Encorafenib (BRAFTOVI)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Encorafenib is a kinase inhibitor that targets BRAF V600E as well as wild-type BRAF and CRAF, part of the RAS/RAF/MEK/ERK pathway. It also inhibited in vitro tumor growth of cell lines expressing BRAF V600 E, D, and K. Mutations in the BRAF gene result in constitutively activated BRAF kinase that can stimulate tumor growth. Encorafenib also binds to other kinases such as JNK 1-3, LIMK 1-2, MEK4, and STK36.

Indication(s) Under Review in This Document

- In combination with Binimetinib, for the treatment of unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. It is not indicated for the treatment of wild-type BRAF melanoma.

Dosage Form(s) Under Review

- 75 mg capsule

Clinical Evidence Summary

Efficacy Considerations

- None of the approved BRAF and MEK inhibitor combination therapies are curative. They are associated with serious toxicities including secondary skin malignancies, ocular toxicity, and cardiac failure. There is still an unmet need for the 40-60% of metastatic melanoma patients whose tumor contains a BRAF V600 gene mutation.
- Efficacy data from part 1 are summarized in Table 1

Table 1: Efficacy results from clinical trials

Study	Study Design	ECOG PS	Treatment	Results (n=577; part 1)
Drummer, et al. COLUMBUS[1]	• MC, OL, R, international, Phase 3 **Inclusion** • Locally advanced (Stage IIIB, IIIC, or	0-1	**Part 1** Encorafenib 450mg QD plus binimetinib 45 mg BID versus	**Primary: PFS by BIRC encorafenib combination versus vemurafenib** **Secondary:** PFS encorafenib combination versus encorafenib; PFS encorafenib vs vemurafenib; best ORR; disease control

	IV)unresectable or metastatic BRAF V600-mutantmelanoma • BRAF V600E or V600K mutation or both • Adequate organ function and baseline labs • At least 1 measurable lesion • Treatment naïve or 1 previous immunotherapy **Exclusion** • Untreated CNS lesions • Uveal or mucosal melanoma • Positive serology for HIV • Active HepB or C or both • Leptomeningeal mets • Risk for retinal vein occlusion • History of BMT or solid organ transplant • Prior BRAF or MEK inhibitor therapy • Previous systemic chemo other than immunotherapy • Clinically significant CV disease • Uncontrolled arterial hypertension • Pregnancy		encorafenib 300mg QD or vemurafenib 960 mg BID **Part 2** Encorafenib 300 mg QD plus binimetinib 45 mg BID versus encorafenib 300mg QD	rate; duration of response; time to response Combo/E/V Male: 60-56-58% ECOG 0: 71-72-73% LDH ≥ULN: 29-24-27% BRAF V600E: 89-89-88% Previous immunotherapy: 30-30-30% Median follow-up: 16.7 months Median PFS: 14.9/9.6/7.3 mos per arm **PFS Combo vs V: HR 0.54 (95%CI 0.41-0.71)** **Updated PFS Combo vs V:**[2] **HR 0.61 (95%CI 0.39-0.67)** **1 yr PFS: 56% vs 32%** **2 yr PFS: 37% vs 20%** **3 yr PFS: 29% vs 14%** Median PFS Combo/E: 14.9 vs 9.6 mos HR (95%CI 0.75-1.00) Median PFS E/V: HR 0.68 (95%CI 0.52-0.90)

MC=multicenter; OL=open-label; R=randomized; BMT=bone marrow transplant; CV=cardiovascular; QD=daily; BID =twice a day; PFS=progression-free survival; BIRC=blinded independent review committee; ORR=objective response rate; Combo/E/V=combination encorafenib + binimetinib/encorafenib/vemurafenib; LDH=lactic dehydrogenase; ULN=upper limits of normal

- Purpose: To describe part 1 of the COLUMBUS trial comparing encorafenib plus binimetinib with encorafenib or vemurafenib monotherapy in patients with BRAF mutant unresectable melanoma
- Part 2: Encorafenib 300mg + Binimetinib 45mg versus Encorafenib 300mg (parts 1 and 2)[3]
  - PFS 12.9 vs 9.2 mos (parts 1+2) HR 0.77 (95%CI 0.61-0.97)
  - PFS 12.0 vs 7.4 mos (part 2 only) HR 0.57 (95%CI 0.41-0.78)
- Most patients had Stage IVM1c which is melanoma that has spread to any other internal organ (with or without spread to skin/soft tissue or lungs) that does not include the central nervous system
- Most patients had LDH under the upper limit of normal

- At the time of publication there was no Overall Survival (OS) data for part 1. **OS and updated efficacy at 18 months for part 1**: median follow-up 32.1 months[4]
  - Median OS 33.6/23.5/16.9 months per arm
  - OS combo vs vemurafenib: HR 0.61 (95%CI 0.47-0.79)
  - OS combo vs encorafenib: HR 0.81 (95%CI 0.61-1.06)
  - OS encorafenib vs vemurafenib: HR 0.76 (95%CI 0.58-0.98)
  - 1 year OS: 75.5%/74.6%/63.1%
  - 2 year OS: 57.6%/ 49.1%/43.2%
  - 3 year OS: 47%/NA/31%
  - Median PFS Combo vs V: HR 0.51 (95%CI 0.39-0.67)
- Objective Response Rate
  - Combination: 63% (CR 11%)
  - Encorafenib 51% (CR 7%)
  - Vemurafenib 40% (8%)
- Time to response (median): 1.8/1.9/1.9 months
- Duration of response (median): 16.1/14.9/12.3 months
- Quality of Life-combination versus vemurafenib[5]
  - Median time to 10% decrease in global QoL scores: 46.9 vs 17.5 months; HR 0.48 (95%%CI 0.33-0.68)
  - Median time to 10% decrease in FACT-M scores: not reached for combination; HR 0.40 (95%CI 0.26-0.63)
  - Mean change in baseline scores for FACT-M and QLQ-C30 improved in combination arm compared to vemurafenib arm
- Systemic treatment after discontinuation-primarily and anti-PD-1 or anti-PF-L1 containing therapy
  - Combination: 42%
  - Encorafenib: 56%
  - Vemurafenib: 62%

Safety Considerations

Safety Results from Clinical Trials:

- Results from part 1 of COLUMBUS trial

Table 2: Safety results from clinical trials

Study	Results
COLIMBUS	**Grade 3-4:** 58% (C) vs 63% (V) **Serious adverse events:** 34% (C) vs 37% (V) **AEs leading to discontinuation:** 13% (C) vs 17% **AEs leading to dose interruption/modification:** 48% (C) vs 61% (V) **Deaths due to AE:** 5 vs 2 (not related to study drugs)

- **Boxed warnings: None**
- **Contraindications: None**
- **Other warnings / precautions**:(in combination with binimetinib)
  - **New primary malignancies, cutaneous and non-cutaneous** cutaneous squamous cell carcinoma (cuSCC), including keratoacanthoma (KA) in 2.6% and basal cell carcinoma (BCC) in 1.6% in combination with binimetinib. When used alone, cuSCC in 8%, BCC in 1% and new primary melanoma in 5%. May promote malignancies associated with activation of RAS.
  - **Tumor promotion in BRAF Wild-Type tumors** via paradoxical activation of MAP-kinase signaling.
  - **Hemorrhage** in 19% (most frequently gastrointestinal); ≥grade 3 in 3.2%. Fatal intracranial hemorrhage in new or progressive brain metastases in 1.6%.
  - **Uveitis** in 4%; assess for visual symptoms at each visit.
  - **QT prolongation** increased QTc to >500 msec in 0.5%. Correct hypokalemia and hypomagnesemia prior to initiation of therapy.
  - **Embryo-fetal toxicity**
- **Adverse reactions** (in combination with binimetinib)
  - **Common** fatigue, nausea, vomiting, abdominal pain, arthralgia
  - **Serious Adverse events / Deaths / Discontinuation:**
    - **Discontinuation** 5% (most common headache, hemorrhage)

Other Considerations [6]

- **Binimetinib**: may be taken with or without food and is stored at room temperature
- **Encorafenib:** Has a dissociation half-life that more than 10 times longer than either dabrafenib or vemurafenib
- **Adverse events more common with encorafenib + binimetinib than vemurafenib:** serious retinopathy, left ventricular dysfunction
- **Encorafenib monotherapy**: increased risk compared to encorafenib used in combination for palmar-plantar eythrodysesthesia syndrome, hyperkeratosis, dry skin, erythema, rash, alopecia, pruritis, arthralgia, myopathy, dysgeusia, acneiform dermatitis
- **Adverse events more common with vemurafenib than encorafenib + binimetinib**: Pyrexia, arthralgia, hyperkeratosis, photosensitivity

Risk-Benefit Assessment (for Oncology NMEs only)

- **Outcome in clinically significant area: Progression-Free Survival**
- **Effect Size: HR 0.51 (95%CI .39-0.67) versus vemurafenib**
- **Potential Harms: Grade 3-4: 58%**
- **Net Clinical Benefit: Moderate (high risk of benefit/high risk of harm)**

Other Therapeutic Options

Alternative treatments for unresectable BRAF V600-mutant melanoma are listed in table 3 below

Table 3 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
Encorafenib plus binimetinib	TBD	• Metastatic Melanoma Drug Sequencing in VA • Versus vemurafenib (NCCN Category 1)	• Unresectable/metastatic BRAF V600E or K mutated melanoma in combination with binimetinib • Metastatic colorectal cancer with BRAF V600E mutation in combination with cetuximab
Dabrafenib plus trametinib	F	• Metastatic Melanoma Drug Sequencing in VA • Phase 2 data in melanoma brain metastases • Versus vemurafenib • (NCCN Category 1)	• Unresectable/metastatic BRAF-V600E or K mutated melanoma in combination with trametinib including 4 and 5 year OS data • Adjuvant resected BRAF-V600E or K mutated melanoma in combination with trametinib including 5 year follow-up • Metastatic BRAF-V600E mutant NSCLC in combination with trametinib • Advanced BRAF-V600E mutant anaplastic thyroid cancer in combination with trametinib
Vemurafenib plus cobimetinib	NF	• Metastatic Melanoma Drug Sequencing in VA • Versus vemurafenib (NCCN Category 1)	• Patients with BRAF V600E-mutated metastatic melanoma • Erdheim-Chester disease with BRAF V600E mutation
Nivolumab plus ipilimumab	F	• Metastatic Melanoma Drug Sequencing in VA • Versus nivolumab or ipilimumab monotherapy (NCCN Category 1)	• patients with unresectable or metastatic melanoma, as a single agent (nivolumab) or in combination with ipilimumab. • Adjuvant melanoma following resection in patients with lymph node involvement (nivolumab)
Pembrolizumab	F	• Metastatic Melanoma Drug Sequencing in VA • Versus ipilimumab (NCCN Category 1)	• treatment of patients with unresectable or metastatic melanoma • Adjuvant therapy of resected melanoma

Projected Place in Therapy

- Melanoma is an aggressive form of skin cancer that can metastasize to any organ and represents a small percentage of skin cancers. About 9% of melanomas are diagnosed with advanced disease (stage III or IV) and approximately 20% of patients treated at an early-stage progress to advanced disease. Once metastasized, melanoma has a poor prognosis. BRAF V600 mutations are the most frequent observed mutations in approximately half of melanomas and have a poor prognosis.
- In the VA there are approximately 17,000 patients with a diagnosis code for cutaneous melanoma. Of those, approximately 6400 patients have a prescription for one of the drugs used in first-line therapy.
- Standard of care for first-line therapy of metastatic melanoma includes either immunotherapy (IO) given alone or in combination (IO-IO) or BRAF targeted therapy for BRAF-mutant melanoma using the combination of a BRAF inhibitor and a MEK inhibitor. BRAF plus MEK inhibitors generally have higher initial response rates than IO based therapies, but patients eventually relapse due to acquired resistance.
- There are no head-to-head trials between first-line therapies. Until recently, guidelines have not agreed on first-line therapy, with NCCN recommending either anti-PD-1 monotherapy or in combination with anti-CTLA-4 inhibitor or BRAF+MEK inhibitors, with EMSO recommending anti-PD-1 combined with anti-CTLA-4 as first-line therapy regardless of BRAF mutation status if immunotherapy can be given safely, i.e. tumors not progressing quickly or not threatening major organ function.[7]
- Abstract publication of the phase III DREAMseq trial in BRAF-mutated melanoma found that the sequence of nivolumab + Ipilimumab followed by dabrafenib + trametinib at progression resulted in a longer OS and duration of response than the opposite sequence of dabrafenib + trametinib followed by nivolumab + ipilimumab.[8]
- Network meta-analysis:[9]
    - Dabrafenib + trametinib: Long-term PFS and OS data showed continued clinically meaningful reductions in 3 trials versus vemurafenib
    - Vemurafenib + cobimetinib: 4 year survival analysis showed favor of vemurafenib + cobimetinib versus vemurafenib in 1 trial
    - Encorafenib + binimetinib: 4 year PFS and OS analysis showed favor of encorafenib + binimetinib versus vemurafenib in 1 trial
    - Nivolumab + ipilimumab: 5 year PFS and OS analysis showed favor for the combination versus nivolumab or ipilimumab alone with median OS not yet reached in 3 trials
    - Pembrolizumab: 5 year survival analysis showed continued PFS and OS reduction versus ipilimumab
    - PFS network analysis: dabrafenib + trametinib associated with a better PFS against most therapies except: other BRAF + MEK inhibitor combinations and nivolumab plus ipilimumab (no difference)
    - OS network analysis: dabrafenib + trametinib associated with a better OS against some therapies (dacarbazine, vemurafenib, dabrafenib); no difference compared to other

BRAF + MEK inhibitor combinations, encorafenib, ipilimumab, ipilimumab + dacarbazine, nivolumab, or pembrolizumab. Nivolumab + ipilimumab had a statistically better OS.

- Safety:
  - Dabrafenib + trametinib- most common AEs: pyrexia, nausea, diarrhea, chills, headache, vomiting, hypertension, arthralgia.
  - Vemurafenib + cobimetinib-most common AEs: rash, arthralgia, diarrhea, fatigue, nausea, pyrexia, decreased appetite, photosensitivity, alanine aminotransferase and aspartate aminotransferase increase, serious retinopathy.
  - Encorafenib + binimetinib-most common AEs: rash, arthralgia, diarrhea, fatigue, vomiting, nausea, constipation, blood creatine phosphokinase increase, blurred vision
  - Nivolumab + ipilimumab-most common AEs: rash, pruritus, arthralgia, diarrhea, fatigue, nausea, vomiting, pyrexia, decrease appetite, photosensitivity, alanine and aspartate aminotransferase increase, hypothyroidism, serious retinopathy

- NICE Single Technology Appraisal[10]
  - Evidence Review Group (ERG) critique of manufacturer's submission on the use of encorafenib/binimetinib for BRAF mutation-positive unresectable or metastatic cutaneous melanoma
  - Direct evidence from COLUMBUS trial as previously stated above.
  - Indirect evidence from a network meta-analysis (NMA) to assess relative effects of efficacy (PFS and OS), safety, and Health-Related Quality of Life (HRQoL)
    - Results from NMA found no statistically significant difference in PFS and OS between encorafenib + binimetinib and dabrafenib + trametinib.
    - HRQoL favored encorafenib + binimetinib numerically but intervals crossed 0 and there was no statistically significant differences.
    - Safety results for grade ≥3 AEs favored dabrafenib + trametinib but results for serious AEs favored encorafenib + binimetinib but neither was statistically significant.
  - Overall conclusion: There is no direct evidence to confirm any differences in effectiveness and the available indirect evidence showed no statistically significant difference in efficacy (PFS and OS), safety, and HRQoL between encorafenib + binimetinib and dabrafenib + trametinib but the evidence is unreliable.

- Summary: For BRAF mutated cutaneous melanoma, any of the combination BRAF inhibitors and MEK inhibitors produce PFS and OS that are not statistically significantly different from each other based on indirect comparisons and network metanalyses. Dabrafenib + trametinib has the longest follow-up data for survival (5 years vs 4 years) shown in 3 clinical trials plus FDA indications in non-small cell lung cancer and anaplastic thyroid cancer. Clinically, encorafenib + binimetinib is thought to be better tolerated, and while the incidence of serious adverse events numerically favors encorafenib + binimetinib, this difference was not statistically significant in a network meta-analysis. The adverse event profiles for the BRAF/MEK inhibitor combinations overlap, but there are some differences which may be clinically important in specific patients. Based on the DREAMseq preliminary data, the combination of nivolumab + ipilimumab is likely

to be the preferred 1st choice independent of BRAF mutation status if the patient is a candidate for immunotherapy and does not require more immediate results due to bulky disease.

References

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Appendix A. Acquisition Prices and Cost Considerations

Refer to VA pricing sources for updated information.