

For the Treatment of Adults With Unresectable or
Metastatic Melanoma With a BRAF V600 Mutation^{1,2}

BRAFTOVI + MEKTOVI:^{s6_c3}

STRIKING IMPACT IN FIRST LINE³



Major Efficacy Outcome Measure: Progression-Free Survival (PFS)⁴

BRAFTOVI® (encorafenib) + MEKTOVI® (binimatinib)

14.9 MONTHS
MEDIAN PFS

(n=192) (95% CI: 11.0-18.5)

vemurafenib^{s11_c3}

7.3 MONTHS^{s13_c2}
MEDIAN PFS^{s16_c4}

(n=191) (95% CI: 5.6-8.2)^{s17_c8}

Primary Analysis: (HR=0.54 [95% CI: 0.41-0.71], P<0.001)^{s18_c7}

In the metastatic setting, 30% of patients receiving BRAFTOVI + MEKTOVI in the COLUMBUS trial had prior treatment with immunotherapy.⁴

EDA Approval No. HFO098A9695/032024
EDA Invalidation Date: 03/03/2027

PP-BMK-EGY-0003

 **BRAFTOVI® + MEKTOVI®**
(encorafenib) 75 mg Hard Gelatin Capsules
(binimatinib) 15 mg Film Coated Tablets



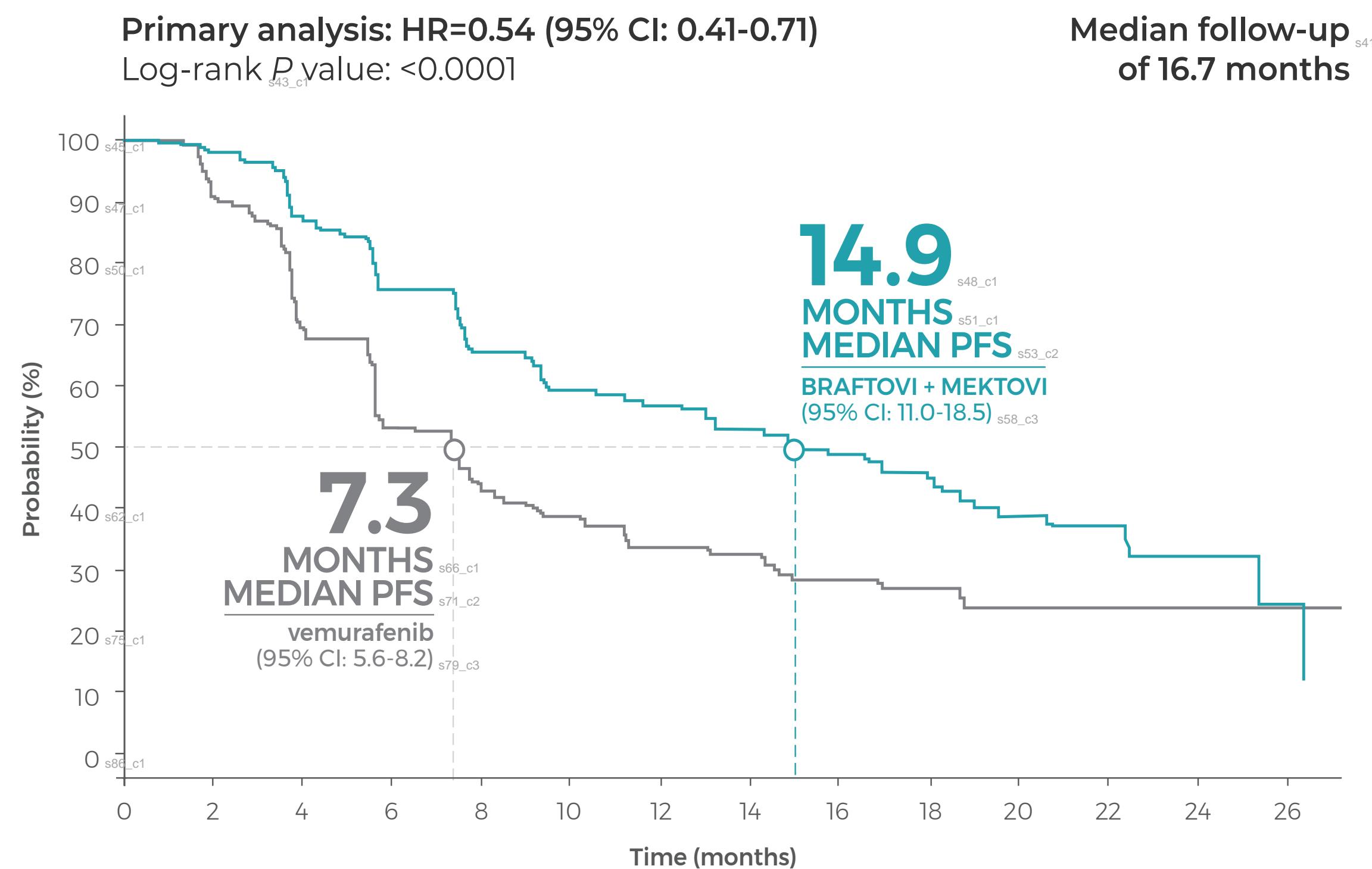
An oral treatment combination for adults with unresectable or metastatic melanoma
with a *BRAF* V600 mutation^{1,2}



Primary and updated post hoc PFS results by BIRC⁴

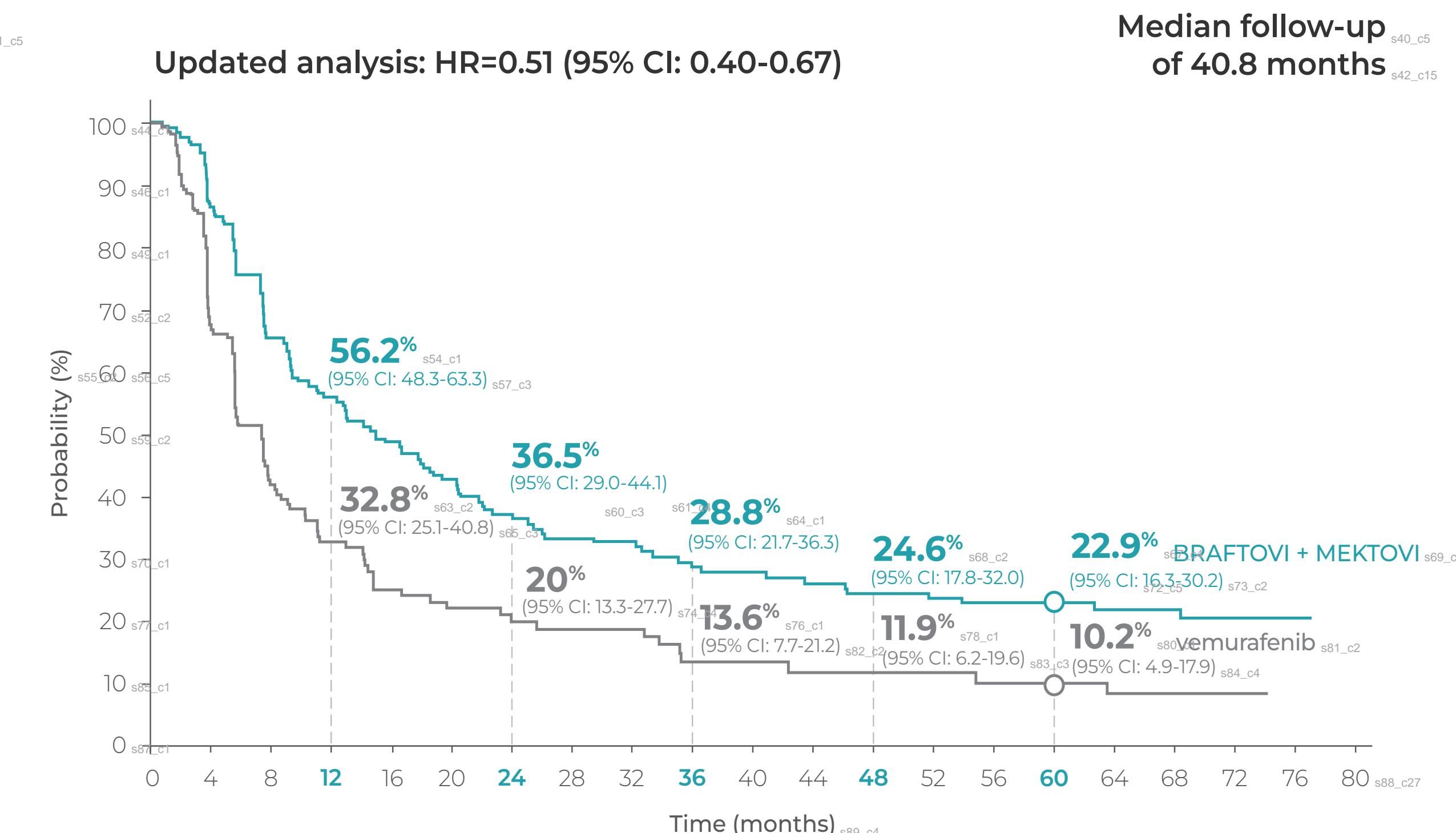
The 5-year PFS update is a descriptive post hoc analysis and
should be interpreted in the context of this limitation.⁵

Primary analysis: PFS⁴



| Patients at risk | | | | | | | | | | | | |
|--------------------|-----|-----|-----|-----|----|----|----|----|----|----|----|----|
| BRAFV600 + MEKTOVI | | | | | | | | | | | | |
| 192 | 171 | 151 | 128 | 107 | 92 | 87 | 70 | 57 | 41 | 28 | 14 | 4 |
| vemurafenib | 191 | 149 | 101 | 75 | 56 | 45 | 36 | 32 | 23 | 18 | 13 | 10 |

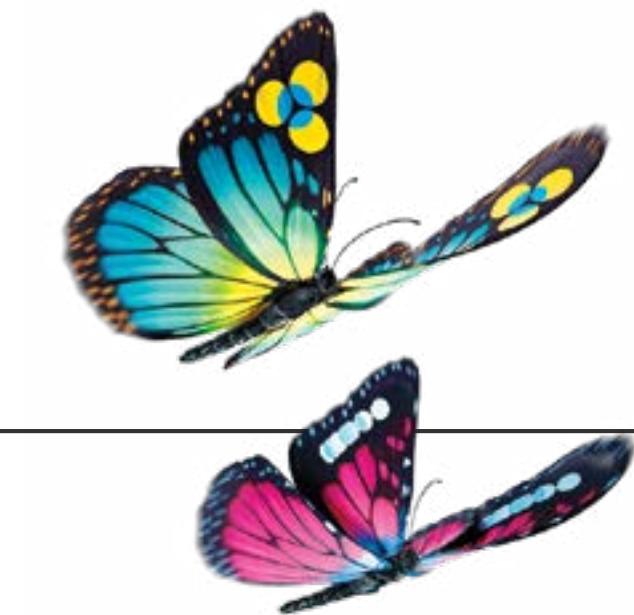
Updated post hoc PFS analysis at 5 years⁵



| Patients at risk | | | | | | | | | | | | | | | | | | | | |
|--------------------|-----|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|---|---|
| BRAFV600 + MEKTOVI | | | | | | | | | | | | | | | | | | | | |
| 192 | 151 | 108 | 87 | 73 | 63 | 50 | 45 | 43 | 35 | 33 | 31 | 29 | 28 | 27 | 26 | 23 | 19 | 9 | 2 | 0 |
| vemurafenib | 191 | 98 | 55 | 36 | 26 | 22 | 18 | 16 | 15 | 10 | 10 | 7 | 7 | 7 | 6 | 5 | 3 | 1 | 0 | 0 |

PFS, progression-free survival; BIRC, blinded independent review committee.

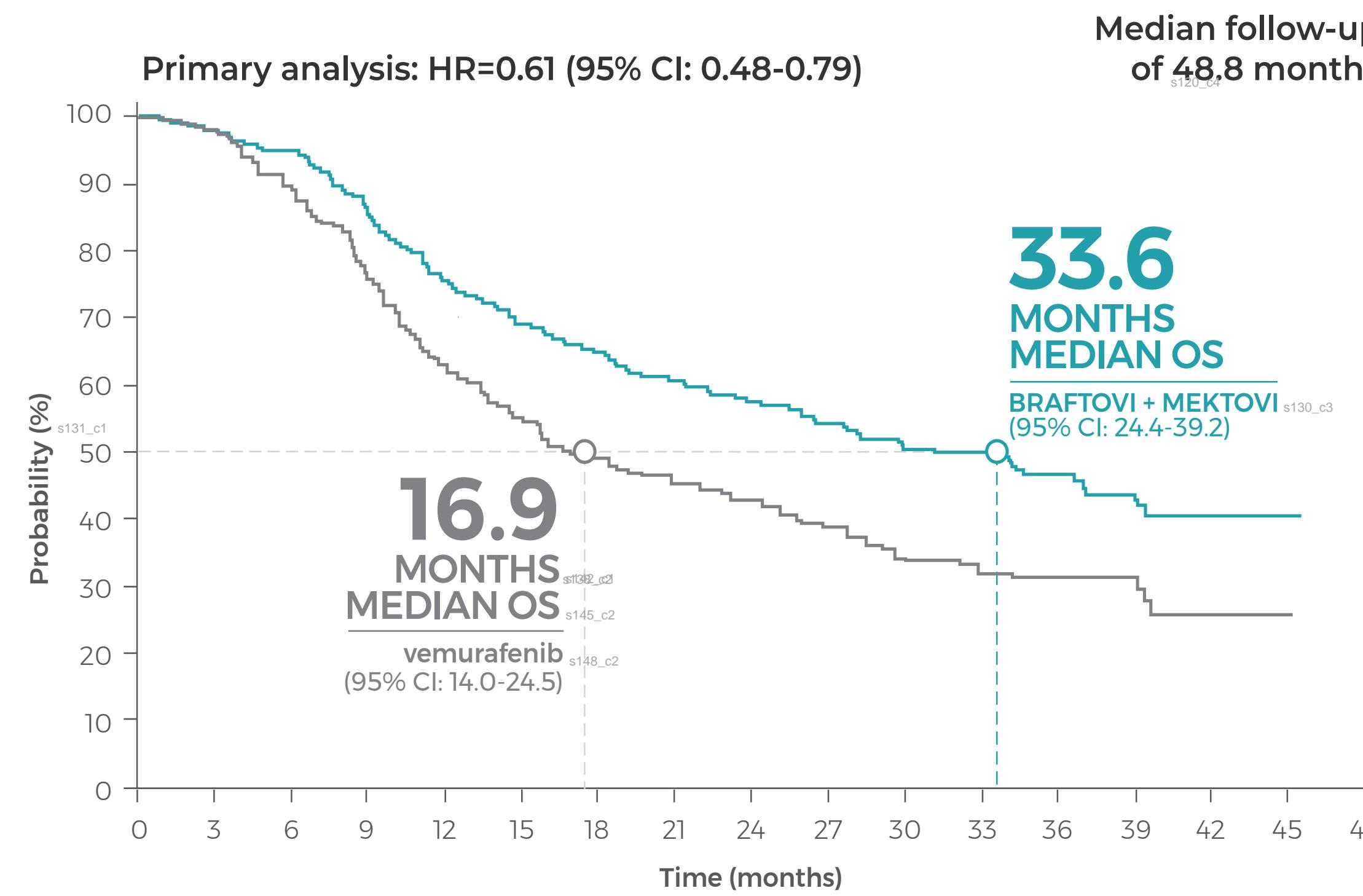
An oral treatment combination for adults with unresectable or metastatic melanoma
with a *BRAF* V600 mutation^{1,2}



Primary and updated post hoc OS results

The hierarchical testing procedure prevented formal assessment of the statistical significance of OS; therefore, the OS results are descriptive in nature only.⁵

Primary analysis: OS⁶

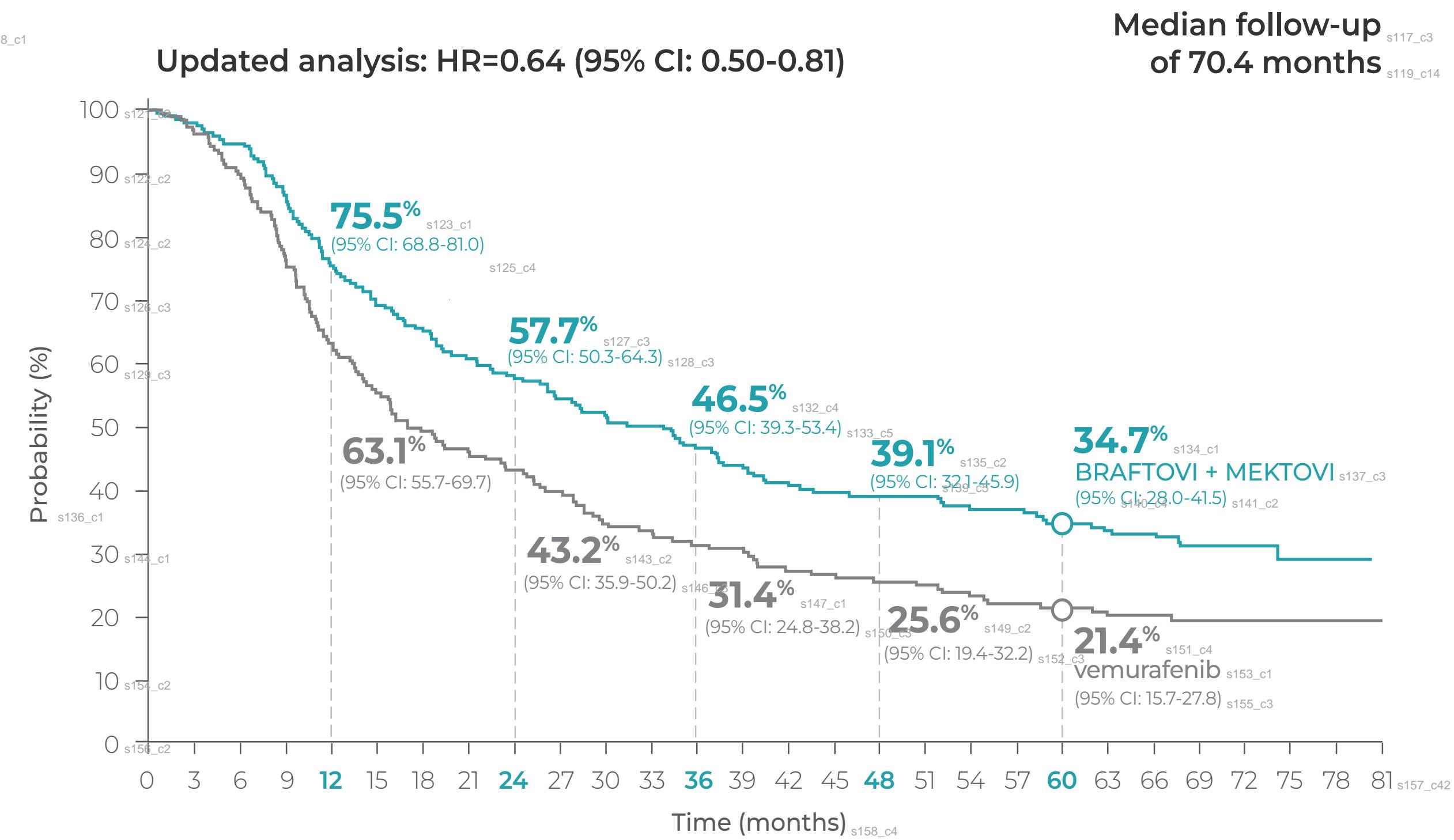


| Patients at risk | |
|---|--|
| BRAFTOVI + MEKTOVI | |
| 192 188 182 166 144 132 124 115 108 102 95 82 57 30 9 1 0 | |

| Patients at risk | |
|---|--|
| vemurafenib | |
| 191 184 166 140 115 100 89 83 77 71 62 56 30 19 8 1 0 | |

The 5-year OS update is a descriptive post hoc analysis and should be interpreted in the context of this limitation.⁵

Updated post hoc OS analysis at 5 years⁵



| Patients at risk | |
|--|--|
| BRAFTOVI + MEKTOVI | |
| 192 188 182 166 144 132 124 116 109 103 96 95 88 81 76 74 73 73 68 66 62 59 53 42 22 8 3 0 | |

| Patients at risk | |
|--|--|
| vemurafenib | |
| 191 184 166 141 115 100 89 83 77 71 62 58 54 52 47 45 44 43 39 37 34 32 29 22 13 6 2 0 | |

OS, overall survival.

- In the **primary analysis** of OS (data cutoff: November 7, 2017), the number of events observed in each arm was 105/192 (54.7%) with BRAF TOVI® (encorafenib) + MEKTOVI® (binimetinib) and 127/191 (66.5%) with vemurafenib¹
s167_c17 s168_c8
- In this updated post hoc analysis, the median OS of BRAF TOVI + MEKTOVI was 33.6 months (95% CI: 24.4-39.2) and 16.9 months (95% CI: 14.0-24.5) with vemurafenib⁵
s172_c6 s174_c2 s173_c3
- In this updated post hoc analysis of OS (minimum follow-up of 65 months; data cutoff: September 15, 2020), the number of events observed in each arm was 131/192 (68.2%) with BRAF TOVI + MEKTOVI and 145/191 (75.9%) with vemurafenib⁵
s176_c5 s175_c6 s180_c1 s179_c5 s177_c15

Primary analysis of ORR and median duration of response (mDoR) by BIRC^{4*†} s181_c8

| | ORR | mDoR |
|--|--|--|
| BRAF TOVI + MEKTOVI (n=192) <small>s185_c4</small> | 63% (95% CI: 56-70; CR: 8%; PR: 55%) | 16.6 months (95% CI: 12.2-20.4) <small>s184_c3 s186_c10</small> |
| vemurafenib (n=191) <small>s188_c2</small> | 40% (95% CI: 33-48; CR: 6%; PR: 35%) | 12.3 months (95% CI: 6.9-16.9) <small>s187_c3 s189_c10</small> |

*ORRs and DoRs were assessed at the time of the primary PFS analysis (data cutoff: May 19, 2016).⁴
s150_c16 s191_c5

†ORR and DoR were both prespecified analyses assessed by BIRC using RECIST v1.1, but did not evaluate statistical significance; therefore, the ORR and DoR results are descriptive in nature only.⁴
s192_c17 s194_c5 s193_c15

CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; OS, overall survival; PFS, progression-free survival; BIRC, blinded independent review committee; ORR, objective response rate; mDoR, median duration of response
s199_c2 s198_c3 s201_c3 s202_c1 s200_c9 s204_c1

An oral treatment combination for adults with unresectable or metastatic melanoma^{s207_c1}
with a BRAF V600 mutation^{1,2}^{s206_c10}^{s208_c4}

Dosing and administration^{s211_c1}^{s210_c2}



Confirm the presence of BRAF V600 mutation by an FDA-approved test before treatment.^{1,2}^{s214_c1}^{s213_c3}^{s212_c9}

Recommended dose^{s215_c2}

BRAFTEVI®
(encorafenib) + MEKTOVI®
(binimatinib)
450 mg **45 mg**

Six 75-mg BRAFTEVI capsules¹
and three 15-mg MEKTOVI tablets²



MEKTOVI
45 mg

Three 15-mg MEKTOVI tablets²^{s224_c6}^{s221_c10}

1st DOSE

2nd DOSE

Treatment with BRAFTEVI + MEKTOVI should be continued until disease progression or unacceptable toxicity^{1,2}^{s229_c4}

- Instruct patients not to take a missed dose of:^{s231_c2}
 - BRAFTEVI within 12 hours of the next dose¹^{s232_c8}
 - MEKTOVI within 6 hours of the next dose²^{s233_c8}
- In case of vomiting, do not take an additional dose of BRAFTEVI + MEKTOVI; resume dosing with the next scheduled dose^{1,2}^{s235_c5}^{s234_c16}
- No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh A). As encorafenib is not recommended in patients with moderate (Child Pugh B) or severe hepatic impairment (Child-Pugh C), administration of binimatinib is not recommended in these patients²^{s237_c7}^{s236_c12}^{s238_c8}^{s241_c1}

Selected BRAFTEVI drug interactions¹^{s243_c1}^{s242_c3}

Effects of other medicinal products on encorafenib: Encorafenib is primarily metabolised by CYP3A4.^{s244_c12}

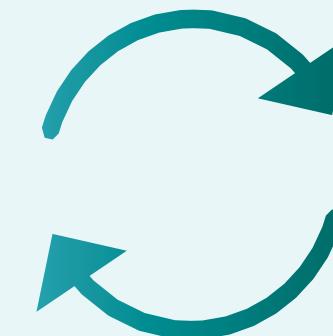
- CYP3A4 inhibitors: concomitant administration of encorafenib with strong CYP3A4 inhibitors should be avoided (due to increased encorafenib exposure and potential increase in toxicity). Examples of strong CYP3A4 inhibitors include, but are not limited to, ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole and grapefruit juice. If concomitant use of a strong CYP3A inhibitor is unavoidable, patients should be carefully monitored for safety. Moderate CYP3A4 inhibitors should be co-administered with caution. Examples of moderate CYP3A4 inhibitors include, but are not limited to, amiodarone, erythromycin, fluconazole, diltiazem, amprenavir and imatinib. When encorafenib is co-administered with a moderate CYP3A inhibitor, patients should be carefully monitored for safety.¹

- CYP3A4 inducers: Co-administration of encorafenib with a CYP3A4 inducer was not assessed in a clinical study; however, a reduction in encorafenib exposure is likely and may result in compromised efficacy. Examples of moderate or strong CYP3A4 inducers include, but are not limited to carbamazepine, rifampicin, phenytoin and St. John's Wort. Alternative agents with no or minimal CYP3A induction potential should be considered.¹

- Effects of encorafenib on other medicinal products:¹

CYP substrates: Encorafenib is both an inhibitor and inducer of CYP3A4. Concomitant use with agents that are substrates of CYP3A4 (e.g., hormonal contraceptives) may result in increased toxicity or loss of efficacy of these agents. Agents that are CYP3A4 substrates should be co-administered with caution. Encorafenib is an inhibitor of UGT1A1. Concomitant agents that are substrates of UGT1A1 (e.g. raltegravir, atorvastatin, dolutegravir) may have increased exposure and should be therefore administered with caution. Effect of encorafenib on binimetinib: While encorafenib is a relatively potent reversible inhibitor of UGT1A1, no differences in binimetinib exposure have been observed clinically when binimetinib was co-administered with encorafenib. Transporter substrates: In vivo, encorafenib is an inhibitor of OATP1B1, OATP1B3 and/or BCRP. Coadministration of encorafenib with OATP1B1, OATP1B3 or BCRP substrates (such as rosuvastatin, atorvastatin, methotrexate) can result in increased. In vitro, encorafenib potentially inhibits a number of other transporters. Agents that are substrates of renal transporters OAT1, OAT3, OCT2 (such as furosemide, penicillin) or agents that are substrates of the hepatic transporters OCT1 (such as, bosentan) or substrates of P-gp (e.g. posaconazole) may also have increased exposure. Therefore, these agents, substrates of transporters should be co-administered with caution.

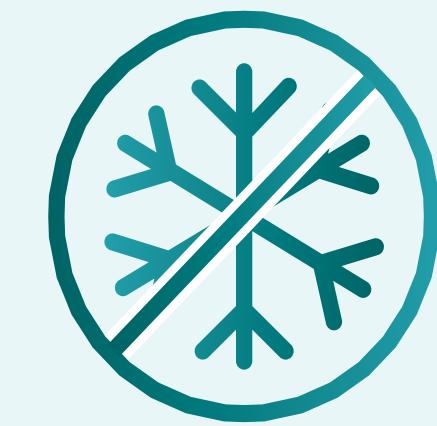
The BRAF inhibitor + MEK inhibitor combination with continuous dosing and no fasting or refrigeration requirements^{1,2}



Continuous
dosing schedule^{1,2}



May be taken with
or without food^{1,2}



No refrigeration
requirement^{1,2}

- BRAFTOVI + MEKTOVI should be stored at room temperature^{1,2}

BCRP, breast cancer resistance protein; CYP3A4, cytochrome P450 3A4; OATP1B1, organic anion transporting polypeptide 1B1; OATP1B3, organic anion transporting polypeptide 1B3.

For the Treatment of Adults With Unresectable or Metastatic
Melanoma With a *BRAF* V600 Mutation^{1,2}

BRAFTOVI® (encorafenib)^{310_c1} + MEKTOVI® (binimatinib):^{309_c5}

STRIKING IMPACT IN FIRST LINE³



NCCN Category 1* Recommendation³

Encorafenib (BRAFTOVI) in combination with binimatinib (MEKTOVI) as a first-line systemic therapy option for patients with metastatic or unresectable cutaneous melanoma with a *BRAF* V600–activating mutation.^{318_c18}

*Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.^{320_c15}



14.9 months median PFS per primary analysis⁴

- BRAFTOVI + MEKTOVI (n=192) more than doubled median PFS vs vemurafenib (n=191): 14.9 months (95% CI: 11.0-18.5) vs 7.3 months (95% CI: 5.6-8.2) (HR=0.54 [95% CI: 0.41-0.71], $P<0.0001$) per primary analysis of major efficacy outcome measure^{325_c21}



OS per primary analysis⁵

[†]The hierarchical testing procedure prevented formal assessment of the statistical significance of OS; therefore, the OS results are descriptive in nature only.^{330_c14}

- 33.6 months median OS observed with BRAFTOVI + MEKTOVI (95% CI: 24.4-39.2) (n=192) and 16.9 months with vemurafenib (95% CI: 14.0-24.5) (n=191) (HR=0.61 [95% CI: 0.47-0.79]) in the primary OS analysis^{333_c21}



The most common adverse reactions ($\geq 25\%$) with BRAFTOVI + MEKTOVI were fatigue (43.8%), nausea (41.6%), diarrhea (38%), vomiting (28.1%), abdominal pain (27.4%), and arthralgia^{1,2}

NCCN, National Comprehensive Cancer Network® (NCCN®); OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.^{337_c18}



References s339_c1

1. Braftovi 50, 75 mg .Egypt LPD. Revision Date July 2022 Egyptian Drug Authority Leaflet Approval Date: 12-02-2023 s341_c5 s340_c15
2. Mektovi 15mg .Egypt LPD. Revision Date September 2021 Egyptian Drug Authority Leaflet Approval Date: 12-03-2023 s343_c5 s342_c13
3. National Comprehensive Cancer Network (NCCN). Melanoma: Cutaneous. Available at <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492>. s344_c11
Last accessed 16/11/2023. s345_c3
4. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, Garbe C, Schadendorf D, Krajsova I, Gutzmer R, Chiarion-Sileni V. Encorafenib plus binimatinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. s346_c24
The Lancet Oncology. 2018 May 1;19(5):603-15. s347_c1 s350_c5
5. Dummer R, Flaherty KT, Robert C, Arance A, B de Groot JW, Garbe C, Gogas HJ, Gutzmer R, Krajsová I, Liszkay G, Loquai C. COLUMBUS 5-year update: a randomized, open-label, phase III trial of encorafenib plus binimatinib versus vemurafenib or encorafenib in patients with BRAF. s352_s353_c3
Future Oncology. 2023 Jun(0). s354_c18
6. Ascierto PA, Dummer R, Gogas HJ, Flaherty KT, Arance A, Mandala M, Liszkay G, Garbe C, Schadendorf D, Krajsova I, Gutzmer R. Update on tolerability and overall survival in COLUMBUS: Landmark analysis of a randomised phase 3 trial of encorafenib plus binimatinib vs vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma. s356_c2
European Journal of Cancer. 2020 Feb 1;126:33-44. s357_c25 s361_c10

Braftovi® Abbreviated Prescribing Information / Summary of Product Information

TARGET AUDIENCE: For Healthcare Professionals

Braftovi® Abbreviated Prescribing Information / Summary of Product Information

GENERIC NAME: Encorafenib

PRESENTATION: 50 mg and 75 mg Hard Capsule

NATURE AND CONTENT OF THE CONTAINER: No. of stripes, as applicable

Braftovi 50 mg: Pack of 28 Capsules, including 7 blisters, each of 4 hard capsules.

Braftovi 75 mg: Pack of 42 Capsules, including 7 blisters, each of 6 hard capsules.

INDICATION(s): Encorafenib is indicated:

in combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.

DOSAGE AND ADMINISTRATION:

Melanoma The recommended dose of encorafenib is 450 mg (six 75 mg capsules) once daily, when used in combination with binimetinib. Colorectal cancer The recommended dose of encorafenib is 300 mg (four 75 mg capsules) once daily, when used in combination with cetuximab. Braftovi is for oral use. The capsules are to be swallowed whole with water. They may be taken with or without food. The concomitant administration of encorafenib with grapefruit juice should be avoided

MISSED DOSES:

If a dose of encorafenib is missed, the patient should only take the missed dose if it is more than 12 hours until the next scheduled dose

SPECIAL POPULATION:

Elderly patients No dose adjustment is required for patients aged 65 years and older.

Hepatic impairment Patients with mild to severe hepatic impairment may have increased encorafenib exposure. Administration of encorafenib should be undertaken with caution at a dose of 300 mg once daily in patients with mild hepatic impairment (Child-Pugh Class A). No dosing recommendation can be made in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

Renal impairment No dose adjustment is required for patients with mild or moderate renal impairment based on a population pharmacokinetics (PK) analysis. There are no clinical data with encorafenib in patients with severe renal impairment. Therefore, the potential need for dose adjustment cannot be determined. Encorafenib should be used with caution in patients with severe renal impairment.

Paediatric population The safety and efficacy of encorafenib have not yet been established in children and adolescents. No data are available.

Fertility, pregnancy and lactation

Women of childbearing potential /Contraception in females Women of childbearing potential must use effective contraception during treatment with encorafenib and for at least 1 month following the last dose. Encorafenib may decrease the efficacy of hormonal Contraceptives. Therefore, female patients using hormonal contraception are advised to use an additional or alternative method such as a barrier method (e.g. condom) during treatment with encorafenib and for at least 1 month following the last dose.

Pregnancy

There are no data from the use of encorafenib in pregnant women. Studies in animals have shown reproductive toxicity. Encorafenib is not recommended during pregnancy and in women of child bearing potential not using contraception. If encorafenib is used during pregnancy or if the patient becomes pregnant while taking encorafenib, the patient should be informed of the potential hazard to the foetus.

Breast-feeding

It is unknown whether encorafenib or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue encorafenib therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility

There are no data on the effects of encorafenib on fertility in humans. Based on findings in animals, the use of encorafenib may impact fertility in males of reproductive potential. As the clinical relevance of this is unknown, male patients should be informed of the potential risk for impaired spermatogenesis.

CONTRAINDICATIONS:

Hypersensitivity to the active substance or to any of the excipients

WARNING AND PRECAUTIONS:

Encorafenib is to be given in combination with binimetinib (for patients with BRAF V600 mutant unresectable or metastatic melanoma), or in combination with cetuximab (for patients with BRAF V600E mutant metastatic colorectal cancer). For additional information on warnings and precautions associated with binimetinib

Braftovi® Abbreviated Prescribing Information / Summary of Product Information

or cetuximab treatment, see section 4.4 of binimetinib SmPC or cetuximab SmPC.

BRAF mutation testing:

Before taking encorafenib, patients must have unresectable or metastatic melanoma with BRAF V600 mutation or metastatic colorectal cancer with BRAF V600E mutation confirmed by a validated test. The efficacy and safety of encorafenib have been established only in patients with melanoma tumours expressing BRAF V600E and V600K mutations or colorectal tumours expressing BRAF V600E mutation. Encorafenib should not be used in patients with wild type BRAF malignant melanoma or wild type BRAF colorectal cancer. Encorafenib in combination with binimetinib in patients who have progressed on a BRAF inhibitor. There are limited data for the use of the combination of encorafenib with binimetinib in patients who have progressed on a prior BRAF inhibitor given for the treatment of unresectable or metastatic melanoma with BRAF V600 mutation. These data show that the efficacy of the combination would be lower in these patients. Encorafenib in combination with binimetinib in patients with brain metastases. There are limited efficacy data with the combination of encorafenib and binimetinib in patients with a BRAF V600 mutant melanoma which have metastasised to the brain.

Left ventricular dysfunction (LVD)

LVD defined as symptomatic or asymptomatic decreases in ejection fraction has been reported when encorafenib is used in combination with binimetinib. It is recommended that left ventricular ejection fraction (LVEF) is assessed by echocardiogram or multi-gated acquisition (MUGA) scan before initiation of encorafenib and binimetinib, one month after initiation, and then at approximately 3-month intervals or more frequently as clinically indicated, while on treatment. If during treatment LVD occurs. The safety of encorafenib in combination with binimetinib has not been established in patients with a baseline LVEF that is either below 50% or below the institutional lower limits of normal. Therefore, in these patients, binimetinib should be used with caution and for any symptomatic left ventricular dysfunction, Grade 3-4 LVEF decrease or for absolute decrease of LVEF from baseline of ≥ 10%, binimetinib and encorafenib should be discontinued and LVEF should be evaluated every 2 weeks until recovery.

Haemorrhage

Haemorrhages, including major hemorrhagic events, can occur with encorafenib. The risk of haemorrhage may be increased with concomitant use of anticoagulant and antiplatelet therapy. The occurrence of Grade ≥3 Hemorrhagic events should be managed with dose interruption or treatment discontinuation and as clinically indicated.

Ocular toxicities

Ocular toxicities including uveitis, iritis, and iridocyclitis can occur when encorafenib is administered. RPED has also been reported in patients treated with encorafenib in combination with binimetinib. Patients should be assessed at each visit for symptoms of new or worsening visual disturbance. If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, a prompt ophthalmologic examination is recommended. If uveitis including iridocyclitis and iritis occurs during treatment. If during treatment patient develops RPED or RVO.

QT prolongation

QT Prolongation has been observed in patients treated with BRAF-inhibitors. A thorough QT study to evaluate the QT prolongation potential of encorafenib has not been conducted. Overall, results suggest that single agent encorafenib has the potential to cause mild increases in heart rate. Across pooled combination studies of encorafenib and binimetinib at the recommended doses and a single-agent encorafenib study, results suggest that encorafenib has the potential to result in small increases in QTc interval. There are insufficient data to exclude a clinically significant exposure dependent QT prolongation. Due to the potential risk for QT prolongation, it is recommended that serum electrolytes abnormalities, including magnesium and potassium, are corrected and risk factors for QT prolongation controlled (e.g. congestive heart failure, bradycardia, arrhythmias) before treatment initiation and during treatment. It is recommended that an electrocardiogram (ECG) is assessed before initiation of encorafenib, one month after initiation, and then at approximately 3-month intervals or more frequently as clinically indicated, while on treatment. The occurrence of QTc prolongation can be managed with dose reduction, interruption or discontinuation with correction of abnormal electrolytes and control of risk factors.

New primary malignancies

New primary malignancies, cutaneous and non-cutaneous, have been observed in patients treated with BRAF inhibitors and can occur when encorafenib is administered.

Cutaneous malignancies

Cutaneous malignancies such as cutaneous squamous cell carcinoma (cuSCC) including keratoacanthoma have been observed in patients treated with BRAF-inhibitors including encorafenib. New primary melanoma has been observed in patients treated with BRAF inhibitors including encorafenib. Dermatologic evaluations should be performed prior to initiation of therapy with encorafenib, every 2 months while on therapy and for up to 6 months following treatment discontinuation. Suspicious skin lesions should be managed with dermatologic excision and dermatopathologic evaluation. Patients should be instructed to immediately inform their physicians if new skin lesions develop. Encorafenib should be continued without any dose modification.

Braftovi® Abbreviated Prescribing Information / Summary of Product Information

Non-cutaneous malignancies

Based on its mechanism of action, encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms. Patients receiving encorafenib should undergo a head and neck examination, chest/abdomen computerised tomography (CT) scan, anal and pelvic examinations (for women) and complete blood cell counts prior to initiation, during and at the end of treatment as clinically appropriate. It should be considered to permanently discontinue encorafenib in patients who develop RAS mutation-positive non-cutaneous malignancies. Benefits and risks should be carefully considered before administering encorafenib to patients with a prior or concurrent cancer associated with RAS mutation.

Liver laboratory abnormalities

Liver laboratory abnormalities including AST and ALT elevations have been observed with encorafenib. Liver laboratory values should be monitored before initiation of encorafenib and monitored at least monthly during the 6 first months of treatment, then as clinically indicated. Laboratory abnormalities should be managed with dose interruption, reduction or treatment discontinuation.

Hepatic impairment:

As encorafenib is primarily metabolised and eliminated via the liver, patients with mild to severe hepatic impairment may have increased encorafenib exposure over the range of inter-subject variability. In the absence of clinical data, encorafenib is not recommended in patients with moderate or severe hepatic impairment. Administration of encorafenib should be undertaken with caution at a dose of 300 mg once daily in patients with mild hepatic impairment. Closer monitoring of encorafenib related toxicities in patients with mild hepatic impairment is recommended, including clinical examination and liver function tests, with assessment of ECGs as clinically appropriate during treatment.

Renal impairment

There are no data available in patients with severe renal impairment. Encorafenib should be used with caution in patients with severe renal impairment. Creatinine elevation has been commonly reported with encorafenib as single agent or in combination with binimetinib or cetuximab. Observed cases of renal failure including acute kidney injury and renal impairment were generally associated with vomiting and dehydration. Other contributing factors included diabetes and hypertension. Blood creatinine should be monitored as clinically indicated and creatinine elevation managed with dose modification or discontinuation. Patients should ensure adequate fluid intake during treatment.

Effects of other medicinal products on encorafenib

concurrent use of strong CYP3A inhibitors during treatment with encorafenib should be avoided. If concomitant use with a strong CYP3A inhibitor is necessary, patients should be carefully monitored for safety. Caution should be exercised if a moderate CYP3A inhibitor is co-administered with encorafenib. EXCIPIENTS: For the full list of excipients, see section 6.1.

EFFECT ON ABILITY TO DRIVE AND USE MACHINES:

Encorafenib has minor influence on the ability to drive or use machines. Visual disturbances have been reported in some patients treated with encorafenib during clinical studies. Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse reactions that may affect their ability to drive and use machines.

DRUG Interactions:

No drug drug interaction was evidenced between encorafenib and cetuximab.

Effect of CYP enzymes on encorafenib

Encorafenib is metabolised by CYP3A4, CYP2C19 and CYP2D6. In vitro, CYP3A4 was predicted to be the major enzyme contributing to total oxidative clearance of encorafenib in human liver microsomes (~83.3%), followed by CYP2C19 and CYP2D6 (~16.0% and 0.71%, respectively). Effect of encorafenib on CYP substrates In vitro experiments indicate encorafenib is a relatively potent reversible inhibitor of UGT1A1, CYP2B6, CYP2C9 and CYP3A4/5, as well as a time-dependent of CYP3A4. Encorafenib induced CYP1A2, CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes. Simulations of 450 mg encorafenib coadministered with probe substrates for CYP2B6, CYP1A2, CYP2C9, CYP2C19 and CYP2D6 on Day 1 and Day 15 all indicated no clinically relevant interactions are expected. For co-administration with CYP3A4 and UGT1A1 substrates that undergo gut extraction, a minor to moderate interaction is expected. While binimetinib is a UGT1A1 substrate, it does not undergo gut extraction and therefore no DDI with encorafenib is expected. Additionally, no differences in exposure have been observed clinically when binimetinib is co-administered with encorafenib.

Effect of transporters on encorafenib

Encorafenib was found to be a substrate of the P-glycoprotein (P-gp) transporters. Inhibition of P-gp is unlikely to result in a clinically important increase in encorafenib concentrations as encorafenib exhibits high intrinsic permeability. The involvement of several uptake transporter families (OCT 1, OATPIB1, OATPIB3 and OATPBI) was

Braftovi® Abbreviated Prescribing Information / Summary of Product Information

investigated in vitro using relevant transponer inhibitors. The data suggest that hepatic uptake transponers are not involved in encorafenib distribution into primary human hepatocytes.

Effect of encorafenib on transporters

Repeated administration of encorafenib 450 mg once daily and binimetinib 45 mg twice daily with a single dose of rosuvastatin (a OATPIB1, OATPIB3 and BCRP substrate) increased rosuvastatin Cmax by 2.7-fold and AUC by 1.6-fold indicating a mild inhibition of OATPIB1, OATPIB3 and/or BCRP transporters. In vitro, encorafenib inhibited the hepatic transponer OCT 1, but is unlikely to be an effective inhibitor clinically. Based on in vitro studies, there is potential for encorafenib to inhibit renal transporters OCT 2, OAT 1, OAT 3. at clinical concentrations. In addition, encorafenib may inhibit P-gp in the gut at the expected clinical concentrations.

OVERDOSE: Symptoms

At doses of encorafenib between 600 to 800 mg once daily, renal dysfunction (Grade 3 hypercreatininaemia) was observed in 3 out of 14 patients. The highest administered dose occurred as a dosing error in one patient who took encorafenib at a dose of 600 mg twice daily for 1 day (total dose 1200 mg). Adverse reactions reported by this patient were Grade 1 events of nausea, vomiting and blurred vision; all subsequently resolved.

Management

There is no specific treatment for overdose. Since encorafenib is moderately bound to plasma proteins, haemodialysis is likely to be ineffective in the treatment of overdose with encorafenib. There is no known antidote for encorafenib. In the event of an overdose, encorafenib treatment should be interrupted and renal function must be monitored as well as adverse reactions. Symptomatic treatment and supportive care should be provided as needed.

ADVERSE REACTION:

The safety of encorafenib (450 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) was evaluated in 274 patients with BRAF V600 mutant unresectable or metastatic melanoma (hereafter referred to as the pooled Combo 450 population), based on two Phase II studies (CMEK162X2110 and CLGX81SX2109) and one Phase III study (CMEK162B2301, Part 1). At the recommended dose (n = 274) in patients with unresectable or metastatic melanoma, the most common adverse reactions (>25%) occurring in patients treated with encorafenib administered with binimetinib were fatigue, nausea, diarrhoea, vomiting, retinal detachment, abdominal pain, althralgia, blood CK increased and myalgia. The safety of encorafenib (300 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) was evaluated in 257 patients with BRAF V600 mutant unresectable or metastatic melanoma (hereafter referred to as the Combo 300 population), based on the Phase III study (CMEK162B2301, Part 2). The most common adverse reactions (>25%) occurring in patients treated with encorafenib 300 mg administered with binimetinib were fatigue, nausea and diarrhoea. The encorafenib single agent (300 mg orally once daily) safety profile is based on data from 217 patients with unresectable or metastatic BRAF V600-mutant melanoma (hereafter referred to as the pooled encorafenib 300 population). The most common adverse drug reactions (ADRs) (>25%) reported with encorafenib 300 were hyperkeratosis, alopecia, PPES, fatigue, rash, althralgia, dry skin, nausea, myalgia, headache, vomiting and pruritus. The safety of encorafenib (300 mg orally once daily) in combination with cetuximab (dosed as per its SmPC) was evaluated in 216 patients with BRAF V600E- mutant metastatic colorectal cancer, based on the phase III study ARRAY-818-302. The most common ADRs (>25%) reported in this population were: fatigue, nausea, diarrhea, dermatitis acneiform, abdominal pain, althralgia/musculoskeletal pain, decreased appetite, rash and vomiting. The rate of all study drug discontinuation due to any adverse reaction was 1.9 % in patients treated with encorafenib 300 mg in combination with cetuximab.

DOSE MODIFICATIONS (IF APPLICABLE):

Recommended dose modifications for encorafenib when used in combination with binimetinib in melanoma indication

Starting dose Six 75 mg (450 mg) capsules once daily 1st dose reduction Four 75 mg (300 mg) capsules once daily 2nd dose reduction Three 75 mg (225 mg) capsules once daily Subsequent modification, There are limited data for dose reduction to 100 mg once daily. Encorafenib should be permanently discontinued if patient is unable to tolerate 100 mg (two 50 mg capsules) once daily.

Recommended dose modifications for encorafenib when used in combination with cetuximab in CRC indication

starting dose Four 75 mg (300 mg) capsules once daily 1st dose reduction Three 75 mg (225 mg) capsules once daily 2nd dose reduction Two 75 mg (150 mg) capsules once daily If encorafenib is permanently discontinued, cetuximab should be discontinued. If cetuximab is permanently discontinued, encorafenib should be discontinued.

PHARMACEUTICAL PRECAUTIONS Special precautions for disposal:

Keep out of the sight and reach of children. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PHARMACOKINETICS / PHARMACODYNAMICS (If required per local regulations)

The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumours, including advanced and unresectable or metastatic cutaneous melanoma harbouring a BRAF-V600E or K mutation, and in adult patients with metastatic colorectal cancer with a BRAF V600E mutation. The pharmacokinetics of encorafenib have been shown to be approximatively dose linear after single and multiples doses. After repeat once-daily dosing, steady-state conditions were reached within 15 days. The accumulation ratio of approximately 0.5 is likely due to auto-induction of CYP3A4. The inter- subject variability (CV%) of AUC is ranged from 12.3% to 68.9%. Absorption After oral administration, encorafenib is rapidly absorbed with a median Tmax of 1.5 to 2 hours. Following a single oral dose of 100 mg [14C]

Braftovi® Abbreviated Prescribing Information / Summary of Product Information

encorafenib in healthy subjects, at least 86% of the encorafenib dose was absorbed. Administration of a single 100 mg dose of encorafenib with a highfat, high-calorie meal decreased the Cmax by 36%, while the AUC was unchanged. A drug interaction study in healthy subjects indicated the extent of encorafenib exposure was not altered in the presence of a gastlic pH-altering agent (rabeprazole). Distribution Encorafenib is moderately (86.1%) bound to human plasma proteins in vitro. Following a single oral dose of 100 mg [¹⁴C] encorafenib in healthy subjects, the mean (SD) blood-to-plasma concentration ratio is 0.58 (0.02) and the mean (CV%) apparent volume of distribution (Vz/F) of encorafenib is 226 L (32.7%).

SHELF LIFE:

Do not use Braftovi after the expiry date which is stated on the blister foil and canon after "EXP". The expiry date refers to the last day of that month.

STORAGE AND HANDLING:

Store below 300C. Store in the original package in order to protect from moisture.

Further details can be found in the full prescribing information. Full Prescribing Information is available upon request.

REFERENCE:

Braftovi 50 ,^{s662_c1} 75 mg_Egypt LPD_(Revision Date July 2022). Egyptian Drug Leaflet Approval Date: 12-February-2023.^{s661_c2}

- Always read the full prescribing information.^{s663_c6}
- Healthcare professionals are asked to report any suspected adverse reactions to Egyptian pharmacovigilance center (EPVC) ^{s664_c10} pv.report@edaegypt.gov.eg Pfizer Reporting email: EGY. ^{s666_c8} AEReporting@pfizer.com
- Braftovi 50 ,^{s667_c1} 75 mg Egyptian Drug Authority Leaflet Approval Date: 12-February-2023 ^{s668_c9}

Mektovi® Abbreviated Prescribing Information / Summary of Product Information

TARGET AUDIENCE: For Healthcare Professionals

[Mektovi]® Abbreviated Prescribing Information / Summary of Product Information

GENERIC NAME: Binimetonib

PRESENTATION: 15 mg film-coated tablets

NATURE AND CONTENT OF THE CONTAINER:

Carton box containing 7 blisters, each of 12 tablets (Pack of 84 tablets).

INDICATION(s):

Binimetonib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

DOSAGE AND ADMINISTRATION:

The recommended dose of binimetonib is 45 mg (three 15 mg tablets) twice daily, corresponding to a total daily dose of 90 mg approximately 12 hours apart.

MISSED DOSES:

If a dose of binimetonib is missed, it should not be taken if it is less than 6 hours until the next dose is due.

SPECIAL POPULATION:

Elderly patients No dose adjustment is required for patients aged 65 years and older. Hepatic impairment No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh A). As encorafenib is not recommended in patients with moderate (Child Pugh B) or severe

hepatic impairment

(Child-Pugh C), administration of binimetonib is not recommended in these patients.

Renal impairment

No dose adjustment is recommended for patients with renal impairment.

Paediatric population The safety and efficacy of binimetonib in children and adolescents have not yet been established. No data are available

FERTILITY, PREGNANCY AND LACTATION:

Women of child bearing potential/Contraception in females: Women of childbearing potential must use effective contraception during treatment with binimetonib and for at least 1 month following the last dose.

Pregnancy

There are no data from the use of binimetonib in pregnant women. Studies in animals have shown reproductive toxicity. Binimetonib is not recommended during pregnancy and in women of child bearing potential not using contraception. If binimetonib is used during pregnancy, or if the patient becomes pregnant while taking binimetonib, the patient should be informed of the potential hazard to the foetus.

Breast-feeding

It is unknown whether binimetonib or its metabolite are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Mektovi therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility

There are no data on the effect on fertility in humans for binimetonib.

CONTRAINDICATIONS:

Hypersensitivity to the active substance or to any of the excipients.

WARNING AND PRECAUTIONS:

Binimetonib is to be given in combination with encorafenib. For additional information on warnings and precautions associated with encorafenib treatment, see section 4.4 of encorafenib SmPC.

BRAF mutation testing

Before taking binimetonib in combination with encorafenib, patients must have BRAF V600 mutation confirmed by validated test. The efficacy and safety of binimetonib in combination with encorafenib have been established only in patients with tumours expressing BRAF V600E and V600K mutations. Binimetonib in combination with encorafenib should not be used in patients with wild type BRAF malignant melanoma. Binimetonib in combination with encorafenib in patients who have progressed on a BRAF inhibitor There are limited data for use of the combination of binimetonib with encorafenib in patients who have progressed on a prior BRAF inhibitor given for the treatment of unresectable or metastatic melanoma with BRAF V600 mutation. These data show that the efficacy of the combination would be lower in these patients. Binimetonib in combination with encorafenib in patients with brain metastases There are limited efficacy data with the combination of binimetonib and

Mektovi® Abbreviated Prescribing Information / Summary of Product Information

encorafenib in patients with a BRAF V600 mutant melanoma which have metastasised to the brain (see section 5.1).^{s733_c18}

Left ventricular dysfunction (LVD)

defined as symptomatic or asymptomatic decreases in ejection fraction can occur when binimatinib is administered. It is recommended that LVEF is assessed by echocardiogram or multi-gated acquisition (MUGA) scan before initiation of binimatinib, 1 month after initiation, and then at approximately 3-month intervals or more frequently as clinically indicated, while on treatment. The occurrence of LVEF decrease can be managed with treatment interruption, dose reduction or with treatment discontinuation (see section 4.2). The safety of binimatinib in combination with encorafenib has not been established in patients with a baseline LVEF that is either below 50 % or below the institutional LLN. Therefore, in these patients, binimatinib should be used with caution and for any symptomatic left ventricular dysfunction, Grade 3-4 LVEF, or absolute decrease of LVEF from baseline of 10 %, binimatinib should be discontinued and LVEF should be evaluated every 2 weeks until recovery.^{s736_c23}^{s737_c22}^{s738_c23}^{s739_c25}^{s740_c24}^{s741_c24}^{s743_c2}

Haemorrhages

including major hemorrhagic events, can occur when binimatinib is administered (see section 4.8). The risk of hemorrhage may be increased with concomitant use of anticoagulant and antiplatelet therapy. The occurrence of Grade 3 hemorrhagic events should be managed with dose interruption, reduction or treatment discontinuation (see Table 2 in section 4.2) and as clinically indicated.^{s745_c20}^{s746_c2}^{s747_c22}

Ocular toxicities

Ocular toxicities including RPED and R VO can occur when binimatinib is administered. Uveitis including ilidocyclitis and iritis have been reported in patients treated with binimatinib in combination with encorafenib (see section 4.8). Binimatinib is not recommended in patients with a history of R VO. The safety of binimatinib has not been established in patients with predisposing factors for R VO including uncontrolled glaucoma, ocular hypertension, uncontrolled diabetes mellitus or a history of hyperviscosity or hypercoagulability syndromes. Therefore, binimatinib should be used with caution in these patients. Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, a prompt ophthalmologic examination is recommended. The occurrence of symptomatic RPED can be managed with treatment interruption, dose reduction or with treatment discontinuation (see Table 1 in section 4.2). Binimatinib should be permanently discontinued with the occurrence of R VO (see Table 1 in section 4.2). If during treatment patient develops uveitis, see section 4.2 of encorafenib SmPC for guidance. CK elevation and rhabdomyolysis Asymptomatic CK elevations are seen in patients treated with binimatinib (see section 4.8), and, rhabdomyolysis was uncommonly reported. Special attention should be paid to patients with neuromuscular conditions associated with CK elevation and rhabdomyolysis. CK and creatinine levels should be monitored monthly during the first 6 months of treatment and as clinically indicated. The patient should be advised to maintain an adequate fluid intake during treatment. Depending on the severity of symptoms, degree of CK elevation or creatinine elevation, dose reduction, dose interruption or pulmonary discontinuation of binimatinib may be required (see Table 1 in section 4.2).^{s749_c2}^{s750_c24}^{s751_c26}^{s752_c22}^{s753_c22}^{s754_c22}^{s755_c22}^{s756_c19}^{s758_c25}^{s759_c24}^{s760_c23}^{s761_c23}^{s763_c1}^{s764_c23}

Hypertension

Hypertension, or worsening of pre-existing hypertension, can occur with the use of binimatinib. Blood pressure should be measured at baseline and monitored during treatment, with control of hypertension by standard therapy as appropriate. In case of severe hypertension, temporarily interruption of binimatinib is recommended until hypertension is controlled (see Table 2 in section 4.2).^{s766_c1}^{s767_c1}^{s768_c22}^{s769_c1}^{s770_c20}

Venous thromboembolism (VTE)

VTE can occur when binimatinib is administered (see section 4.8). Binimatinib should be used with caution in patients who are at risk for, or who have a history of VTE. If during treatment patient develops VTE or pulmonary embolism, it should be managed with dose interruption, reduction or treatment discontinuation (see Table 1 in section 4.2).^{s773_c3}^{s774_c30}^{s775_c23}

Pneumonitis/Interstitial lung disease

Pneumonitis/ILD can occur with binimatinib. Treatment with binimatinib should be withheld in patients with suspected pneumonitis or ILD, including patients presenting new or progressive pulmonary symptoms or findings such as cough, dyspnoea, hypoxia, reticular opacities or pulmonary infiltrates (see Table 1 in section 4.2). Binimatinib should be permanently discontinued in patients diagnosed with treatment related pneumonitis or ILD.^{s777_c2}^{s779_c20}^{s780_c22}^{s782_c15}

New primary malignancies

cutaneous and non-cutaneous, have been observed in patients treated with BRAF inhibitors and can occur when binimatinib is administered in combination with encorafenib (see section 4.8).^{s783_c4}^{s784_c21}^{s786_c3}

Cutaneous malignancies

such as cutaneous squamous cell carcinoma (cuSCC) including keratoacanthoma has been observed in patients treated with binimatinib when used in combination with encorafenib. Dermatologic evaluations should be performed prior to initiation of therapy with binimatinib in combination with encorafenib, every 2 months.^{s787_c4}^{s788_c20}^{s789_c1}^{s791_c1}^{s790_c20}

Mektovi® Abbreviated Prescribing Information / Summary of Product Information

while on therapy and for up to 6 months following discontinuation of the combination. Suspicious skin lesions should be managed with dermatologic excision and dermatopathologic evaluation. Patients should be instructed to immediately inform their physicians if new skin lesions develop. Binimetonib and encorafenib should be continued without any dose modifications. Non-cutaneous malignancies Based on its mechanism of action, encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms. Patients receiving binimetonib in combination with encorafenib should undergo a head and neck examination, chest/abdomen computerised tomography (CT) scan, anal and pelvic examinations (for women) and complete blood cell counts prior to initiation, during and at the end of treatment as clinically appropriate. permanent discontinuation of binimetonib and encorafenib should be considered in patients who develops RAS mutation-positive non-cutaneous malignancies. Benefits and risks should be carefully considered before administering binimetonib in combination with encorafenib to patients with a prior or concurrent cancer associated with RAS mutation.

Liver laboratory abnormalities

Liver laboratory abnormalities including AST and ALT elevations can occur with binimetonib (see section 4.8). Liver laboratory values should be monitored before initiation of binimetonib and encorafenib and at least monthly during the 6 first months of treatment, and then as clinically indicated. Liver laboratory abnormalities should be managed with dose interruption, reduction or treatment discontinuation (see Table 1 in section 4.2).

Hepatic impairment

Liver metabolism mainly via glucuronidation is the primarily route of elimination of binimetonib (see section 5.2). As encorafenib is not recommended in patients with moderate (Child Pugh B) and severe hepatic impairment (Child Pugh C), administration of binimetonib is not recommended in these patients (see sections 4.2 and 5.2).

Lactose intolerance

Mektovi contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

EXCIPIENTS: Excipient with known effect: Each film-coated tablet contains 133.5 mg of lactose monohydrate. For the full list of excipients, see section 6.1 in the LPD.

EFFECT ON ABILITY TO DRIVE AND USE MACHINES:

Binimetonib has minor influence on the ability to drive or use machines. Visual disturbances have been reported in patients treated with binimetonib during clinical studies. Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse reaction that may affect their ability to drive and use machines.

DRUG INTERACTIONS:

Effects of other medicinal products on binimetonib Binimetonib is primarily metabolised through UGT1A1 mediated glucuronidation. The extent of drug interactions mediated by UGT1A1 is unlikely to be clinically relevant; however, as this has not been evaluated in a formal clinical study, UGT1A1 inducers (such as rifampicin and phenobarbital) and inhibitors (such as indinavir, atazanavir, sorafenib) should be co-administered with caution. While encorafenib is a relatively potent reversible inhibitor of UGT1A1, no differences in binimetonib exposure have been observed clinically when binimetonib is co-administered with encorafenib. Inducers of CYP1A2 enzymes (such as carbamazepine and rifampicin) and inducers of Pgp transport (such as Saint John's wort or phenytoin) may decrease binimetonib exposure, which could result in a decrease of efficacy. Effects of binimetonib on other medicinal products Binimetonib is a potential inducer of CYP1A2, and caution should be taken when it is used with sensitive substrates (such as duloxetine or theophylline). Binimetonib is a weak inhibitor of OAT 3, and caution should be taken when it is used with sensitive substrates (such as pravastatin or ciprofloxacin). Effect of UGT1A1 inducers or inhibitors on binimetonib Binimetonib is primarily metabolised through UGT1A1 mediated glucuronidation. In clinical study sub-analysis, however, there was no apparent relationship observed between binimetonib exposure and UGT1A1 mutation status. In addition, simulations to investigate the effect of 400 mg atazanavir (UGT1A1 inhibitor) on the exposure of 45 mg binimetonib predicted similar binimetonib Cmax in the presence or absence of atazanavir. Therefore, the extent of drug interactions mediated by UGT1A1 is minimal, and unlikely clinically relevant; however, as this has not been evaluated in a formal clinical study, UGT1A1 inducers or inhibitors should be administered with caution.

Effect of CYP enzymes on binimetonib

In vitro, CYP1A2 and CYP2C19 catalyse the formation of the active metabolite, AR00426032 (M3) by oxidative N-desmethylation. Effect of binimetonib on CYP substrates Binimetonib is a weak reversible inhibitor of CYP1A2 and CYP2C9. Effect of transporters on binimetonib In vitro experiments indicate that binimetonib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Inhibition of P-gp or BCRP is unlikely to result in a clinically important increase in binimetonib concentrations as binimetonib exhibits moderate to high passive permeability. Effect of binimetonib on transporters Binimetonib is a weak inhibitor of OAT3. No clinically significant drug-drug interactions caused by binimetonib on other transporters is expected. Binimetonib is metabolised by UGTs and CYP1A2 and is a substrate for Pgp. Specific inducers of these enzymes have not been studied and may result in a loss of efficacy.

Mektovi® Abbreviated Prescribing Information / Summary of Product Information

s860_c2

s859_c7

OVERDOSE: s861_c1

The highest dose of binimetinib evaluated as single agent in clinical studies was 80 mg administered orally twice daily and was associated with ocular (chorioretinopathy) and skin toxicities (dennatitis acneifonn). There is no specific treatment of overdose. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Since binimetinib is highly bound to plasma proteins, haemodialysis is likely to be ineffective in the treatment of overdose with binimetinib.

ADVERSE REACTION s868_c2

| System Organ Class | Adverse reaction | Frequency (All grades) |
|---|--|------------------------|
| Neoplasms benign, malignant and unspecified s874_c3 | Cutaneous squamous cell carcinoma ^a s872_c1 | Common |
| | Basal cell carcinoma [*] s873_c1 | Common |
| | Skin papilloma [*] s875_c3 | Common |
| Blood and lymphatic system disorders s878_c1 | Anaemia | Very common s876_c6 |
| Immune system disorders s880_c1 | Hypersensitivity ^b s879_c3 | Common |
| Nervous system disorders s882_c1 | Neuropathy peripheral [*] s881_c3 | Very common |
| | Dizziness [*] s883_c3 | Very common |
| | Headache [*] s884_c3 | Very common |
| | Dysgeusia [*] s886_c1 | Common |
| | Facial paresis ^c s887_c3 | Uncommon |
| Eye disorders s889_c1 | Visual impairment [*] s889_c3 | Very common |
| | RPED [*] s891_c4 | Very common |
| | Uveitis [*] s893_c2 | Common |
| Cardiac disorders | Left ventricular dysfunction ^d s894_c5 | Common |
| Vascular disorders s896_c1 | Haemorrhage ^e s895_c2 | Very common |
| | Hypertension [*] s898_c1 s897_c4 | Very common |
| Gastrointestinal disorders s900_c1 | Abdominal pain [*] s899_c2 | Very common |
| | Diarrhoea [*] s901_c1 s903_c2 | Very common |
| | Vomiting [*] s904_c3 | Very common |
| | Nausea | Very common s905_c5 |
| | Constipation | Very common s906_c3 |
| | Colitis ^g s907_c2 | Common |
| | Pancreatitis [*] s908_c1 | Uncommon |
| Skin and subcutaneous tissue disorders s916_c3 | Hyperkeratosis [*] s909_c3 | Very common |
| | Rash [*] s910_c1 s911_c2 | Very common |
| | Dry skin [*] s912_c1 s913_c3 | Very common |
| | Pruritus [*] s914_c2 | Very common |
| | Alopecia [*] s915_c2 | Very common |
| | Photosensitivity [*] s917_c2 | Common |
| | Dermatitis acneiform [*] s918_c2 | Common |
| | Palmar-plantar erythrodysesthesia syndrome (PPES) [*] s920_c2 s921_c2 | Common |

Mektovi® Abbreviated Prescribing Information / Summary of Product Information

| | | |
|---|---|-------------|
| | Erythema* | Common |
| | Panniculitis* | Common |
| Musculoskeletal and connective tissue disorders | Arthralgia* | Very common |
| | Muscular disorders/Myalgia ^b | Very common |
| | Back pain | Very common |
| | Pain in extremity | Very common |
| | Rhabdomyolysis | Uncommon |
| | Renal failure* | Common |
| General disorders and administration site conditions | Pyrexia* | Very common |
| | Peripheral oedema ⁱ | Very common |
| | Fatigue* | Very common |
| Investigations | Blood creatine phosphokinase increased | Very Common |
| | Transaminase increased* | Very Common |
| | Gamma-glutamyl transferase increased* | Very Common |
| | Blood creatinine increased* | Common |
| | Blood alkaline phosphatase increased | Common |
| | Amylase increased | Common |
| | Lipase increased | Common |

DOSE MODIFICATIONS:

The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation. For patients receiving 45 mg binimatinib twice daily, the recommended reduced dose of binimatinib is 30 mg twice daily. Dose reduction below 30 mg twice daily is not recommended. Therapy should be discontinued if the patient is not able to tolerate 30 mg orally twice daily. If the adverse reaction that resulted in a dose reduction is under effective management, dose re-escalation to 45 mg twice daily may be considered. Dose re-escalation to 45 mg twice daily is not recommended if the dose reduction is due to left ventricular dysfunction (LVD) or any Grade 4 toxicity. If treatment-related toxicities occur when binimatinib is used in combination with encorafenib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose reductions are necessary for encorafenib only (adverse reactions primarily related to encorafenib) are: palmar-plantar erythrodysesthesia syndrome (PPES), uveitis including iritis and ridocyclitis and QTc prolongation. If one of these toxicities occurs, see section 4.2. of encorafenib Summary of Product Characteristics (SmPC) for dose modification instructions for encorafenib. If binimatinib is temporarily interrupted, encorafenib should be reduced to 300 mg once daily during the time of binimatinib dose interruption as encorafenib is not well-tolerated at the dose of 450 mg as a single agent. If binimatinib is permanently discontinued, encorafenib should be discontinued. If encorafenib is temporally interrupted (see section 4.2 of encorafenib SmPC), binimatinib should be interrupted. If encorafenib is permanently discontinued, then binimatinib should be discontinued. For information on the posology and recommended dose modifications of encorafenib, see section 4.2 of encorafenib SmPC.

PHARMACEUTICAL PRECAUTIONS Special precautions for disposal

Keep out of the sight and reach of children. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PHARMACOKINETICS / PHARMACODYNAMICS:

The mean (CV %) Cmax,ss was 654 ng/mL (34.7 %) and mean AUC_{0-ss} was 2.35 ug.h/mL (28.0 %) in combination with encorafenib as estimated by population PK modelling. After oral administration, binimatinib is rapidly absorbed with a median Tmax of 1.5 hours Binimatinib pharmacokinetics have been shown to be approximately dose-linear. The mean (CV %) apparent clearance (CL/F) of binimatinib was 28.2 L/h (17.5 %). The median (range) binimatinib terminal half-life (T 1/2) was 8.66 h (8.10 to 13.6 h). SHELF LIFE: Do not use Mektovi after the expiry date which is stated on the blister foil and carton after "EXP". The expiry date refers to the last day of that month.

Mektovi® Abbreviated Prescribing Information / Summary of Product Information

STORAGE AND HANDLING:

Store below 300C.

Further details can be found in the full prescribing information. Full Prescribing Information is available upon request.

REFERENCE:

Mektovi_(15 mg)_Egypt LPD_(Revision Date September-2021). Egyptian Drug Authority Leaflet Approval Date: 22-March-2023

- Always read the full prescribing information.
- Healthcare professionals are asked to report any suspected adverse reactions to Egyptian pharmacovigilance center (EPVC) pv.report@edaegypt.gov.eg Pfizer Reporting email: EGY.AEReporting@pfizer.com
- (Mektovi 15 mg) Egyptian Drug Authority. EDA Leaflet Approval date: 22-March-2023.



Further information is available upon request
Pfizer Service Company BV
Cairo, Egypt Scientific Office
5th settlement, Cairo Festival city, Taha Hussein street, Podium Building number 4, 5th floor
Postal code:11835, Cairo, Egypt



**ADVERTISING/PROMOTIONAL MATERIAL APPROVAL FORM** s1020_c4

| [1] Product Names: BRAFTOVI MEKTOVI | [2] Type of promotion: s1021_c7 Digital Sales Presentation (DSP) s1022_c6 | | |
|---|--|-------------------------------------|---------------------------------|
| [3] Identification No : PP-BMK-EGY-0003 | [5] Date of Piece 12/12/2023 | Date of Expiry 3/3/2026 s1024_c3 | [6] Other Identifier: s1023_c14 |
| [7] Description: s1025_c2 Localized From Global Marterial "PP-BMK-SAU-0001" s1026_c5 | | | |
| Marketing Representative s1027_c2 | | | |
| [8] Approved by: s1028_c3 I have reviewed the attached promotional material or activity and certify that it meets the requirements set forth in the s1029_c20 Global Policy on Interactions with Healthcare Professionals and the Policy on Preparing, Reviewing and Approving s1030_c15 Promotional Activities and/or Materials. s1031_c4 | | | |
| In addition, for our Pfizer Country Office, we have reviewed the promotional material or activity and s1032_c16 certify that it meets all local laws and regulations and complies with local ethical and medical standards. s1033_c17 | | | |
| Name | Date | Role s1034_c4 | |
| Name: Salma Farghaly (salma.farghaly@pfizer.com) on s1035_c5 behalf of Mostafa Nada Title: s1037_c1 | 26-Mar-2024 14:02:19 GMT+0000 Operation Acceptance s1036_c10 | | |