)	2 (2.8%)
– Commercial/employer-sponsored	149 (52.7%)	73 (46.5%)	98 (52.1%)	49 (57.0%)	24 (33.8%)
– Other/unknown	6 (2.1%)	8 (5.1%)	3 (1.6%)	5 (5.8%)	3 (4.2%)
M-stage at diagnosis:					
– M0, M1a, M1b	114 (40.3%)	76 (48.4%)	71 (37.8%)	39 (45.3%)	37 (52.1%)
– M1c	169 (59.7%)	81 (51.6%)	117 (62.2%)	47 (54.7%)	34 (47.9%)
Site of metastases†:					
– Lung	192 (67.8%)	110 (70.1%)	131 (69.7%)	58 (67.4%)	52 (73.2%)
– Liver	131 (46.3%)	55 (35.0%)	85 (45.2%)	32 (37.2%)	23 (32.4%)
– Brain	28 (9.9%)	15 (9.6%)	16 (8.5%)	7 (8.1%)	8 (11.3%)
– Bone	47 (16.6%)	25 (15.9%)	30 (16.0%)	18 (20.9%)	7 (9.9%)
– Lymph nodes	65 (23.0%)	42 (26.8%)	43 (22.9%)	23 (26.7%)	19 (26.8%)
– Subcutaneous tissue	32 (11.3%)	14 (8.9%)	19 (10.1%)	4 (4.7%)	10 (14.1%)
– Other	15 (5.3%)	7 (4.5%)	9 (4.8%)	4 (4.7%)	3 (4.2%)
Total number of distant metastatic sites at initiation of 1L:					
– 1–3	229 (80.9%)	131 (83.4%)	148 (78.7%)	67 (77.9%)	64 (90.1%)
– ≥4	54 (19.0%)	26 (16.6%)	40 (21.3%)	19 (22.1%)	7 (9.9%)
ECOG-PS at metastatic diagnosis:					
– 0/1	245 (86.6%)	129 (82.2%)	158 (84.0%)	77 (89.5%)	52 (73.2%)
– ≥2	38 (13.4%)	28 (17.8%)	30 (16.0%)	9 (10.5%)	19 (26.8%)
LDH (n, %):					
– Normal	103 (36.4%)	81 (51.6%)	73 (38.8%)	39 (45.3%)	42 (59.2%)
– Abnormal	173 (61.1%)	67 (42.7%)	111 (59.0%)	44 (51.2%)	23 (32.4%)
– Unknown	7 (2.5%)	9 (5.7%)	4 (2.1%)	3 (3.5%)	6 (8.5%)
Any comorbidity (n, %)	133 (47.0%)	91 (58.0%)	97 (51.6%)	47 (54.7%)	44 (62.0%)
Mean months of follow-up from 1L treatment initiation (median)	14.1 (12.4%)	14.5 (13.05)	14.3 (12.4%)	14.1 (12.5%)	15.0 (13.1%)
Total lines of therapy (n, %):					
– 1	141 (49.8%)	64 (40.8%)	91 (48.4%)	36 (41.9%)	28 (39.4%)
– 2	123 (43.5%)	84 (53.5%)	85 (45.2%)	44 (51.2%)	40 (56.3%)
– ≥3	19 (6.7%)	9 (6.3%)	12 (6.3%)	6 (7.0%)	3 (4.2%)

Shaded cells indicate statistically significant difference ($p < 0.05$) compared with D+T.

† Categories are not mutually exclusive.

ECOG-PS: Eastern Cooperative Oncology Group Performance Status; IO: Immuno-oncology; ipi: Ipilimumab; LDH: Lactate dehydrogenase; nivo: Nivolumab; TT: Targeted therapy.

Table 2. Treatment patterns in first-line and second-line.

First-line treatment regimen (number receiving second-line)	Second-line treatment regimen, number receiving (row %)						
	D+T	V+C	ipi/nivo	PD-1 mono	ipi	Single-agent TT	Other
D+T (n = 97)	0 0.0%	4 4.1%	21 21.6%	58 59.8%	7 7.2%	2 2.1%	5 5.2%
ipi/nivo (n = 50)	31 62.0%	10 20.0%	0 0.0%	3 6.0%	0 0.0%	3 6.0%	2 4.0%
PD-1 mono (n = 43)	19 44.2%	10 23.3%	2 4.7%	3 7.0%	1 2.3%	8 18.6%	0 0.0%

ipi: Ipilimumab; nivo: Nivolumab; TT: Targeted therapy.

Figure 1. TOnT and ToffT for (A) TT vs IO therapy, (B) D+T vs ipi/nivo, and (C) D+T vs PD-1 monotherapy. IO: Immuno-oncology; ipi: Ipilimumab; nivo: Nivolumab; TT: Targeted therapy.

Disease response during 1L therapy

Response to 1L therapy, both provider-reported and retrospectively measured using RECIST v1.1 criteria are summarized in Table 3. The ORR, based on provider report, was 79.2% for 1L TT, compared with 71.3% for 1L IO ($p = 0.06$). Rates of CR, PR, SD, and PD were significantly different between TT and IO ($p = 0.01$).

The retrospectively calculated disease response rates using RECIST v1.1 criteria were directionally similar to the rates based on provider report, but were of a smaller absolute difference, except the 56.2% PR rate for TT-treated compared to 40.8% for IO-treated among those patients with measurable lesions (Table 3). The ORR for TT was 60.1 vs 45.9% for IO ($p < 0.01$); the ORR for D+T was 60.6%, significantly greater than the 42.3% reported for PD-1 monotherapy ($p = 0.01$). Comparing the two methods of disease response measurement, the overall concordance between provider-reported versus RECIST-calculated was 75.9% (277/365).

In the adjusted model, odds of objective response in 1L (via RECIST) were 49% lower for IO compared with TT (odds ratio = 0.51; 95% CI: 0.32–0.81; $p = 0.004$), 60% lower for those treated with PD-1 monotherapy compared with D+T (odds ratio = 0.40; 95% CI: 0.21–0.74; $p = 0.004$), and 45% lower for patients treated with ipi/nivo versus D+T (odds ratio = 0.55; 95% CI: 0.30–1.00; $p = 0.05$).

Figure 1. TOnT and ToffT for (A) TT vs IO therapy, (B) D+T vs ipi/nivo, and (C) D+T vs PD-1 monotherapy (cont.).
IO: Immuno-oncology; ipi: Ipilimumab; nivo: Nivolumab; TT: Targeted therapy.

Response	TT (n = 283)	IO (n = 157)	D+T (n = 188)	ipi/nivo (n = 86)	PD-1 mono (n = 71)
Per provider report					
CR	39 13.8%	29 18.5%	23 12.2%	22 25.6%	7 9.9%
PR	185 65.4%	83 52.9%	126 67.0%	43 50.0%	40 56.3%
SD	32 11.3%	15 9.6%	25 13.3%	3 3.5%	12 16.9%
PD	27 9.5%	30 19.1%	14 7.4%	18 20.9%	12 16.9%
p-value	–	0.01 (vs TT)	–	<0.01 (vs D+T)	0.1 (vs D+T)
ORR per provider report	224 79.2%	112 71.3%	149 79.3%	65 75.6%	47 66.2%
p-value	–	0.06 (vs TT)	–	0.49 (vs D+T)	0.03 (vs D+T)
Per RECIST v1.1^a calculation					
CR	11 3.9%	8 5.1%	5 2.7%	5 5.8%	3 4.2%
PR	159 56.2%	64 40.8%	109 58.0%	37 43.0%	27 38.0%
SD	37 13.1%	28 17.8%	28 14.9%	12 14.0%	16 22.5%
PD	34 12.0%	24 15.3%	21 11.2%	14 16.3%	10 14.1%
Not evaluable	42 14.8%	33 21.0%	25 13.3%	18 20.9%	15 21.1%
p-value	–	0.07 (vs TT)	–	0.16 (vs D+T)	0.1 (vs D+T)
ORR per RECIST v1.1 ^a	170 60.1%	72 45.9%	114 60.6%	42 48.8%	30 42.3%
p-value	–	<0.01 (vs TT)	–	0.07 (vs D+T)	0.01 (vs D+T)

CR: Complete response; IO: Immuno-oncology; ipi: Ipilimumab; nivo: Nivolumab; ORR: Objective response rate; PD: Progressive disease; PR: Partial response; SD: Stable disease; TT: Targeted therapy.

Discussion

To investigate outcomes of 1L treatment for BRAF mutant MM patients, we described and compared real-world patients receiving 1L TT or IO, their disease response, the duration of response through the surrogates of TOnT and ToffT and OS. We observed an apparent provider preference for TT as 1L treatment in real-world BRAF mutant MM patients. This appeared to be especially the case for patients with higher risk disease at diagnosis as indicated by a higher proportion of patients in the TT-cohort with liver metastases and an elevated LDH. This real-world finding may be of particular importance to the optimal application of TT surrounding optimal application of TT, given clinical trial evidence that patients with low LDH derive longer-term benefit from D+T [17].

Although overall follow-up was short, nearly half of patients ($n = 207$) received 2L therapy. We observed a longer TOnT for TT versus IO therapy; however, the median ToffT was significantly longer for IO-treated patients at 1.5 months versus 0.6 months for TT-treated. This was driven by the 4.6-month average ToffT for ipi/nivo-treated patients prior to initiating 2L [18]. Given the short ToffT for TT-treated patients, TOnT may be a close approximation to progression free survival (PFS) in the TT-treated cohort. TOnT among TT-treated patients was 11.4 months which is consistent, if slightly shorter, than the median PFS observed in the D+T trials (12.6 months), and equivalent to that of the V+C trials (11.4 months) [19]. For the IO-treated patients, the observed median PFS in CheckMate 067 was 11.5 months in the ipi/nivo arm. Our results, considering both the TOnT (at 4.6 months) and the ToffT (4.6 months), show a slightly shorter PFS interval for ipi/nivo-treated patients. For patients treated with PD-1 monotherapies, we observed a TOnT nearly double (12.0 months) the median PFS estimates observed in both CheckMate 067 (6.9 months) [5] and *post hoc* analyses of treatment-naïve pembro-treated patients in KEYNOTE-006 (6.2 months with only 26.6% of patients BRAF-mutated) [20].

Regarding long-term outcomes, the median OS of all patients was 37.1 months (74 death events); however, we were unable to assess OS by therapeutic sequencing given the relatively short median duration of follow-up in the cohort (TT = 14.5 months, IO = 14.1 months from initiation of 1L). The OS observed in our study was within the range of estimates from respective RCTs, but further follow-up on par with those trials is needed and may lead to different conclusions [17–19,21]. A recent study of patients who received sequential BRAF inhibitor followed by ipi demonstrated a median OS of 28 months [14]. Comparisons of IO trial results to our study are difficult given a lack of any *post hoc* published estimates of BRAF-mutated subgroup outcomes analyses. Further research, such as the ECOG-ACRIN trial (NCT02224781), will hopefully answer many of these outstanding questions regarding how treatment sequence impacts OS.

Finally, we found both provider-reported and retrospectively measured disease response rates higher among patients treated with TT than IO in 1L. The ORR for TT was significantly higher by retrospective classification according to the RECIST criteria ($p < 0.01$) but not provider-reported ($p = 0.06$). Of note, the RECIST calculated rates were approximately 20% lower than those in the medical record as reported by providers. The response benefit persisted after adjusting for baseline clinical differences (odds of response for IO- versus TT-treated = 0.52; 95% CI: 0.34–0.80; $p < 0.01$). In comparison, a retrospective analysis of 114 patients with MM who had received PD-1 treatments either before or after a BRAF inhibitor alone, or with a MEK inhibition, found RECIST-based response rates to 1L PD-1 therapy of 41%, compared with 46% observed in our population (the corresponding ORR to 1L BRAF-mutated TT was not reported) [11]. A recent analysis exploring differences in response between BRAFv600K and v600E found patients with v600K mutations had greater mutational burden and derived greater benefit from IO compared with TT which may explain differences should our population of patients had higher proportion of v600E mutations [22]. In CheckMate 067 the ORR for ipi/nivo-treated patients was 58 and 44% in the nivo-treated arm, which is approximately 10% higher compared with our study [5]. We note that a major difference is that CheckMate 067 includes a significant proportion of BRAF wild-type patients (68%) for which response to IO therapy may be higher. Comparing ORRs for D+T-treated patients to RCTs, we found greater consistency. The ORR in our study for D+T-treated patients was also lower at 61% compared with 69 and 64% in the COMBI-d and COMBI-v trials, respectively [2,23]. Altogether these findings reinforce the idea that the diversity of patients treated in the real-world requires a treatment decision based on a comprehensive evaluation of the goals of treatment, the clinical characteristics of the patients and likelihood of toxicity.

There are several important limitations that the authors acknowledge: first, providers were not randomly selected and cases were identified by providers and not all eligible patients treated by the providers may have been included (convenience sample), resulting in a possible selection bias. Second, providers entered data manually into the eCRF which may result in transcription errors (e.g., incorrect dates). We attempted to minimize these errors through

eCRF validation; however, only 10% (randomly selected) of charts were validated. Next, date of death was per provider record in the patient's chart and not based on mapping of patients to external databases such as the social security death index master file. Fourth, LDH levels were not collected. It was assumed that providers classified the patient's LDH value based on the upper limits provided by the laboratory at the time of reporting; however, this could not be verified as source laboratory reports were not evaluated. Finally, the rationale for the selection of TT versus IO therapy for each individual patient was not ascertained. Unmeasured confounding due to insurance coverage, patient choice or other undocumented clinical factors may have existed. However in adjusted analyses, we attempted to control for these factors by using a hierarchical model which simultaneously controls for provider factors, patient demographics, and clinical characteristics..

The major strengths of this research were the size of the study population (which to our knowledge is the largest real-world, US-based cohort study of BRAF mutant MM), its contemporaneity (last follow-up January 2018), and the evaluation of both provider-reported and objective (albeit retrospective) assessment of disease response per RECIST v1.1. Overall, our findings emphasize a comfort level for providers to treat BRAF mutant MM patients consistent with guidelines recommending TT for patients needing rapid disease response. Approaches utilizing IO appeared to be more likely chosen in patients with a more favorable clinical profile, potentially indicating a greater ability to tolerate those therapies. With no observed difference in OS, the selection of a 1L treatment for BRAF mutant MM patients requires a critical evaluation of the disease burden and likelihood of toxicity.

Conclusion

Community oncologists in the US may prefer 1L TT for BRAF mutant MM, especially in higher-risk patients with liver metastases and elevated LDH. Combination TT was associated with a significantly higher ORR and significantly longer TOnT than 1L IO therapy and may be explained by differences in the mutational burden of patients. Our OS estimates were longer than those previously reported for D+T in clinical trials, and median OS was not reached among patients treated with IO therapy. However, no significant differences in OS were observed.

Financial & competing interests disclosure

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Ethical conduct

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Summary points

- Seven drugs, including targeted therapy (TT) and immunotherapy agents, were approved by the US FDA for treating metastatic BRAF mutant metastatic melanoma (MM) over a 4-year period.
- Clinical decision-making for these patients is hampered by a lack of head-to-head randomized controlled trials comparing TT and IO for BRAF mutant MM and a paucity of real-world observational research.
- This retrospective, observational study of BRAF mutant MM patients, conducted using a chart review methodology, evaluated characteristics of BRAF mutant MM patients prescribed 1L TT or IO, the duration of first-line therapy (1L), time to second-line therapy (2L), the extent and duration of treatment response and overall survival (OS).
- A total of 440 patients were analyzed. The TT cohort had significantly higher proportions of patients with liver metastases (46.3 vs 35.0%) and abnormal lactate dehydrogenase (61.1 vs 42.7%).
- Provider-reported objective response rates were 79.2% for 1L TT versus 71.3% for 1L IO ($p = 0.06$); per RECIST v1.1 criteria, corresponding rates were 60.1 versus 45.9%, respectively ($p < 0.01$). Per an adjusted model, odds of objective response in 1L (via RECIST) were 49% lower for IO versus TT ($p = 0.004$).
- For 1L, time on treatment was significantly longer for patients treated with TT versus IO (11.4 vs 7.2 months) whereas time off treatment (calculated from discontinuation of 1L to the initiation of 2L) was significantly longer for patients treated with IO versus TT (1.5 vs 0.6 months).
- Median OS from 1L initiation of TT was 33.1 months (95% CI: 26.1–37.1 months) and was not reached with IO, with no statistical significance between the cohorts.
- Overall, these results suggest that providers may have prioritized treatment of patients with BRAF mutant MM-consistent with guidelines recommending TT for patients needing rapid disease response.
- With no observed difference in OS, the selection of a 1L treatment for a BRAF mutant MM patient requires a critical evaluation of the disease burden and likelihood of toxicity.

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