Stage IV Melanoma Comparison of Drug Regimens Persistence within 17 Million Commercially Insured Lives

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BACKGROUND

- There will be an estimated 100,350 new melanoma cases (5.6% of all cancer cases) and 6,850 deaths in the United States in 2020.[1]
- Until 2011, therapy for malignant melanoma included cytotoxic chemotherapy with poor response rates (5–15%). With the approval of a CTA-4 inhibitor, PD-1 inhibitors and BRAF/MEK inhibitors, there has been an increase in response rates, progression free survival, and overall survival in this disease setting.[1,2]
- The National Comprehensive Cancer Network (NCCN) Guidelines now recommend that immuno-oncology agents or BRAF/MEK inhibitors be used for first-line treatment of stage IV melanoma.[3] Considerations in choice of treatment depend on the staging, location of metastases, BRAF mutational status and toxicity profiles.
- 50% of stage IV melanoma cases have a BRAF mutation.[4]
- First-line treatments include:
  - Immuno-oncology (IO) agents
    - Nivolumab (Opdivo®)
    - Nivolumab (Opdivo) with Ipilimumab (Yervoy®)
    - Pembrolizumab (Keytruda®)
  - BRAF/MEK Inhibitors (if BRAF-mutation positive)
    - Dabrafenib/Trametinib (Tafinlar®/Mekinist®)
    - Encorafenib/Binimetinib (Braftovi®/Mektovi®)
    - Vemurafenib/Cobimetinib (Zelboraf®/Cotellic®)
- While BRAF/MEK inhibitors have high overall response rates, the potential for a long survival tail in IO therapies makes them a preferred choice among some providers, even in BRAF-mutation positive patients.[5]
- IO and BRAF/MEK therapy for stage IV melanoma real-world utilization patterns and persistence can help inform managed care pharmacy program development.

OBJECTIVE

- To characterize the persistence of first-line IO and BRAF/MEK therapy and compare utilization patterns across lines of therapy for stage IV melanoma treatment regimens in a commercially insured population.

METHODS

- Commercially insured members with available pharmacy and medical claims between January 2016 and December 2019 (average of 17 million members per month) were analyzed.
- Members must have had ≥ 3 medical claims with melanoma diagnosis codes not including melanoma *in situ* or personal history of melanoma.
- Members must have had ≥ 180 days continuous eligibility before and after their earliest claim incurred date for any NCCN-listed melanoma drug (Index Day 0).
- Members who received one of the IO or BRAF/MEK therapies of interest on Index Day 0 and were categorized as stage IV melanoma, based on metastases claims, were included in the Kaplan-Meier analysis. (See Figure 1 for full population selection details.)
- Members in the study population had an additional six months (January–June 2020) of pharmacy claims data included for BRAF/MEK inhibitor therapy assessment only.
- Persistency analysis
  - Persistence of first-line therapy was assessed via Kaplan-Meier analysis. Members were censored if they did not meet discontinuation criteria by the end of the analysis period.
  - Discontinuation was defined as >45-day gap in days of therapy or a switch in therapy.
  - Persistence of first-line therapy was calculated as the time from the index melanoma IO agent or BRAF/MEK inhibitor claim to discontinuation plus the days' supply or the infusion schedule.
- Utilization of medications through lines of therapy
  - For members included in the persistency analysis, manual review was performed to assess discrete lines of therapy used during the analysis period.
  - The first four lines of therapy were characterized. In lines 3 and 4, BRAF/MEK retrial was seen.

FIGURE 1

Stage IV Melanoma Analytic Population Identification

~17 million (monthly average) commercially insured members between Jan 2016 and Dec 2019 with pharmacy and medical claims data.

↓

19,719 had ≥ 3 medical claims with a melanoma diagnosis code, excluding codes for *in situ* or "personal history" of melanoma.

↓

2,943 had a pharmacy or medical benefit drug claim for one of the antineoplastic agents listed by NCCN for melanoma.*

↓

1,060 had ≥ 180 days continuous eligibility before and after their earliest claim date (Index Day 0), and the index claim was for binimetinib, cobimetinib, dabrafenib, encorafenib, ipilimumab, nivolumab, pembrolizumab, trametinib or vemurafenib.

↓

991 had <3 medical claims for anything with a diagnosis code for another malignant neoplasm or, if an immuno-oncology (IO) therapy (defined as ipilimumab, nivolumab, or pembrolizumab), then the member had at ≥ 1 melanoma diagnosis code on an IO medical claim.

↓

The **991** members were subcategorized based on diagnosis codes for metastases on any medical claims incurred within 180 days before or after Index Day 0.

498 comprising analytic population† subcategorized as stage IV melanoma
→ 437 with metastases to non-skin or lymph node sites (e.g., lung, brain, bone, liver)
→ 61 additional with intrathoracic, intra-abdominal, intrapelvic lymph node or multiple regional lymph node metastases‡

493 excluded from subcategorization as stage IV melanoma
→ 435 with lymph node, skin, or unspecified metastasis
→ 58 without evidence of metastasis

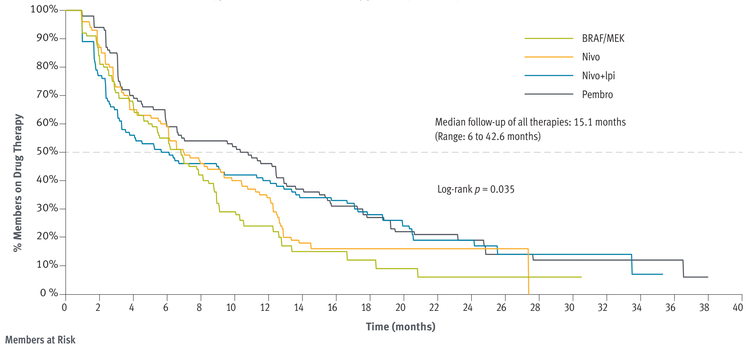
*Adesleukin, binimetinib, carboplatin, cisplatin, cobimetinib, dabrafenib, dacarbazine, encorafenib, entrectinib, imatinib mesylate, interferon alfa-2b, ipilimumab, larotrectinib, nivolumab, paclitaxel protein-bound, paclitaxel, peginterferon alfa-2b, pembrolizumab, talimogene laherparepvec, temozolomide, trametinib, vemurafenib, or vinblastine

†Three members were excluded from the persistency analysis based on manual review: two for investigational regimen use and one for treatment associated with primary esophageal cancer, and 21 members were excluded for receiving ipilimumab monotherapy in the first-line resulting 474 members in the persistency analyses.

‡Melanoma is categorized as stage III if metastases are limited to nearby skin or regional lymph nodes. Researchers assumed these metastases were inconsistent with stage III.

FIGURE 2

Persistence of First-line Immuno-oncology (IO) and BRAF/MEK Therapy Among 474 Stage IV Melanoma Members



Members at Risk

BRAF/MEK	75	63	51	41	28	18	11	6	5	4	3	2	2	1	1	1	0				
Nivo	136	119	89	81	59	47	32	11	6	3	3	3	2	1	0						
Nivo+Ipi	140	108	79	70	60	51	43	33	28	19	14	8	8	5	4	4	3	1	0		
Pembro	123	115	86	73	65	56	48	35	26	22	17	16	10	6	3	3	3	2	2	0	

BRAF/MEK (BRAF/MEK inhibitors, all regimens combined for reporting purposes), Immuno-oncology therapies: Nivo (nivolumab), Nivo+Ipi (nivolumab with ipilimumab), Pembro (pembrolizumab)

Eligibility: 474 members who met the population identification criteria (Figure 1) were included. All members were required to have 180 days continuous eligibility from their Index date. See Methods for analytic population identification.

Discontinuation was defined as a >45-day gap in days of therapy or a switch in therapy.

Censoring occurred if a member had not met discontinuation criteria at the end of follow-up.

TABLE 1

First-line Immuno-oncology and BRAF/MEK Regimen Use Among 474 Stage IV Melanoma Members

Regimen	Members (N=474) (%)	Median Time to Discontinuation, Months (95% CI)
BRAF/MEK Inhibitors	**75 (15.8)**	**6.8 (4.6-8.5)**
Dabrafenib/Trametinib	52 (11.0)	Not reported*
Encorafenib/Binimetinib	12 (2.5)	
Vemurafenib/Cobimetinib	11 (2.3)	
Immuno-oncology Therapy	**399 (84.2)**	
Nivolumab	136 (28.7)	7.0 (6.1-9.4)
Nivolumab + Ipilimumab	140 (29.5)	5.9 (3.3-10.1)
Pembrolizumab	123 (25.9)	10.3 (6.6-12.9)

*Individual BRAF/MEK member counts precluded reporting at the specific combination level.
Discontinuation was defined as a >45-day gap in days of therapy or a switch in therapy.
For the 474 members analyzed, follow-up was 17.5 months (524 days) mean and 15.1 months (453 days) median from index drug claim to the end of eligibility or the end of the analysis period.

TABLE 2

Stage IV Melanoma Medication Use Through Lines of Therapy

	BRAF/MEK	Nivo	Nivo + Ipi	Pembro	Other
Line of Therapy	**Number of Members (% Total Line of Therapy)**				
First-Line (N=474)	75 (15.8)	136 (28.7)	140 (29.5)	123 (25.9)	-
Second-Line (N=169)	57 (33.7)	11 (6.5)	49 (29.0)	13 (7.7)	39 (23.1)
Third-Line (N=59)	14 (23.7)	8 (13.6)	10 (16.9)	6 (10.2)	21 (35.6)
Fourth-Line (N=23)	7 (30.4)	1 (4.3)	4 (17.4)	3 (13.0)	8 (34.8)

BRAF/MEK (BRAF/MEK inhibitors, all regimens combined for reporting purposes), Immuno-oncology therapies: Nivo (nivolumab), Nivo+Ipi (nivolumab with ipilimumab), Pembro (pembrolizumab).
Lines of therapy were determined through a manual review of individual members' medical and pharmacy benefit claims.
Other therapies were agents used in the treatment of melanoma but not recommended first-line in stage IV by the NCCN including: cytotoxic chemotherapies, ipilimumab monotherapy and investigational combinations of BRAF/MEK inhibitors with IO therapies.

RESULTS

Stage IV melanoma population identification (Figure 1)

- 498 members met the analytic criteria for the study and are reasonably considered to have had stage IV melanoma with their initial first-line IO or BRAF/MEK therapy initiated between July 1, 2016 through June 30, 2019.
- Of note, three members were excluded from the persistency analysis based on manual review: two for investigational regimen use and one for treatment associated with primary esophageal cancer and 21 members were excluded for receiving ipilimumab monotherapy in the first-line. This treatment was excluded from analysis because it is only indicated for 12 weeks (four doses). It is also no longer recommended by the NCCN as a first-line therapy in this population.[3]

Persistence of first-line therapy among 474 stage IV melanoma members (Figure 2)

- Follow-up was 17.5 months (524 days) mean and 15.1 months (453 days) median from index drug claim to the end of eligibility or the end of the analysis period.
- Median time to discontinuation for the different regimens was:
  - 6.8 months (95% CI, 4.6-8.5) for BRAF/MEK inhibitors
  - 7 months (95% CI, 6.1-9.4) for nivolumab
  - 5.9 months (95% CI, 3.3-10.1) for nivolumab with ipilimumab
  - 10.3 months (95% CI, 6.6-12.9) for pembrolizumab
- The persistency curves were significantly different from each other (log-rank P-value: 0.035), likely due to differences in persistence after six months.

First-line regimen use among 474 stage IV melanoma members (Table 1)

- IO therapy use in the first-line (84.2%) was divided between nivolumab (28.7%), nivolumab with ipilimumab (29.5%) and pembrolizumab (25.9%).
- BRAF/MEK inhibitor use in the first-line (15.8%) was divided between dabrafenib/trametinib (11.0%), encorafenib/binimetinib (2.5%) and vemurafenib/cobimetinib (2.3%).
- The combinations of dabrafenib/trametinib and vemurafenib/cobimetinib were first FDA approved in January 2014 and November 2015, respectively. Encorafenib/binimetinib was first approved in June 2018, halfway into the data collection period.
- 24.5% of members were censored (Range: 18.7% of BRAF/MEK members to 27.1% of nivolumab with ipilimumab members).

Utilization of medications through lines of therapy (Table 2)

- 79.2% of all IO therapy use was in the first-line compared to only 49.0% of all BRAF/MEK inhibitor use.
- 50.7% of members who received first-line BRAF/MEK inhibitors went on to receive a second-line therapy while only 32.8% of members with first-line IO therapy received second-line therapy.

LIMITATIONS

- The data used in this study is limited to a continuously enrolled commercial population in the United States. The findings of this study may not be generalizable to Medicare or Medicaid populations.
- Administrative pharmacy and medical claims have the potential to be miscoded and may reflect assumed diagnoses. Reasonable care was taken to find a population of members with stage IV melanoma; however, given the uncertainties of claims data and without access to data contained within an electronic health record, definitive diagnoses are not known.
- BRAF/MEK inhibitors are only indicated for V600E or V600K BRAF-mutation positive members. However, the BRAF mutation status of this study's population was unknown.
- Encorafenib/binimetinib was FDA approved during the later portion of the data collection period of the study. Therefore, less data was gathered for this regimen compared to the others.
- Limited number of members precluded evaluation of differences among the BRAF/MEK inhibitors.
- 24% of members in the Kaplan-Meier persistency analysis remained on therapy and were censored at the end of their available follow-up. The actual duration of first-line therapy in these members is unknown. The analysis requires the assumption that these members have the same probability of discontinuation as those remaining under observation.
- Member selection criteria was designed for analysis of first-line therapy only; differences in follow-up time may impact the findings for subsequent lines of therapy.
- Antineoplastic agents that members received more than 180 days prior to their index date may not be captured in the analysis if they received them prior to the start of the 2016 data collection period.

CONCLUSIONS

- In this real-world study of a large commercially insured population, among members newly initiating therapy for stage IV melanoma, the median discontinuation of first-line treatment was similar for the BRAF/MEK inhibitors category and the immuno-oncology drugs.
- Overall persistence differed significantly among these therapies. Further evaluation of the persistence difference is warranted, though it is likely due to the prolonged persistence past six months of treatment with some of the IO therapies: pembrolizumab and nivolumab with ipilimumab.
- Although it was expected that members were more likely to receive first-line IO therapy, it was surprising to observe a 6 to 1 ratio of IO therapy compared to BRAF/MEK therapy.
- One in four members received BRAF/MEK across the first two lines of treatment, which is lower than the 50% of members expected to have a BRAF mutation.
- Total cost of care evaluations will be important in understanding treatment selection financial implications for first-line treatment of stage IV melanoma.
- These findings can help inform commercial insurance formulary and/or pathway development, managed care pharmacy care management program development and pharmaceutical manufacturer value-based contracting.

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