Treatment Patterns and Overall Survival (OS) in Patients With Advanced BRAF-Mutant (mt) Melanoma Treated With Immunotherapy and Targeted Therapy (TT) in a Real-World Setting

BACKGROUND

- Approximately half of advanced (unresectable or metastatic) melanomas harbor a mutation in the BRAF gene, with V600E being the most common mutation^{1,2}
- Recommended first-line (1L) treatments include immunotherapy with checkpoint inhibitors (CPI) and targeted therapy (TT) with BRAF and MEK inhibitors, both of which are associated with significant long-term treatment benefits^{2,3}
- However, studies are currently underway to evaluate and determine the optimal treatment sequence of TT and immunotherapy with regard to extending OS in patients with *BRAF*-mutated melanoma³

OBJECTIVE

• This observational, noninterventional cohort study aimed to assess OS in patients with advanced BRAFmt melanoma who received CPI and/or BRAF-MEK TT as 1L and second-line (2L) treatment and the impact of treatment sequence

METHODS

Data Source

- A retrospective analysis was conducted using the nationwide Flatiron Health electronic health record (EHR)-derived de-identified advanced melanoma enhanced data mart (EDM), which contains structured and unstructured data curated via technology-enabled abstraction from January 1, 2011, to June 30, 2020^{4,5}
- This longitudinal database is based on EHRs from approximately 280 cancer clinics (≈800 sites of care, primarily community-based cancer centers)

Patient Population

- This analysis included adults \geq 18 years old diagnosed with advanced BRAFmt melanoma treated after January 1, 2015, with 1L CPI (ipilimumab, nivolumab, ipilimumab/nivolumab or pembrolizumab) or 1L TT (dabrafenib/trametinib, binimetinib/encorafenib or cobimetinib/vemurafenib)
- Patients were required to have 2 visits before starting 1L therapy as well as 6 months of potential follow-up

Statistical Analysis

- Cox proportional hazards models were used to investigate the association between OS and treatment type
- Data were adjusted for baseline confounders, including age, region, practice type, year of initial diagnosis, lactate dehydrogenase (LDH) level, albumin level, Eastern Cooperative Oncology Group (ECOG) performance status, number of metastases, and the presence of brain and/or liver metastases
- Practices that preferentially prescribed treatments of interest were identified in order to characterize patients who likely received the treatment sequence
- Practices were eligible for sequencing sub-analysis if they treated >8 patients in 2L given 1L and exceeded 75% on-sequence 2L

RESULTS

- A total of 853 patients were included in the analysis; 553 (64.8%) and 300 (35.2%) patients received CPI and TT in 1L, respectively (Figure 1) - 199 patients (23.3%) died during 1L treatment; of the survivors, 155 patients (23.7%) and 132 patients (20.2%) received 2L treatment with CPI and TT, respectively

- Of the 553 patients who received CPI in 1L, 123 (22.2%) received TT in 2L - Of the 300 patients who received TT in 1L, 115 (38.3%) received CPI in 2L

Total Patients (N = 853)

[‡]87 patients died following 1L TT.

Table 1. Patient Characteristics by 11 Treatment Sequence

Age at diagnosis, <65 years Sex, n (%) Female Region, n (%) Midwest Northeast South West Unknown Practice type, n (% Academic Community Year of initial diagn <2010 2010-2014 2015-2019 PD-L1, n (%) Positive Negative Unknown LDH, n (%) Normal Above normal Missing ECOG performance 0-1 ≥2 Unknown Albumin, mean (SD Metastases, n (%) <3 metastases With liver metasta With brain/CNS m

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Figure 1. Treatment Patterns in Patients With Advanced BRAFmt Melanoma



Other includes chemotherapy, censored/died and "other" categories. ⁺112 patients died following 1L CPI.

• A higher proportion of patients who received CPIs in 1L had normal LDH levels, <3 sites of metastases and no liver metastases compared with patients receiving TT in the 1L setting (Table 1)

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	CPI (n = 553)	TT (n = 300)	P value
n (%)			
	289 (52.3)	175 (58.3)	0.103
	184 (33.3)	103 (34.3)	0.762
	72 (13.0)	57 (19.0)	<0.001
	71 (12.8)	15 (5.0)	
	222 (40.1)	128 (42.7)	
	86 (15.6)	67 (22.3)	
	102 (18.4)	22 (11.0)	
)			
	97 (17.5)	27 (9.0)	0.001
	456 (82.5)	273 (91.0)	
nosis, n (%)			
	66 (11.9)	36 (12.0)	0.328
	137 (24.8)	61 (20.3)	
	350 (63.3)	203 (67.7)	
	27 (4.9)	9 (3.0)	0.379
	47 (8.5)	29 (9.7)	
	479 (86.6)	262 (87.3)	
	225 (40.7)	58 (19.3)	<0.001
	94 (17.0)	75 (25.0)	
	234 (42.3)	167 (55.7)	
e status, n (%)			
	297 (53.7)	160 (53.3)	0.101
	46 (8.3)	38 (12.7)	
	210 (38.0)	102 (34.0)	
))	39.8 (5.5)	37.4 (5.7)	<0.001
	382 (69.1)	174 (58.0)	0.002
Ses	116 (21.0)	95 (31.7)	0.001
netastases	160 (28.9)	92 (30.7)	0.652
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CNS, central nervous system; PD-L1, programmed cell death 1 ligand.



*HR (95% CI) adjusted for age, region, practice type, year of initial diagnosis, LDH level, albumin level, ECOG performance status, number of metastases and presence of brain and/or liver metastases.

- prescribing patterns
- CPI-TT cohort (n=118) (**Figure 3**)

*Estimated HR (95% CI) adjusted for stage at initial diagnosis, LDH level, albumin level, ECOG performance status, age at advanced diagnosis, number of metastases and presence of brain and/or liver metastases. NR, not reached.

• Our study was unable to detect or rule out clinically relevant differences in OS between TT and CPIs in 1L (HR, 1.17; 95% CI, 0.90 to 1.56) or 2L (HR, 1.00;

• Of the 300 TT and 553 CPI initiators in 1L, 100 and 118, respectively, were determined likely to receive the sequence of interest based on practice

• For patients receiving CPI and TT sequentially, median (95% CI) OS was 13.7 (9.5 to 24.7) months in the TT-CPI cohort (n=100) and not reached in the

Figure 3. Overall Survival in Patients With Advanced BRAFmt Melanoma by Likely Treatment Sequence

LIMITATIONS

- Data on PD-L1 and LDH levels was missing for a high percentage of patients
- Time-varying confounders may not be adequately controlled (eg, the physicians in a practice may not have a 2L preference)
- Practices may differ in ways that impact survival and treatment sequence

CONCLUSIONS

- In the absence of standardized treatment for patients with advanced *BRAF*mt melanoma, CPI and TT are the preferred options, and more patients are initiating treatment with CPI in the real-world setting
- A higher proportion of patients who received CPI in 1L had normal LDH levels, no liver metastases and less than 3 metastases sites compared with patients receiving TT
- Median OS was shorter in patients with BRAFmt melanoma receiving TT than in those receiving CPI at 36 months in both 1L and 2L
- Subanalysis limited to practices who likely prescribed the sequence of interest resolved most imbalances observed in the overall population but was underpowered to detect a clinically relevant benefit of one treatment sequence over another
- Randomized, prospective evaluation is required to evaluate whether TT or CPI should be administered first in patients with advanced BRAFmt melanoma

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AUTHOR DISCLOSURES

Michael B. Atkins has participated in advisory boards with BMS, Merck, Novartis, Arrowhead, Pfizer, Werewolf, Fathom, Pneuma, Leads, Pyxis Oncology, PACT, Elpis, X4Pharma; been a consultant for BMS, Merck, Novartis, Pfizer, Genentech-Roche, Exelixis, Eisai, Aveo, ImmunoCore, Iovance, Surface, COTA, Idera, Agenus, Apexigen, TRV, Neoleuken, Adagene; been involved in clinical trials with Merck, Pfizer, BMS, X4Pharma, Genentech, Aveo; and has stock options from Werewolf, Pyxis Oncology, Elpis. Cristina Julian, Matthew Secrest, Janet Lee and Edward McKenna are employed by Genentech, Inc and own stock in Roche. Ana Abajo is employed by and owns stock in Roche

