ビラフトビカプセル50mg
ビラフトビカプセル75mg
に関する資料

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1.5 起原又は発見の経緯及び開発の経緯

小野薬品工業株式会社

1.5　起原又は発見の経緯及び開発の経緯

エンコラフェニブの開発の経緯図を図 1.5-1 に示した。

1.5.1　品質に関する試験

本申請に際して、品質に関して新たに提出する資料はない。

1.5.2　非臨床試験

本申請に際して、非臨床試験に関して新たに提出する資料はない。

1.5.3　臨床試験

本申請の臨床試験に係る開発の経緯は、［2.5.1］に記載した。

図 1.5-1　エンコラフェニブの開発の経緯図

試験項目			実施会社		2020 年	2021 年	2022 年	2023 年	2024 年	2025 年
			ONO	Pfizer						
臨床#	第III相試験	ONO-7702-03/C4221015 試験	―	●	⑫			⑫	⑫	①

本申請の臨床データパッケージに含まれる試験を記載した。
ONO：小野薬品工業株式会社、Pfizer：Pfizer Inc.
囲み数値は左から順に、治験開始月（最初の被験者の最初の来院月）、奏効率主解析データカットオフ月、本一変申請月及び無増悪生存期間主解析データカットオフ月を表す。

1.6 外国における使用状況等に関する資料

小野薬品工業株式会社

1.6　外国における使用状況等に関する資料

1.6.1　外国における使用状況

エンコラフェニブはビニメチニブとの併用療法で、米国では BRAF V600E 若しくは V600K 変異陽性の切除不能又は遠隔転移を有する悪性黒色腫、及び BRAF V600E 変異陽性の遠隔転移を有する非小細胞肺がん、欧州では BRAF V600 変異陽性の切除不能又は遠隔転移を有する悪性黒色腫、及び BRAF V600E 変異陽性の遠隔転移を有する非小細胞肺がんに関する効能・効果で承認されている。また、エンコラフェニブはセツキシマブとの併用療法で、米国及び欧州で BRAF V600E 変異陽性の遠隔転移を有する結腸・直腸がんに関する効能・効果で承認されている。

エンコラフェニブは、2025 年 6 月現在、米国、欧州連合（EU）、アイスランド、アルゼンチン、イスラエル、オーストラリア、カナダ、スイス、ノルウェー、ブラジル、リヒテンシュタイン、英国、韓国及び日本等を含めた 69 の国又は地域で承認されている。主要な既承認国として米国及び欧州におけるエンコラフェニブの使用状況を表 1.6-1 に示した。

今回日本で製造販売承認事項一部変更承認申請するエンコラフェニブの効能又は効果、並びに用法及び用量について、米国では Pfizer 社が 2024 年 12 月 20 日に迅速承認を取得している。効能又は効果は「セツキシマブ及び mFOLFOX6 との併用で、FDA が承認した検査法で検出された BRAF V600E 変異陽性の遠隔転移を有する CRC 患者の治療」、用法及び用量は「疾患進行又は許容できない毒性が認められるまで、セツキシマブの隔週投与及び mFOLFOX6（フルオロウラシル、ロイコボリン及びオキサリプラチン）との併用で、300 mg（75 mg を 4 カプセル）で 1 日 1 回経口投与する。」である。

表 1.6-1　主要な既承認国における使用状況

国名	販売名	剤型・含量	承認年月日	効能・効果	用法・用量
米国	BRAFTOVI®	硬ゼラチンカプセル： ・75 mg	2018 年 6 月 27 日	BRAFTOVI は binimetinib との併用療法で、FDA の承認した検査法により検出された BRAF V600E 若しくは V600K 変異陽性の切除不能又は遠隔転移を有する悪性黒色腫患者の治療を適応とする。	BRAFTOVI の推奨用量は、疾患進行又は許容できない毒性が認められるまで、binimetinib との併用療法で、450 mg（75 mg を 6 カプセル）を 1 日 1 回経口投与とする。
			2020 年 4 月 8 日	BRAFTOVI はセツキシマブとの併用療法で、FDA の承認した検査法により検出された BRAF V600E 変異陽性の遠隔転移を有する結腸・直腸がん（CRC）成人患者の治療を適応とする。	BRAFTOVI の推奨用量は、疾患進行又は許容できない毒性が認められるまで、セツキシマブとの併用療法で、300 mg（75 mg を 4 カプセル）を 1 日 1 回経口投与とする。
			2023 年 10 月 11 日	BRAFTOVI は binimetinib との併用療法で、FDA の承認した検査法により検出された BRAF V600E 変異陽性の遠隔転移を有する非小細胞肺がん（NSCLC）成人患者の治療を適応とする。	BRAFTOVI の推奨用量は、疾患進行又は許容できない毒性が認められるまで、binimetinib との併用療法で、450 mg（75 mg を 6 カプセル）を 1 日 1 回経口投与とする。

1.6 外国における使用状況等に関する資料
エンコラフェニブ　mCRC 一次治療

			2024 年 12 月 20 日	BRAFTOVI はセツキシマブ及び mFOLFOX6 との併用療法で、FDA が承認した検査法により検出された BRAF V600E 変異陽性の遠隔転移を有する CRC 患者の治療を適応とする。 本適応症は、奏効率及び奏効の持続性に基づき迅速承認された。本適応症に対する承認の継続は、検証的試験における臨床的ベネフィットの検証及び説明を条件とする。	BRAFTOVI の推奨用量は、疾患進行又は許容できない毒性が認められるまで、セツキシマブの隔週投与及び mFOLFOX6（フルオロウラシル、ロイコボリン及びオキサリプラチン）の隔週投与との併用療法で、300 mg（75 mg を 4 カプセル）を 1 日 1 回経口投与とする。
欧州[*1]	Braftovi 50 mg hard capsules Braftovi 75 mg hard capsules	硬カプセル 1 カプセル当たり encorafenib を 50 mg 又は 75 mg を含有	2018 年 9 月 20 日	Binimetinib との併用療法で、BRAF V600 変異陽性の切除不能又は遠隔転移を有する悪性黒色腫成人患者の治療	Encorafenib の推奨用量は、binimetinib との併用療法で、450 mg（75 mg を 6 カプセル）を 1 日 1 回経口投与とする。
			2020 年 6 月 3 日	セツキシマブとの併用療法で、BRAF V600E 変異陽性で全身療法による前治療歴があり遠隔転移を有する CRC 成人患者の治療	Encorafenib の推奨用量は、セツキシマブとの併用療法で、300 mg（75 mg を 4 カプセル）を 1 日 1 回経口投与とする。
			2024 年 8 月 30 日	Binimetinib との併用療法で、BRAF V600E 変異陽性の遠隔転移を有する NSCLC 成人患者の治療	Encorafenib の推奨用量は、binimetinib との併用療法で、450 mg（75 mg を 6 カプセル）を 1 日 1 回経口投与とする。

*1：EU 加盟 27 カ国、リヒテンシュタイン、アイスランド及びノルウェー

1.6.1.1　　米国添付文書（2025 年 3 月）の概要

1　効能及び効果

1.1　*BRAF V600E* 若しくは *V600K* 変異陽性の切除不能又は遠隔転移を有する悪性黒色腫

BRAFTOVI は binimetinib との併用療法で、FDA の承認した検査法により検出された *BRAF V600E* 若しくは *V600K* 変異陽性の切除不能又は遠隔転移を有する悪性黒色腫患者の治療を適応とする*［用法及び用量（2.1）参照］*。

1.2　*BRAF V600E* 変異陽性の遠隔転移を有する結腸・直腸がん（mCRC）

- BRAFTOVI はセツキシマブ及び mFOLFOX6 との併用療法で、FDA の承認した検査法により検出された *BRAF V600E* 遺伝子変異陽性の遠隔転移を有する CRC 患者の治療を適応とする*［用法及び用量（2.1）参照］*。
    - 本適応は奏効率及び奏効期間に基づき迅速承認で承認される*［臨床成績（14.2）参照］*。本適応に対する承認の継続は、検証的試験での臨床的有用性の検証及び説明を条件とする。
- BRAFTOVI はセツキシマブとの併用療法で、前治療後の、FDA の承認した検査法により検出された *BRAF V600E* 遺伝子変異陽性の mCRC 成人患者の治療を適応とする*［用法及び用量（2.1）参照］*。

1.3　*BRAF V600E* 変異陽性の遠隔転移を有する非小細胞肺がん（NSCLC）

BRAFTOVI は binimetinib との併用療法で、FDA の承認した検査法により検出された *BRAF V600E* 遺伝子変異陽性の遠隔転移を有する NSCLC 成人患者の治療を適応とする*［用法及び用量（2.1）参照］*。

1.4　使用の制限

BRAFTOVI は、BRAF 野生型悪性黒色腫、BRAF 野生型 CRC、又は BRAF 野生型 NSCLC の患者の治療を適応としない*［警告及び使用上の注意（5.2）参照］*。

2　用法及び用量

2.1　患者選択

BRAF V600E 又は *V600K* 変異陽性の切除不能又は遠隔転移を有する悪性黒色腫

BRAFTOVI の投与を開始する前に腫瘍検体の *BRAF V600E* 又は *V600K* 変異の有無を確認する*［警告及び使用上の注意（5.2）、臨床成績（14.1）参照］*。悪性黒色腫の *BRAF V600E* 及び *V600K* 変異を検出するために FDA が承認した検査法に関する情報は以下で確認できる：

http://www.fda.gov/CompanionDiagnostics

BRAF V600E 変異陽性の遠隔転移を有する CRC

BRAFTOVI の投与を開始する前に血漿又は腫瘍の検体の *BRAF V600E* 遺伝子変異の有無を確

認する*［警告及び使用上の注意（5.2）、臨床成績（14.2、14.3）参照］*。血漿検体で変異が検出されない場合、腫瘍細胞を検査する。CRC の *BRAF V600E* 遺伝子変異を検出するために FDA が承認した検査法に関する情報は以下で確認できる：http://www.fda.gov/CcompanionDiagnostics。

BRAF V600E 変異陽性の遠隔転移を有する NSCLC

BRAFTOVI の投与を開始する前に腫瘍又は血漿検体の *BRAF V600E* 変異の有無を確認する*［警告及び使用上の注意（5.2）、臨床成績（14.3）参照］*。もし、血漿検体で変異が確認できない場合は、腫瘍検体で確認する。NSCLC の *BRAF V600E* 変異を検出するために FDA が承認した検査法に関する情報は以下で確認できる：http://www.fda.gov/CompanionDiagnostics

2.2 *BRAF V600E* 又は *V600K* 変異陽性の切除不能又は遠隔転移を有する悪性黒色腫及び *BRAF V600E* 変異陽性の遠隔転移を有する NSCLC に対する推奨用量

BRAFTOVI の推奨用量は、binimetinib との併用療法で、疾患進行又は許容できない毒性が認められるまで、450 mg（75 mg を 6 カプセル）を 1 日 1 回経口投与とする。Binimetinib の推奨投与情報については binimetinib の添付文書を参照のこと。

2.3 *BRAF V600E* 変異陽性の遠隔転移を有する CRC に対する推奨用量

BRAFTOVI の推奨用量は、セツキシマブの隔週投与及び mFOLFOX6（フルオロウラシル、ロイコボリン、及びオキサリプラチン）の隔週投与との併用療法で*［臨床成績（14.2）参照］*、*又は*セツキシマブとの週 1 回投与との併用療法で*［臨床成績（14.3）参照］*、疾患進行又は許容できない毒性が認められるまで、300 mg（75 mg を 4 カプセル）を 1 日 1 回経口投与とする。

2.4 投与

BRAFTOVI は、食事のタイミングに関係なく投与可能である*［臨床薬理（12.3）参照］*。

BRAFTOVI の服用を忘れた場合は、次回投与まで 12 時間以内であれば服用しない。

BRAFTOVI を服用後に嘔吐した場合の追加投与は行わず、次回投与を予定どおり行う。

2.5 副作用に対する用量の調節

BRAF V600E 又は *V600K* 変異陽性の切除不能又は遠隔転移を有する悪性黒色腫又は *BRAF V600E* 変異陽性の遠隔転移を有する NSCLC

Binimetinib の投与を中断する場合、binimetinib の投与再開まで、BRAFTOVI の投与量を最大 300 mg（75 mg を 4 カプセル）、1 日 1 回に減量する*［警告及び使用上の注意（5.9）参照］*。

BRAFTOVI の副作用に対する減量を表 1 に示す。

表 1：副作用に対して推奨される BRAFTOVI の減量 - 悪性黒色腫又は NSCLC

措置	推奨用量
初回の減量	300 mg（75 mg を 4 カプセル）を 1 日 1 回経口投与
2 回目の減量	225 mg（75 mg を 3 カプセル）を 1 日 1 回経口投与
以降の調節	BRAFTOVI 225 mg（75 mg を 3 カプセル）の 1 日 1 回投与に不耐である場合、投与を中止する。

BRAF V600E 変異陽性の遠隔転移を有する CRC

セツキシマブの投与を中止する場合、BRAFTOVI の投与を中止する。

BRAFTOVI の副作用に対する減量を表 2 に示す。

表 2：副作用に対して推奨される BRAFTOVI の減量 - CRC

措置	推奨用量
初回の減量	225 mg（75 mg を 3 カプセル）を 1 日 1 回経口投与
2 回目の減量	150 mg（75 mg を 2 カプセル）を 1 日 1 回経口投与
以降の調節	BRAFTOVI 150 mg（75 mg を 2 カプセル）の 1 日 1 回投与に不耐である場合、投与を中止する。

BRAF V600E 又は *V600K* 変異陽性の切除不能又は遠隔転移を有する悪性黒色腫、*BRAF V600E* 変異陽性の遠隔転移を有する CRC 又は *BRAF V600E* 変異陽性の NSCLC

BRAFTOVI の副作用に対する用量調節を表 3 に示す。

表 3：副作用に対して推奨される BRAFTOVI の用量調節

副作用の重症度 [a]	BRAFTOVI の用量調節
新規の原発性悪性腫瘍［警告及び使用上の注意（5.1）参照］	
RAS 遺伝子変異陽性の非皮膚悪性腫瘍	BRAFTOVI の投与を中止する。
心筋症［警告及び使用上の注意（5.3）参照］	
● 症候性うっ血性心不全又はベースラインから 20%を超える LVEF 絶対値低下かつ LLN 未満	BRAFTOVI の用量を 1 段階減量する*［用法及び用量（2.3）参照］*。 ● LVEF が少なくとも施設基準下限値まで改善し、ベースラインと比較した絶対値が 10%以下となった場合は、減量して BRAFTOVI の投与を継続する*［用法及び用量（2.3）参照］*。 ● 改善が認められない場合、少なくとも施設基準下限値まで改善し、かつベースラインと比較した絶対値が 10%以下になるまで BRAFTOVI の投与を中断し、その後、減量した用量又はさらに減量した用量で投与を再開する。
肝毒性［警告及び使用上の注意（5.4）参照］	
● グレード 2 の AST 又は ALT 増加	BRAFTOVI の用量を維持する。 4 週間以内に改善しない場合、BRAFTOVI の投与を中断し、グレード 0～1 又は治療前／ベースライン値に改善した後に、同じ用量で投与を再開する。
● グレード 3 又	*その他の副作用*を参照。

は 4 の AST 又は ALT 増加	
ぶどう膜炎［警告及び使用上の注意（5.6）参照］	
● グレード 1～3	グレード 1～2 のぶどう膜炎が特異的眼治療に反応しない場合、又はグレード 3 のぶどう膜炎の場合、BRAFTOVI の投与を最長 6 週間中断する。 ● 改善した場合、同じ用量又は減量した用量で投与を再開する。 ● 改善しない場合、BRAFTOVI の投与を中止する。
● グレード 4	BRAFTOVI の投与を中止する。
QTc 延長［警告及び使用上の注意（5.7）参照］	
● QTcF が 500 ms 超かつベースラインから 60 ms 以下の延長	QTcF が 500 ms 以下となるまで BRAFTOVI の投与を中断する。減量して投与を再開する。 ● 2 回以上再発した場合は BRAFTOVI の投与を中止する。
● QTcF が 500 ms 超かつベースラインから 60 ms 超の延長	BRAFTOVI の投与を中止する。
皮膚（手足皮膚反応［HFSR］以外）［副作用（6.1）参照］	
● グレード 2	2 週間以内に改善しない場合、グレード 0～1 となるまで BRAFTOVI の投与を中断する。同じ用量で投与を再開する。
● グレード 3	グレード 0～1 となるまで BRAFTOVI の投与を中断する。初発は同じ用量、再発は減量した用量で投与を再開する。
● グレード 4	BRAFTOVI の投与を中止する。
その他の副作用（出血を含む）［警告及び使用上の注意（5）参照］及び HFSR［副作用（6.1）参照］）[b]	
● 再発でグレード 2 又は ● 初発でグレード 3	● BRAFTOVI の投与を最長 4 週間中断する。グレード 0～1 又は治療前／ベースライン値に改善した場合、減量した用量で投与を再開する。 ● 改善しない場合、BRAFTOVI の投与を中止する。
● 初発でグレード 4	BRAFTOVI の投与を中止する、又は BRAFTOVI の投与を最長 4 週間中断する。 ● グレード 0～1 又は治療前／ベースライン値に改善した場合、用量を減量して投与を再開する。 ● 改善しない場合、BRAFTOVI の投与を中止する。
● 再発でグレード 3	BRAFTOVI の投与中止を検討する。
● 再発でグレード 4	BRAFTOVI の投与を中止する。

a. 米国国立がん研究所有害事象共通用語規準（NCI CTCAE）v 4.03

b. 以下に対しては binimetinib 又はセツキシマブとの併用療法での BRAFTOVI の用量調節は推奨しない：新規の原発性皮膚悪性腫瘍；ぶどう膜炎、虹彩炎及び虹彩毛様体炎以外の眼障害；間質性肺疾患／肺臓炎；クレアチンホスホキナーゼ（CPK）増加；横紋筋融解症；静脈血栓塞栓症

Binimetinib 又はセツキシマブの副作用に対する用量調節については各製剤の添付文書を適宜

参照のこと。

2.6　強い又は中程度の CYP3A4 阻害剤の併用時の用量調節

BRAFTOVI の投与期間中は、強い又は中程度の CYP3A4 阻害剤の併用を避けること。強い又は中程度の CYP3A4 阻害剤の併用が避けられない場合、表 4 に従って BRAFTOVI の用量を減量する。CYP3A4 阻害剤の投与終了から消失半減期の 3～5 倍の期間が経過した後に、CYP3A4 阻害剤の投与開始前の用量での BRAFTOVI の投与を再開する*［薬物相互作用（7.1）、臨床薬理（12.3）参照］*。

表 4：強い又は中程度の CYP3A4 阻害剤の併用時に推奨される BRAFTOVI の減量

現在の 1 日投与量 [a]	中程度の CYP3A4 阻害剤併用時の用量	強い CYP3A4 阻害剤併用時の用量
450 mg	225 mg（75 mg を 3 カプセル）	150 mg（75 mg を 2 カプセル）
300 mg	150 mg（75 mg を 2 カプセル）	75 mg
225 mg	75 mg	75 mg
150 mg	75 mg	75 mg[b]

a 現在の 1 日投与量は、適応別に規定した BRAFTOVI の推奨用量又は表 1（悪性黒色腫）及び表 2（CRC）で推奨した副作用に応じて減量した BRAFTOVI の推奨用量を示す。
b 強い CYP3A4 阻害剤を併用投与した場合の BRAFTOVI の 75 mg 投与時の曝露量は、CYP3A4 阻害剤を併用せずに BRAFTOVI 150 mg を投与した場合よりも高く、CYP3A4 阻害剤を併用せずに BRAFTOVI 225 mg を投与した場合と同程度であると予想される。強い CYP3A4 阻害剤と BRAFTOVI 150 mg との併用時は、患者に副作用が認められないかを注意深く観察し、臨床的に判断すること。

3　剤形及び含量

カプセル：75 mg、硬ゼラチン、ベージュ色のキャップに図案化した「A」、白色のボディーに「LGX 75 mg」を表示。

4　禁忌

なし

5　警告及び使用上の注意

5.1　新規の原発性悪性腫瘍

BRAF 阻害剤の投与を受けた患者で新規の原発性悪性腫瘍（皮膚及び非皮膚）が観察されており、BRAFTOVI でも発現する可能性がある。

皮膚悪性腫瘍

COLUMBUS 試験で、BRAFTOVI と binimetinib の併用療法を受けた患者の 2.6%でケラトアカントーマ（KA）を含む皮膚扁平上皮癌（cuSCC）が発現し、1.6%で基底細胞癌が発現した。cuSCC/KA の初回発現までの期間の中央値は 5.8 カ月（範囲：1～9 カ月）であった*［副作用（6.1）参照］*。

BRAFTOVI の単剤療法を受けた患者では、患者の 8%で cuSCC/KA、1%で基底細胞癌、5%で新規の原発性悪性黒色腫が報告された。
BEACON CRC 試験では、CRC 患者の 1.4%に cuSCC/KA が発現し、BRAFTOVI とセツキシマブの併用療法を受けた患者の 1.4%で新規の原発性悪性黒色腫が報告された。
PHAROS 試験では、BRAFTOVI と binimetinib の併用療法を受けた患者のそれぞれ 2%で cuSCC 及び皮膚乳頭腫が報告された。
BREAKWATER 試験では、BRAFTOV とセツキシマブ及び mFOLFOX6 の併用療法を受けた患者で、皮膚乳頭腫が 2.6%、基底細胞癌が 1.3%、皮膚有棘細胞癌が 0.9%、ケラトアカントーマが 0.4%、及び悪性黒色腫 in situ が 0.4%で報告された。
投与開始前、投与期間中は 2 カ月間隔及び投与中止 6 カ月後まで皮膚科評価を実施する。疑わしい皮膚病変に対しては切除及び皮膚病理評価を行う。新規の原発性皮膚悪性腫瘍に対する用量調節は推奨しない。
非皮膚悪性腫瘍
BRAFTOVI はその作用機序から、遺伝子変異又は他の機序による RAS 活性化に伴い悪性腫瘍を促進する可能性がある*［警告及び使用上の注意（5.2）参照］*。BRAFTOVI を投与中の患者に非皮膚悪性腫瘍の徴候や症状がないか観察すること。RAS 遺伝子変異陽性の非皮膚悪性腫瘍に対しては BRAFTOVI の投与を中止する*［用法及び用量（2.5）参照］*。

5.2　BRAF 野生型腫瘍における腫瘍促進

In vitro 試験で、BRAF 阻害剤に曝露した BRAF 野生型細胞における MAP キナーゼシグナル伝達の逆説的な活性化と細胞増殖の増大が証明されている。BRAFTOVI の投与を開始する前に *BRAF V600E* 又は *V600K* 変異の存在を確認すること*［効能及び効果（1）、用法及び用量（2.1）参照］*。

5.3　心筋症

BRAFTOVI と binimetinib の併用療法を受けた患者で、症候性又は無症候性の駆出率低下を伴う左室機能不全として心筋症が報告されている。COLUMBUS 試験で、BRAFTOVI と binimetinib の併用療法を受けた患者の 7%で心筋症のエビデンス（心エコー又は MUGA スキャンで検出された、施設基準値下限を下回る LVEF 低下かつベースラインから 10%以上の LVEF 絶対値低下）が認められた。グレード 3 の左室機能不全が患者の 1.6%に発現した。
BRAFTOVI と binimetinib の併用療法を受けた患者において、左室機能不全（全グレード）が最初に発現するまでの期間の中央値は 3.6 カ月（範囲：0~21 カ月）であった。BRAFTOVI と binimetinib の併用療法を受けた患者の 87%で心筋症が回復した。

PHAROS 試験では、BRAFTOVI と binimetinib の併用療法を受けた患者の 11%で心筋症のエビデンス（心エコー又は MUGA スキャンで検出された、施設基準値下限を下回る LVEF 低下かつベースラインから 10%以上の LVEF 絶対値低下）が認められた。グレード 3 の左室機能不全が患者の 1%に発現した。BRAFTOVI と binimetinib の併用療法を受けた患者の 82%で心筋症が回復した。

心エコー又は MUGA スキャンによる駆出率の評価は、投与開始前、投与開始 1 カ月後、及び投与期間中は 2~3 カ月ごとに行う。ベースラインの駆出率が 50%未満又は施設基準値下限（LLN）未満の患者における BRAFTOVI と binimetinib の併用療法の安全性は確立されていない。BRAFTOVI を投与する際は、心血管リスク因子を有する患者を注意深くモニタリングすること。

副作用の重症度に基づいて投与中断、減量又は投与中止を行う*［用法及び用量（2.3）、副作用（6.1）参照］*。

5.4　肝毒性

BRAFTOVI と binimetinib の併用投与により肝毒性が発現する可能性がある。COLUMBUS 試験で、BRAFTOVI と binimetinib の併用療法を受けた患者におけるグレード 3 又は 4 の肝機能検査値上昇の発現率は、アラニンアミノトランスフェラーゼ（ALT）が 6%、アスパラギン酸アミノトランスフェラーゼ（AST）が 2.6%、アルカリホスファターゼが 0.5%であった。PHAROS 試験で BRAFTOVI と binimetinib の併用療法を受けた患者におけるグレード 3 又は 4 の肝機能検査値上昇の発現率は、AST が 10%、ALT が 9%、アルカリホスファターゼが 3.2%であった。

BREAKWATER 試験では、BRAFTOVI とセツキシマブ及び mFOLFOX6 の併用療法を受けたされた患者におけるグレード 3 又は 4 の肝機能検査値上昇の発生率は、アルカリホスファターゼが 2.2%、ALT が 1.3%、AST が 0.9%であった。

BRAFTOVI の投与開始前、投与期間中は月 1 回、及び臨床的に必要な場合は肝機能検査値をモニタリングする。副作用の重症度に基づいて投与中断、減量又は投与中止を行う*［用法及び用量（2.3）、副作用（6.1）参照］*。

5.5　出血

COLUMBUS 試験で、BRAFTOVI と binimetinib の併用療法を受けた患者の 19%に出血が認められた。グレード 3 以上の出血は患者の 3.2%で認められた。最も高頻度に認められた出血事象は消化管出血であり、直腸出血（4.2%）、血便排泄（3.1%）及び痔出血（1%）が含まれた。新規又は進行性の脳転移がある状況下での致死的な頭蓋内出血が患者の 1.6%で認

められた。
BEACON CRC 試験では、BRAFTOVI とセツキシマブの併用療法を受けた患者の 19%で出血が認められた。グレード 3 以上の出血は 1.9%で認められ、致死的な消化管出血は 0.5%で認められた。最も高頻度に認められた出血の事象は鼻出血（6.9%）、血便排泄（2.3%）及び直腸出血（2.3%）であった。
PHAROS 試験で、BRAFTOVI と binimetinib の併用療法を受けた患者の 12%で出血が認められ、この中に致死的な頭蓋内出血（1%）も含まれた。グレード 3 又は 4 の出血は患者の 4.1%に発現した。主な出血の事象は肛門出血及び血胸（各 2%）であった。
BREAKWATER 試験では、BRAFTOVI とセツキシマブ及び mFOLFOX6 の併用療法を受けた患者の 30%で出血が認められ、グレード 3 又は 4 の出血は患者の 3%で認められた。
副作用の重症度に基づいて投与中断、減量又は投与中止を行う*［用法及び用量（2.5）、副作用（6.1）参照］*。

5.6　ぶどう膜炎

BRAFTOVI と binimetinib の併用療法を受けた患者で、虹彩炎及び虹彩毛様体炎を含むぶどう膜炎が報告されている。COLUMBUS 試験で、BRAFTOVI と binimetinib の併用療法を受けた患者におけるぶどう膜炎の発現率は 4%であった。PHAROS 試験で、BRAFTOVI と binimetinib の併用療法を受けた患者におけるぶどう膜炎の発現率は 1%であった。
各来院時に視覚症状がないか評価する。視覚障害の新規発現や悪化がないか評価し、新規又は持続的な眼科所見を追跡するため、定期的に眼科評価を実施する。副作用の重症度に基づいて投与中断、減量又は投与中止を行う*［用法及び用量（2.5）、副作用（6.1）参照］*。

5.7　QT 延長

BRAFTOVI による用量依存的な QTc 間隔延長が一部の患者で認められる*［臨床薬理（12.2）参照］*。COLUMBUS 試験で、BRAFTOVI と binimetinib の併用療法を受けた患者の 0.5%（1/192）で 500 ms 超への QTcF 延長が測定された。PHAROS 試験で、BRAFTOVI と binimetinib の併用療法を受けた患者の 2.1%（2/95）で 500 ms 超への QTcF 延長が測定された。
BREAKWATER 試験では、BRAFTOVI とセツキシマブ及び mFOLFOX6 の併用療法を受けた患者の 3.6%（8/222）で 500 ms 超への QTcF 延長が測定された。
既知の QT 延長症候群、臨床的に問題となる徐脈性不整脈、重症又はコントロール不良の心不全を有する患者や、QT 延長に対して他の医薬品の投与を受けている患者など、QTc 延長が既に認められる患者及び QTc 延長を発現する重大なリスクを有する患者を監視する。

BRAFTOVI の投与前及び投与中の低カリウム血症及び低マグネシウム血症を補正する。500 ms 超の QTc に対して投与中断、減量又は投与中止を行う*［用法及び用量（2.5）、副作用（6.1）参照］*。

5.8　胚・胎児毒性

BRAFTOVI はその作用機序から、妊婦に投与した場合、胎児に害を及ぼす可能性がある。推奨用量である 450 mg でのヒト曝露量の約 26 倍（ラット）及び 178 倍（ウサギ）の曝露量に相当する用量以上で、encorafenib はラット及びウサギで胚・胎児の発育変化を生じ、ウサギで堕胎作用を示した。これよりも低い用量での明らかな所見はなかった。

妊婦及び妊娠可能な女性に胎児への潜在的なリスクを説明すること。BRAFTOVI はホルモン避妊法を無効化する可能性があるため、生殖可能な女性には BRAFTOVI の投与期間中及び最終投与後 2 週間は有効な非ホルモン避妊法を用いるよう指導する*［特定の患者集団への投与（8.1、8.3）参照］*。

5.9　BRAFTOVI の単剤療法に伴うリスク

BRAFTOVI の単剤療法では、BRAFTOVI と binimetinib の併用療法に比べて、ある特定の副作用のリスクが増加する。COLUMBUS 試験では、グレード 3 又は 4 の皮膚反応が、BRAFTOVI と binimetinib の併用療法を受けた患者の 2%で認められたのに対して、BRAFTOVI の単剤療法を受けた患者では 21%で認められた*［警告及び使用上の注意（5.1）、副作用（6.1）参照］*。

Binimetinib の投与を一時中断又は中止する場合、推奨に従い BRAFTOVI の用量を減量する*［用法及び用量（2.5）参照］*。

5.10　併用療法に伴うリスク

BRAFTOVI は binimetinib との併用、セツキシマブとの併用、又はセツキシマブ及び mFOLFOX6 との併用レジメンの一部として適応される。その他のリスク情報については binimetinib、セツキシマブ及び mFOLFOX6 の個々の製剤成分の添付文書を参照のこと。

6　副作用

以下の副作用について本文書の別項に記載した。

- 新規の原発性悪性腫瘍*［警告及び使用上の注意（5.1）参照］*
- BRAF 野生型腫瘍における腫瘍促進*［警告及び使用上の注意（5.2）参照］*
- 心筋症*［警告及び使用上の注意（5.3）参照］*

- 肝毒性*［警告及び使用上の注意（5.4）参照］*
- 出血*［警告及び使用上の注意（5.5）参照］*
- ぶどう膜炎*［警告及び使用上の注意（5.6）参照］*
- QT 延長*［警告及び使用上の注意（5.7）参照］*
- 胚・胎児毒性*［警告及び使用上の注意（5.8）参照］*
- BRAFTOVI の単独投与に伴うリスク*［警告及び使用上の注意（5.9）参照］*
- 併用投与に伴うリスク*［警告及び使用上の注意（5.10）参照］*

6.1　臨床試験における使用経験

臨床試験はさまざまな実施条件のもとで実施され、ある薬剤の臨床試験で観察される副作用の発現率は他の薬剤の臨床試験で認められた副作用の発現率と直接的に比較することは不可能であり、実診療で観察される発現率を反映していない可能性もある。

BRAF V600E 又は *V600K* 変異陽性の切除不能又は遠隔転移を有する悪性黒色腫

無作為化非盲検実薬対照試験（COLUMBUS）で、BRAFTOVI（450 mg、1 日 1 回）と binimetinib（45 mg、1 日 2 回）の併用療法を受けた *BRAF V600* 変異陽性の切除不能又は遠隔転移を有する悪性黒色腫患者 192 名における BRAFTOVI と binimetinib の併用療法の安全性が記述されている。

COLUMBUS 試験*［臨床成績（14.1）参照］*では、ジルベール症候群、左室駆出率異常、QTc 延長（＞480 msec）、コントロール不良の高血圧の既往及び網膜静脈閉塞の既往又は合併を有する患者を除外した。曝露期間の中央値は、BRAFTOVI と binimetinib の併用療法を受けた患者で 11.8 カ月、ベムラフェニブの投与を受けた患者で 6.2 カ月であった。

BRAFTOVI と binimetinib の併用療法を受けた患者で最も高頻度（25%以上）に発現した副作用は、疲労、悪心、嘔吐、腹痛及び関節痛であった。

BRAFTOVI の投与中断に至った副作用は BRAFTOVI と binimetinib の併用療法を受けた患者の 30%で認められ、最も高頻度であったのは、悪心（7%）、嘔吐（7%）及び発熱（4%）であった。BRAFTOVI の減量に至った副作用は、BRAFTOVI と binimetinib の併用療法を受けた患者の 14%で認められ、最も高頻度であったのは関節痛（2%）、疲労（2%）及び悪心（2%）であった。BRAFTOVI と binimetinib の併用療法を受けた患者の 5%で BRAFTOVI の投与中止に至った副作用が発現した。最も高頻度であったのは、出血（2%）及び頭痛（1%）であった。

COLUMBUS 試験で特定された副作用及び臨床検査値異常をそれぞれ表 5 及び表 6 に示す。表 5 に示したいずれの副作用に関して、COLUMBUS 試験のデザインは BRAFTOVI と binimetinib の併用療法をベムラフェニブと比較して副作用発現率の統計的有意差を証明する

ことを目的としていない。

表 5：COLUMBUS 試験で BRAFTOVI と binimetinib の併用療法を受けた患者の 10%以上に発現した副作用 [a]

副作用	BRAFTOVI と binimetinib の併用療法 N=192		ベムラフェニブ N=186	
	全グレード（%）	グレード 3 及び 4[b]（%）	全グレード（%）	グレード 3 及び 4（%）
一般・全身障害および投与部位の状態				
疲労[c]	43	3	46	6
発熱[c]	18	4	30	0
胃腸障害				
悪心	41	2	34	2
嘔吐[c]	30	2	16	1
腹痛[c]	28	4	16	1
便秘	22	0	6	1
筋骨格系および結合組織障害				
関節痛[c]	26	1	46	6
ミオパチー[c]	23	0	22	1
四肢痛	11	1	13	1
皮膚および皮下組織障害				
過角化[c]	23	1	49	1
発疹[c]	22	1	53	13
皮膚乾燥[c]	16	0	26	0
脱毛症[c]	14	0	38	0
そう痒症[c]	13	1	21	1
神経系障害				
頭痛[c]	22	2	20	1
浮動性めまい[c]	15	3	4	0
末梢性ニューロパチー[c]	12	1	13	2
血管障害				
出血[c]	19	3	9	2

a 米国国立がん研究所 CTCAE v4.03 によるグレード
b グレード 4 の副作用は BRAFTOVI と binimetinib の併用療法群での疲労（n=1）、そう痒症（n=1）及び発疹（n=1）の

みであった。
c 関連する複数の基本語の複合

BRAFTOVI の単剤療法では、BRAFTOVI と binimetinib の併用療法に比べて、ある特定の副作用のリスクが増加する。BRAFTOVI 300 mg、1 日 1 回経口投与の単剤療法を受けた患者では、BRAFTOVI と binimetinib の併用療法を受けた患者と比較して、以下の副作用が高率（5%以上）に観察された：手掌・足底発赤知覚不全症候群（51% vs. 7%）、過角化（57% vs. 23%）、皮膚乾燥（38% vs. 16%）、紅斑（16% vs. 7%）、発疹（41% vs. 22%）、脱毛症（56% vs. 14%）、そう痒症（31% vs. 13%）、関節痛（44% vs. 26%）、ミオパチー（33% vs. 23%）、背部痛（15% vs. 9%）、味覚異常（13% vs. 6%）、ざ瘡様皮膚炎（8% vs. 3%）。

BRAFTOVI と binimetinib の併用療法を受けた患者の 10%未満に発現したその他の臨床的に重要な副作用は以下のとおりである。

神経系障害：*顔面不全麻痺*

胃腸障害：*膵炎*

皮膚および皮下組織障害：*脂肪織炎*

免疫系障害：*薬物過敏症*

表 6：COLUMBUS 試験で BRAFTOVI と binimetinib の併用療法を受けた患者の 10%以上に発現した臨床検査値異常（全グレード）[a]

臨床検査値異常	BRAFTOVI と binimetinib の併用療法 N=192		ベムラフェニブ N=186	
	全グレード（%）	グレード 3 及び 4（%）	全グレード（%）	グレード 3 及び 4（%）
血液学的検査				
貧血	36	3.6	34	2.2
白血球減少症	13	0	10	0.5
リンパ球減少症	13	2.1	30	7
好中球減少症	13	3.1	4.8	0.5
生化学検査				
クレアチニン増加	93	3.6	92	1.1
γ－グルタミルトランスフェラーゼ増加	45	11	34	4.8
ALT 増加	29	6	27	2.2
AST 増加	27	2.6	24	1.6
高血糖	28	5	20	2.7
アルカリホスファターゼ増加	21	0.5	35	2.2

低ナトリウム血症	18	3.6	15	0.5
高マグネシウム血症	10	1.0	26	0.5

a 米国国立がん研究所 CTCAE v4.03 によるグレード

セツキシマブ及び mFOLFOX6 併用の *BRAF V600E* 変異陽性の遠隔転移を有する結腸直腸癌（mCRC）

無作為化非盲検実薬対照試験（BREAKWATER）では、BRAFTOVI（300 mg、1 日 1 回）とセツキシマブ（500 mg/m^2、2 週間毎投与）及び mFOLFOX6 の併用療法を受けた *BRAF V600E* 遺伝子変異陽性の遠隔転移を有する CRC 患者 231 例における BRAFTOVI とセツキシマブ及び mFOLFOX6 の併用療法の安全性を評価した*［臨床成績（14.2）参照］*。

BREAKWATER 試験では、膵炎、軟髄膜疾患、医療介入が必要な慢性炎症性腸疾患、及び臨床的に問題となる心血管疾患［心筋梗塞、急性冠動脈症候群、NYHA クラス II 以上のうっ血性心不全、QTcF 間隔延長（480 ms 以上）、QT 延長症候群の既往など］、及び活動性の感染状態がある患者を除外した。

BRAFTOVI を投与された患者のうち、54%が 6 カ月以上曝露され、18%が 1 年以上曝露された。

BRAFTOVI とセツキシマブ及び mFOLFOX6 の併用療法を受けた患者の 38%で重篤な副作用が発現した。患者の 3%を超える重篤な副作用には腸閉塞及び発熱があった（それぞれ 3.5%）。

BRAFTOVI とセツキシマブ及び mFOLFOX6 の併用療法を受けた患者の 0.9%で致死的な消化管穿孔が発現した。

副作用により BRAFTOVI の永続的な中止が患者の 12%で生じた。患者の 1%以上で BRAFTOVI の永続的な中止に至った副作用にはリパーゼ増加があった。

副作用により BRAFTOVI の投与中断が患者の 57%で生じた。患者の 5%以上で BRAFTOVI の投与中断に至った副作用には好中球数減少、発熱、及び貧血があった。

副作用により BRAFTOVI の減量が患者の 22%で生じた。患者の 2%以上で BRAFTOVI の減量に至った副作用にはリパーゼ増加、悪心、及び嘔吐があった。

セツキシマブ及び mFOLFOX6 と併用した場合の BRAFTOVI で最も高頻度の（25%以上）副作用は末梢性ニューロパチー、悪心、疲労、発疹、下痢、食欲減退、嘔吐、出血、腹痛、及び発熱であった。

セツキシマブ及び mFOLFOX6 と併用した場合の BRAFTOVI で最も高頻度の（10%以上）グレード 3 又はグレード 4 の臨床検査値異常はリパーゼ増加、好中球数減少、ヘモグロビン減少、白血球数減少、及びブドウ糖増加であった。

BREAKWATER 試験で特定された副作用及び臨床検査値異常をそれぞれ表 7 及び表 8 に示す。

表 7：BREAKWATER 試験で BRAFTOVI とセツキシマブ及び mFOLFOX6 の併用療法を受けた患者の 10%以上に発現した副作用 [a]

副作用	BRAFTOVI とセツキシマブ及び mFOLFOX6 の併用療法 N=231		mFOLFOX6 ± ベバシズマブ又は FOLFOXIRI ± ベバシズマブ又は CAPOX ± ベバシズマブ N=228	
	全グレード (%)	グレード 3 又は 4 (%)	全グレード (%)	グレード 3 又は 4 (%)
神経系障害				
末梢性ニューロパチー[b]	62	15	53	6
頭痛	13	<1	7	0
味覚不全	12	0	14	0
神経毒性	11	5	8	0
胃腸障害				
悪心	51	3	48	3
下痢	34	1	47	4
嘔吐	33	4	21	2
腹痛 [b]	26	4	27	1
便秘	20	<1	19	<1
一般・全身障害および投与部位の状態				
疲労 [b]	49	7	38	4
発熱 [b]	26	2	14	<1
代謝および栄養障害				
食欲減退	33	2	25	1
筋骨格系および結合組織障害				
関節痛 [b]	23	1	4	0
ミオパチー[b]	14	0	7	<1
皮膚および皮下組織障害				
発疹 [b]	31	1	4	0
脱毛症	21	0	10	0
皮膚乾燥 [b]	17	0	4	0
ざ瘡様皮膚炎 [b]	17	1	1	0
皮膚色素過剰	17	0	2	0
そう痒症	11	0	3	<1
血管障害				
出血 [b]	30	3	18	1
精神障害				
不眠症 [b]	11	0	7	0

a. 米国国立がん研究所 CTCAE v4.03 によるグレード。
b. 複数の関連する用語を表す。

表 8：BREAKWATER 試験で BRAFTOVI とセツキシマブ及び mFOLFOX6 の併用療法を受けた患者の 20%以上（全グレード）に発現した臨床検査値異常 [a]

臨床検査値異常 [b]	BRAFTOVI とセツキシマブ及び mFOLFOX6 の併用療法		mFOLFOX6 ± ベバシズマブ又は FOLFOXIRI ± ベバシズマブ又は CAPOX ± ベバシズマブ	
	全グレード (%)	グレード 3 又は 4 (%)	全グレード (%)	グレード 3 又は 4 (%)
血液学的検査				
好中球数減少	63	36	60	34
白血球数減少	62	12	54	7
ヘモグロビン減少	60	13	47	5
血小板数減少	60	1	50	2
活性化部分トロンボプラスチン時間延長	57	3	38	1
INR 増加	39	1	20	1
生化学検査				
リパーゼ増加	82	51	54	25
クレアチニン増加	64	1	67	1
ブドウ糖増加	49	11	35	2
アラニンアミノトランスフェラーゼ増加	38	1	40	2
アルブミン減少	36	0	24	1
アスパラギン酸アミノトランスフェラーゼ増加	36	1	35	2
カリウム減少	33	4	19	4
アルカリホスファターゼ増加	31	2	31	1
カルシウム減少	24	4	16	2
マグネシウム減少	23	1	11	1

a. 米国国立がん研究所 CTCAE v4.03 によるグレード。
b. 比率を算出するのに用いた分母は、ベースライン及び 1 回以上の治療後の値がある患者数に基づき、220 から 227 の範囲であった。

BRAF V600E 変異陽性の遠隔転移を有する CRC

無作為化非盲検実薬対照試験（BEACON CRC）では、*BRAF V600E* 変異陽性の遠隔転移を有する CRC 患者 216 名における BRAFTOVI（300 mg、1 日 1 回）とセツキシマブ（初回用量 400 mg/m^2、以降は 250mg/m^2 を毎週投与）の併用療法の安全性を評価した。BEACON CRC 試験*［臨床試験（14.2）参照］*では、ジルベール症候群、左室駆出率異常、QTc 延長（＞480 ms）、コントロール不良の高血圧の既往及び網膜静脈閉塞の既往又は合併を有する患者を除外した。曝露期間の中央値は、BRAFTOVI とセツキシマブの併用療法を受けた患者で 4.4 カ月、イリノテカン又は 5-フルオロウラシル（5-FU）／フォリン酸（FA）／イリノテカ

ン（FOLFIRI）とセツキシマブの併用療法を受けた患者で 1.6 カ月であった。

BRAFTOVI とセツキシマブの併用療法を受けた患者で最も高頻度（25%以上）に発現した副作用は、疲労、悪心、下痢、ざ瘡様皮膚炎、腹痛、食欲減退、関節痛及び発疹であった。

BRAFTOVI の投与中断に至った副作用は BRAFTOVI とセツキシマブの併用療法を受けた患者の 33%で認められ、最も高頻度であったのは、嘔吐（4%）、疲労（4%）、悪心（4%）、発熱（3%）及び下痢（3%）であった。BRAFTOVI の減量に至った副作用は、BRAFTOVI とセツキシマブの併用療法を受けた患者の 9%で認められ、最も高頻度であったのは疲労（2%）、関節痛（2%）及び末梢性ニューロパチー（2%）であった。BRAFTOVI とセツキシマブの併用療法を受けた患者の 10%で BRAFTOVI の投与中止に至った副作用が認められたが、複数例（0.5%超）に認められた副作用はなかった。

BEACON CRC 試験で特定された副作用及び臨床検査値異常をそれぞれ表 9 及び表 10 に示す。

表 9：BEACON CRC 試験で BRAFTOVI とセツキシマブの併用療法を受けた患者の 10%以上に発現した副作用 [a]

副作用	BRAFTOVI とセツキシマブの併用療法 N=216		イリノテカン＋セツキシマブ又は FOLFIRI＋セツキシマブ N=193	
	全グレード（%）	グレード 3 以上 [b]（%）	全グレード（%）	グレード 3 以上（%）
一般・全身障害および投与部位の状態				
疲労 [c]	51	7	50	8
発熱 [c]	17	1	15	1
胃腸障害				
悪心	34	1	41	1
下痢 [c]	33	2	48	10
腹痛 [c]	30	4	32	5
嘔吐	21	1	29	3
便秘	15	0	18	1
代謝および栄養障害				
食欲減退	27	1	27	3
筋骨格系および結合組織障害				
関節痛 [c]	27	1	3	0
ミオパチー [c]	15	1	4	0
四肢痛	10	0	1	0

皮膚および皮下組織障害				
ざ瘡様皮膚炎 [c]	32	1	43	3
発疹 [c]	26	0	26	2
そう痒症 [c]	14	0	6	0
メラノサイト性母斑	14	0	0	0
皮膚乾燥 [c]	13	0	12	1
神経系障害				
頭痛 [c]	20	0	3	0
末梢性ニューロパチー[c]	12	1	6	0
血管障害				
出血 [c]	19	2	9	0
精神障害				
不眠症 [c]	13	0	6	0

a 米国国立がん研究所 CTCAE v4.03 によるグレード
b BRAFTOVI とセツキシマブの併用投与群におけるグレード 4～5 の副作用はグレード 5 の出血のみであった（n=1）。
c 複数の関連する基本語の複合を表す。

BRAFTOVI とセツキシマブの併用療法を受けた患者の 10%未満に発現したその他の臨床的に重要な副作用は以下のとおりである。

胃腸障害：*膵炎*

表 10：BEACON CRC 試験で BRAFTOVI とセツキシマブの併用療法を受けた患者の 10%以上（全グレード）に発現した臨床検査値異常 [a]

臨床検査値異常 [b]	**BRAFTOVI とセツキシマブの併用療法**		イリノテカン＋セツキシマブ又は **FOLFIRI**＋セツキシマブ	
	全グレード（%）	グレード 3 及び 4（%）	全グレード（%）	グレード 3 及び 4（%）
血液学的検査				
貧血	34	4	48	5
リンパ球減少症	24	7	35	5
活性化部分トロンボプラスチン時間増加	13	1	7	1
生化学検査				
低マグネシウム血症	19	0	22	1
アルカリホスファターゼ増加	18	4	30	7
ALT 増加	17	0	29	3

AST 増加	15	1	22	2
低カリウム血症	12	3	32	5
低ナトリウム血症	11	2	13	2

a 米国国立がん研究所 CTCAE v4.03 によるグレード
b. ベースライン時及び投与期間中に 1 回以上の臨床検査値が得られた患者数

BRAF V600E 変異陽性の遠隔転移を有する NSCLC

非盲検単群試験（PHAROS）において BRAFTOVI（450 mg 1 日 1 回）と binimetinib（45 mg 1 日 2 回）の併用療法を受けた *BRAF V600E* 変異陽性の遠隔転移を有する NSCLC 患者 98 名を対象に、BRAFTOVI と binimetinib の併用療法の安全性を評価した。

PHAROS 試験 *［臨床試験（14.3）参照］* では、左室駆出率異常、QTc 延長（＞480 ms）、コントロール不良の高血圧、及び網膜静脈閉塞の既往歴又は合併症を有する患者を除外した。

BRAFTOVI 及び binimetinib の投与期間の中央値はそれぞれ 9.2 カ月及び 8.4 カ月であった。

BRAFTOVI の投与を受けた患者で主な（25%以上）な副作用は、疲労、悪心、下痢、筋骨格痛、嘔吐、腹痛、視力障害、便秘、呼吸困難、発疹及び咳嗽であった。

BRAFTOVI の休薬に至った副作用は、BRAFTOVI の投与を受けた患者の 59%で認められた。主な事象（5%以上）は下痢（17%）、悪心（13%）、筋骨格痛、疲労（各 8%）、AST 増加（7%）、ALT 増加、貧血、出血、嘔吐（各 6%）、急性腎障害（5%）であった。

BRAFTOVI の減量に至った副作用は、BRAFTOVI の投与を受けた患者の 30%で認められた。主な事象（5%以上）は下痢、悪心（各 8%）、AST 増加及び疲労（各 5%）であった。

BRAFTOVI の投与を受けた患者の 16%が BRAFTOVI の投与中止に至った副作用を発現した。主な事象（2%以上）は下痢、筋骨格痛（各 3.1%）、疲労、発疹、悪心、視力障害及び嘔吐（各 2%）であった。BRAFTOVI の投与中止に至ったその他の副作用で、2 名以上に発現したものはなかった。

重篤な副作用は、BRAFTOVI と binimetinib の併用療法を受けた患者の 38%に発現した。2%以上に認められた重篤な副作用は、出血（6%）、下痢（4.1%）、貧血、呼吸困難、肺炎（各 3.1%）、不整脈、医療機器関連感染、浮腫、心筋梗塞及び胸水（各 2%）であった。致死的な副作用は、BRAFTOVI（450 mg 1 日 1 回）と binimetinib の併用療法を受けた患者の 2%で認められ、内訳は頭蓋内出血及び心筋梗塞（各 1%）であった。

PHAROS 試験で認められた副作用及び臨床検査値異常をそれぞれ表 11 及び表 12 に示す。

表 11：PHAROS 試験で BRAFTOVI と binimetinib の併用療法を受けた患者の 10%以上に発現した副作用 [a]

副作用	BRAFTOVI と binimetinib の併用療法 N=98	
	全グレード (%)	グレード 3 及び 4[b] (%)

一般・全身障害および投与部位の状態		
疲労[c]	61	8
浮腫[d]	23	1
発熱	22	0
胃腸障害		
悪心	58	3.1
下痢[e]	52	7
嘔吐	37	1
腹痛[f]	32	1
便秘	27	0
眼障害		
視力障害[g]	29	2
筋骨格系および結合組織障害		
筋骨格痛[h]	48	4.1
皮膚および皮下組織障害		
発疹[i]	27	3.1
そう痒症[j]	16	0
皮膚乾燥	13	0
脱毛症	12	0
呼吸器、胸郭および縦隔障害		
呼吸困難[k]	27	8
咳嗽[l]	26	0
神経系障害		
浮動性めまい[m]	17	1
頭痛	11	0
代謝および栄養障害		
食欲減退	14	1
血管障害		
出血[b, n]	12	4.1
高血圧	10	5
心臓障害		
左室機能不全／心筋症[o]	11	1

臨床検査		
体重増加	11	1
精神障害		
不眠症	10	0

a 米国国立がん研究所 CTCAE v4.03 によるグレード
b Grade 5 の出血が 1 件発現した。
c 疲労には疲労、無力症が含まれる。
d 浮腫には、末梢性浮腫、全身性浮腫、腫脹、限局性浮腫、顔面浮腫が含まれる。
e 下痢には下痢、大腸炎が含まれる。
f 腹痛には腹痛、上腹部痛、腹部不快感、心窩部不快感を含む。
g 視力障害には霧視、視力障害、硝子体浮遊物、羞明、視力低下、光視症が含まれる。
h 筋骨格痛には、背部痛、関節痛、四肢痛、筋肉痛、筋骨格系胸痛、非心臓性胸痛、頚部痛が含まれる。
i 発疹には、発疹、斑状皮疹、斑状丘疹状皮疹、丘疹性皮疹、膿疱性皮疹、ざ瘡様皮膚炎、手掌・足底発赤知覚不全症候群、湿疹、皮膚剥脱を含む。
j そう痒症にはそう痒症、陰部そう痒症が含まれる。
k 呼吸困難には、呼吸困難、労作性呼吸困難が含まれる。
l 咳嗽には、咳嗽、湿性咳嗽が含まれる。
m 浮動性めまいには、浮動性めまい、平衡障害などがある。
n 出血には、肛門出血、血胸、消化管出血、血便排泄、血尿、喀血、頭蓋内出血、前房出血、小腸出血、上部消化管出血、膣出血が含まれる。
o 左室機能不全／心筋症には、駆出率減少、心不全、うっ血性心不全が含まれる。

BRAFTOVI と binimetinib の併用療法を受けた患者の 10%未満に発現したその他の臨床的に重要な副作用は以下のとおり:

神経系障害：*末梢性ニューロパチー*、*味覚異常*、*顔面不全麻痺*

胃腸障害：*膵炎*

皮膚及び皮下組織障害：*過角化*、*紅斑*

免疫系障害：*薬物過敏症*

表 12：BRAFTOVI と binimetinib の併用療法を受けた患者の 10%以上（全グレード）に発現した臨床検査値異常 [a]

臨床検査値異常 [b]	**BRAFTOVI と binimetinib の併用療法**	
	全グレード (%)	**グレード 3 及び 4 (%)**
血液学的検査		
貧血	47	11
リンパ球減少症	24	6
血小板減少症	20	1.1
白血球減少症	12	0
好中球減少症	12	1.1
生化学検査		
クレアチニン増加	91	3.2

高血糖	48	6
クレアチニンキナーゼ増加	41	3.3
リパーゼ増加	40	14
ALT 増加	34	9
低アルブミン血症	32	0
AST 増加	31	10
アルカリフォスファターゼ増加	31	3.2
高カリウム血症	31	2.1
低ナトリウム血症	26	11
血清アミラーゼ増加	22	1.1
低カルシウム血症	12	2.1

a. 米国国立がん研究所 CTCAE v4.03 によるグレード
b. ベースライン時及び投与期間中に 1 回以上の臨床検査値が得られた患者数

7　薬物相互作用

7.1　BRAFTOVI への他剤の影響

強い又は中程度の CYP3A4 阻害剤

BRAFTOVI と強い又は中程度の CYP3A4 阻害剤の併用は、encorafenib の血漿中濃度を上昇させ、encorafenib の副作用を増強させる可能性がある*［臨床薬理（12.3）参照］*。BRAFTOVI と強い又は中程度の CYP3A4 阻害剤（グレープフルーツジュースを含む）の併用を避けること。強い又は中程度の CYP3A4 阻害剤の併用が避けられない場合は、推奨に従い BRAFTOVI の用量を減量すること*［用法及び用量（2.6）参照］*。

強い CYP3A4 誘導剤

BRAFTOVI と強い CYP3A4 誘導剤の併用は、encorafenib の血漿中濃度を低下させ、encorafenib の有効性を減弱させる可能性がある*［臨床薬理（12.3）参照］*。強い CYP3A4 誘導剤と BRAFTOVI の併用を避けること。

7.2 他剤への BRAFTOVI の影響

感受性の高い CYP3A4 基質

BRAFTOVI は定常状態で強い CYP3A4 誘導剤である。BRAFTOVI の併用は CYP3A4 基質（ホルモン性避妊薬を含む）の血漿濃度を減少させる可能性があり*［臨床薬理（12.3）参照］*、その基質の有効性を減弱させる可能性がある。血漿濃度の減少が基質の有効性減弱につながる可能性がある BRAFTOVI と CYP3A4 基質との併用投与は避けること。併用投与が

避けられない場合は、CYP3A4 基質の製品ラベル表示で推奨事項を参照すること。

OATP1B1、OATP1B3 又は BCRP の基質

BRAFTOVI と OATP1B1、OATP1B3 又は BCRP の基質となる薬剤の併用は、これらの基質の濃度が上昇し、これらの薬剤の毒性が増強するおそれがある。併用する場合は、曝露量増加を示す徴候及び症状について患者を注意深く観察し、これらの基質の用量調節を考慮すること*［臨床薬理（12.3）参照］*。

7.3　QT 間隔を延長する薬剤

BRAFTOVI では用量依存的な QTc 間隔延長が認められる*［警告及び使用上の注意（5.7）、臨床薬理（12.2）参照］*。QT/QTc 間隔延長の可能性が知られている医薬品と BRAFTOVI の併用を避けること。

8　特定の患者集団への投与

8.1　妊婦

リスクの要約

BRAFTOVI はその作用機序から、妊婦に投与した場合、胎児に害を及ぼす可能性がある*［臨床薬理（12.1）参照］*。妊娠中の BRAFTOVI の投与に関する臨床データはない。動物生殖試験で、臨床用量である 450 mg でのヒト曝露量の約 26 倍（ラット）及び 178 倍（ウサギ）相当以上の用量で、encorafenib はラット及びウサギで胚・胎児の発育変化を生じ、ウサギで堕胎作用を示した。これよりも低い用量での明らかな所見はなかった*（データ参照）*。妊婦及び妊娠可能な女性に胎児への潜在的なリスクについて説明する。

米国の一般集団で、臨床的に確認された妊娠における主要な先天性欠損及び自然流産の背景リスクは、それぞれ 2～4%及び 15～20%と推定されている。

データ

動物データ

生殖毒性試験において、20 mg/kg/日の用量（450 mg、1 日 1 回の推奨臨床用量での濃度時間曲線下面積［AUC］に基づくヒト曝露量の約 26 倍）で、encorafenib を器官形成期のラットに投与したところ、母体毒性、胎児体重減少、及び全身骨格変異の発現率増加を示した。75 mg/kg/日の用量（450 mg、1 日 1 回の推奨臨床用量での AUC に基づくヒト曝露量の約 178 倍）で、encorafenib を器官形成期の妊娠ウサギに投与したところ、母体毒性、胎児体重減少、全身骨格変異の発現率増加及び全妊娠損失を含む着床後胚損失増加を示した。正式な胎盤移行試験は実施していないが、ラット及びウサギの胎児血漿の encorafenib 曝露量は母体曝露量のそれぞれ最大 1.7%及び 0.8%までであった。

8.2　授乳婦

リスクの要約

母乳中の encorafenib 又は代謝物の存在、母乳栄養児又は母乳産生への encorafenib の影響に関するデータはない。BRAFTOVI により母乳栄養児に重篤な副作用が現れる可能性があるため、BRAFTOVI の投与期間中及び最終投与後 2 週間は授乳しないよう女性に説明する。

8.3　生殖可能な女性及び男性

BRAFTOVI を妊婦に投与すると胎児に害を及ぼすおそれがある*［特定の患者集団への投与（8.1）参照］*。

妊娠検査

BRAFTOVI の投与を開始する前に生殖可能な女性の妊娠状況を確認する*［特定の患者集団への投与（8.1）参照］*。

避妊

女性

生殖可能な女性に BRAFTOVI の投与期間中及び最終投与後 2 週間は有効な避妊法を用いるよう指導する。BRAFTOVI はホルモン避妊法を無効化する可能性があるため、非ホルモン避妊法を用いるよう患者に指導する*［薬物相互作用（7.2）参照］*。

不妊

男性

450 mg の臨床用量でのヒト曝露量の約 13 倍の用量での雄性ラットへの投与の結果に基づき、BRAFTOVI の投与は男性の生殖機能に影響を及ぼす可能性がある*［非臨床毒性（13.1）参照］*。

8.4　小児への投与

小児患者における BRAFTOVI の安全性及び有効性は確立していない。

8.5　高齢者への投与

複数の臨床試験において BRAFTOVI と binimetinib の併用療法を受けた BRAF 遺伝子変異陽性の悪性黒色腫患者 690 例のうち、20%が 65～74 歳、8%が 75 歳以上であった*［臨床試験（14.1）参照］*。

BRAFTOVI とセツキシマブ及び mFOLFOX6 の併用療法を受けた *BRAF V600E* 遺伝子変異陽性の遠隔転移を有する CRC 患者 231 例のうち、83 例（36%）が 65～75 歳、16 例（7%）が 75 歳以上であった*［臨床試験（14.2）参照］*。

BRAFTOVI とセツキシマブの併用療法を受けた *BRAF V600E* 遺伝子変異陽性の遠隔転移を有する CRC 患者 216 例のうち、62 例（29%）が 65～75 歳、20 例（9%）が 75 歳以上であった*［臨床試験（14.3）参照］*。

BRAFTOVI と binimetinib の併用療法を受けた *BRAF V600E* 遺伝子変異陽性の遠隔転移を有する NSCLC 患者 98 例のうち、62 例（63%）が 65～75 歳、20 例（20%）が 75 歳以上であった*［臨床試験（14.4）参照］*。

高齢患者における BRAFTOVI＋binimetinib、BRAFTOVI＋セツキシマブ、又は BRAFTOVI＋セツキシマブ及び mFOLFOX6 の併用療法の安全性及び有効性に、若年患者との差は全体として認められなかった。

8.6　肝機能障害

軽度の肝機能障害（Child-Pugh 分類 A）患者における BRAFTOVI の用量調節は推奨されない*［臨床薬理（12.3）参照］*。中等度（Child-Pugh 分類 B）又は重度（Child-Pugh 分類 C）の肝機能障害を有する患者における推奨用量は確立されていない。

8.7　腎機能障害

軽度及び中等度の腎機能障害（CLcr 30～＜90 mL/min）患者における BRAFTOVI の用量調節は推奨されない*［臨床薬理（12.3）参照］*。重度の腎機能障害（CLcr＜30 mL/min）患者における推奨用量は確立されていない。

10　過量投与

Encorafenib の血漿蛋白結合率が 86%であることから、BRAFTOVI を過量投与した場合の治療に血液透析は無効と考えられる。

1.6.1.2　欧州添付文書（2025 年 7 月）の概要

1. 製品名／販売名

Braftovi 50 mg 硬カプセル

Braftovi 75 mg 硬カプセル

2. 成分・含量

Braftovi 50 mg 硬カプセル

硬カプセル 1 カプセル当たり encorafenib 50 mg を含有する。

Braftovi 75 mg 硬カプセル

硬カプセル 1 カプセル当たり encorafenib 75 mg を含有する。

賦形剤の一覧は 6.1 項を参照のこと。

3. 剤形

硬カプセル（カプセル）

Braftovi 50 mg 硬カプセル

カプセルのキャップは乳橙色、ボディーはベージュ色で、キャップには図案化した「A」のロゴが、ボディーには「LGX 50mg」が印字されており、カプセル長は約 22 mm である。

Braftovi 75 mg 硬カプセル

カプセルのキャップはベージュ色、ボディーは乳白色で、キャップには図案化した「A」、ボディーには「LGX 75mg」が印字されており、カプセル長は約 23 mm である。

4. 臨床的特性

4.1 適応症

悪性黒色腫

Encorafenib は binimetinib との併用療法で、BRAF V600 遺伝子変異陽性の切除不能又は遠隔転移を有する悪性黒色腫成人患者の治療に適応される。

結腸直腸癌（CRC）

Encorafenib はセツキシマブとの併用療法で、全身療法歴のある BRAF V600E 遺伝子変異陽性の遠隔転移を有する結腸・直腸がん成人患者の治療に適応される。

非小細胞肺癌（NSCLC）

Encorafenib は binimetinib との併用療法で、BRAF V600E 遺伝子変異陽性の進行した非小細胞肺癌成人患者の治療に適応される。

4.2　用法・用量

Encorafenib の投与は、抗癌剤の使用に精通した医師の責任下で開始され、監督されなければならない。

BRAF 変異検査

患者は encorafenib を服用する前に、対応する意図された目的に従い、CE マークの付いた *in vitro* 診断（IVD）医療機器で評価した BRAF V600E 変異があることを確認されなければならない。CE マークの付いた IVD が利用できない場合は、代替となる有効な試験を使用する必要がある。

Encorafenib の有効性及び安全性は、BRAF V600E 遺伝子変異及び V600K 遺伝子変異を発現している悪性黒色腫、BRAF V600E 遺伝子変異を発現している CRC、又は BRAF V600E 遺伝子変異を発現している NSCLC 患者でのみ確立されている。BRAF 野生型悪性黒色腫患者、BRAF 野生型 CRC 患者、又は BRAF 野生型 NSCLC 患者には encorafenib を投与してはならない。

用量

悪性黒色腫及びNSCLC

Encorafenib の推奨用量は、binimetinib との併用療法で、450 mg（75 mg を 6 カプセル）を 1 日 1 回経口投与とする。

CRC

Encorafenib の推奨用量は、セツキシマブとの併用療法で、300 mg（75 mg を 4 カプセル）を 1 日 1 回経口投与とする。

用量調節

悪性黒色腫及びNSCLC

副作用を管理するうえで、減量、投与の中断及び中止が必要となる場合がある（表 1、表 3 及び表 4 を参照）。

Binimetinib の用量及び推奨される用量調節に関する情報は、binimetinib 欧州製品概要（SmPC）の 4.2 項を参照のこと。

Encorafenib を減量する場合の推奨用量を表 1 に示す。

表 1：Binimetinib との併用下で推奨される encorafenib 用量調節 - 悪性黒色腫又は NSCLC

用量レベル	**Encorafenib の用量** （binimetinib と併用）

開始用量	75 mg カプセルを 6 カプセル（450 mg）1 日 1 回
初回の減量	75 mg カプセルを 4 カプセル（300 mg）1 日 1 回
2 回目の減量	75 mg カプセルを 3 カプセル（225 mg）1 日 1 回
以降の用量調節	悪性黒色腫の適応症について： 100 mg 1 日 1 回に減量した場合のデータは限られている。 Encorafenib 100 mg（50 mg カプセルを 2 カプセル）1 日 1 回に不耐性の患者の場合は encorafenib を永続的に中止する。 NSCLC の適応症について： Encorafenib 225 mg（75 mg カプセルを 3 カプセル）1 日 1 回に不耐性の患者の場合は encorafenib を永続的に中止する。

Encorafenib 450 mg 1 日 1 回の単剤投与は推奨されない。Encorafenib 450 mg を単剤投与した場合の忍容性は低いため、binimetinib を一次中断する場合は、binimetinib を中断している間、encorafenib を 300 mg 1 日 1 回に減量する（binimetinib SmPC の 4.2 項を参照）。
Binimetinib を永続的に中止する場合は、encorafenib も中止すること。
Encorafenib を一時的に中断する場合（表 3 及び表 4 参照）は、binimetinib も中断する。
Encorafenib を永続的に中止する場合は、binimetinib も中止すること。
治験薬との因果関係を否定できない毒性が認められた場合は、encorafenib 及び binimetinib を減量、中断又は中止すること。Binimetinib が主な原因となる以下の副作用、網膜色素上皮剥離（RPED）、網膜静脈閉塞（RVO）、間質性肺疾患/肺臓炎、心機能不全、クレアチンホスホキナーゼ（CK）増加及び横紋筋融解症、並びに静脈血栓塞栓症（VTE）のいずれかの毒性が発現した場合には、binimetinib のみ用量調節が必要である。
Binimetinib の用量及び推奨される用量調節に関する情報は、binimetinib SmPC の 4.2 項を参照のこと。

CRC

副作用を管理するうえで、減量、投与の中断及び中止が必要となる場合がある（表 2、表 3 及び表 4 を参照）。
セツキシマブの用量及び推奨される用量調節に関する情報は、セツキシマブ SmPC の 4.2 項を参照のこと。
Encorafenib を減量する場合の推奨用量を表 2 に示す。

表 2：セツキシマブとの併用下で推奨される encorafenib の用量調節 - CRC

用量レベル	**Encorafenib の用量** （セツキシマブとの併用）
開始用量	75 mg カプセルを 4 カプセル（300 mg）1 日 1 回
初回の減量	75 mg カプセルを 3 カプセル（225 mg）1 日 1 回
2 回目の減量	75 mg カプセルを 2 カプセル（150 mg）1 日 1 回

Encorafenib の投与を永続的に中止する場合は、セツキシマブの投与も中止すること。

セツキシマブの投与を永続的に中止する場合、encorafenib の投与も中止すること。

悪性黒色腫、CRC 及びNSCLC

副作用が発現した場合の用量調節を表 3 及び表 4 に示す。

*新規の原発性皮膚悪性腫瘍：*Encorafenib の用量調節は不要である。

*新規の原発性非皮膚 RAS 遺伝子変異陽性悪性腫瘍：*Encorafenib の永続的中止を検討する。

表 3：特定の副作用に対して推奨される encorafenib（binimetinib 又はセツキシマブと併用）の用量調節

副作用の重症度 [a]	**Encorafenib**
皮膚反応	
● グレード 2	Encorafenib を継続する。 発疹が増悪した又は治療開始後 2 週間以内に改善しない場合は、グレード 0 又は 1 に回復するまで encorafenib を中断した後、同一用量で再開する。
● グレード 3	グレード 0 又は 1 に改善するまで encorafenib を中断した後、初発の場合は同一用量で再開し、グレード 3 の反応の再発の場合は減量して再開する。
● グレード 4	Encorafenib を永続的に中止する。
手掌・足底発赤知覚不全症候群（PPES）	
● グレード 2	Encorafenib を継続し、局所療法などの支持療法を施す。 支持療法を施しても 2 週間以内に改善しない場合は、グレード 0 又は 1 に回復するまで encorafenib を中断した後、同一用量で又は減量して再開する。
● グレード 3	Encorafenib を中断し、局所療法などの支持療法を施し、週 1 回患者を再評価する。 グレード 0 又は 1 に回復したら、encorafenib を同一用量で又は減量して再開する。
虹彩炎及び虹彩毛様体炎を含むぶどう膜炎	
● グレード 1～3	グレード 1 又は 2 のぶどう膜炎が特定の眼科治療（局所療法など）に反応しない場合又はグレード 3 のぶどう膜炎の場合、encorafenib を中断し、2 週間以内に眼科的モニタリングを継続的に実施する。 グレード 1 のぶどう膜炎がグレード 0 に改善した場合は、同一用量で投与を再開する。 グレード 2 又は 3 のぶどう膜炎がグレード 0 又は 1 に改善した場合は、減量して投与を再開する。 6 週間以内に改善が認められない場合、眼科的モニタリングを再度実施し、encorafenib の投与を中止すること。
● グレード 4	Encorafenib を永続的に中止し、眼科的モニタリングによる経過観察を実施する。

QTc 延長	
● QTcF が 500 ms 超で、治療前の値からの変化量が 60 ms 以下	Encorafenib を中断する（モニタリングに関しては 4.4 項を参照）。 QTcF が 500 ms 以下の場合、encorafenib を減量して再開する。 複数回にわたり再発する場合は encorafenib を中止する。
● QTcF が 500 ms 超で、治療前の値から 60 ms 超延長	Encorafenib を永続的に中止する（モニタリングに関しては 4.4 項を参照）。
肝機能検査値異常	
● グレード 2 のアスパラギン酸アミノトランスフェラーゼ（AST）又はアラニンアミノトランスフェラーゼ（ALT）の基準値上限（ULN）の 3 倍超～5 倍以下の値	Encorafenib を継続する。 4 週間以内に回復しない場合は、グレード 0 若しくは 1、又は治療前／ベースライン値に回復するまで encorafenib を中断した後、同一用量で再開する。
● グレード 3 の初発（AST 又は ALT が ULN の 5 倍超及び血中ビリルビンが ULN の 2 倍超）	Encorafenib を最長 4 週間中断する。 ● グレード 0 若しくは 1、又はベースライン値に改善した場合は、減量して再開する。 ● 改善しない場合は、encorafenib を永続的に中止する。
● グレード 4 の初発（AST 又は ALT が ULN の 20 倍超）	Encorafenib を最長 4 週間中断する。 ● グレード 0 若しくは 1、又はベースライン値に改善した場合は、減量して再開する。 ● 改善しない場合は、encorafenib を永続的に中止する。 又は、encorafenib を永続的に中止する。
● グレード 3 の再発（AST 又は ALT が ULN の 5 倍超及び血中ビリルビンが ULN の 2 倍超）	Encorafenib の永続的中止を検討する。
● グレード 4 の再発（AST 又は ALT が ULN の 20 倍超）	Encorafenib を永続的に中止する。

a 米国国立がん研究所有害事象共通用語規準（NCI CTCAE）v 4.03

表 4：その他の副作用に対して推奨される encorafenib（binimetinib 又はセツキシマブと併用）の用量調節

副作用の重症度	**Encorafenib**
● 再発又は許容できないグレード 2 の副作用 ● グレード 3 の副作用の初発	Encorafenib を最長 4 週間中断する。 ● グレード 0 若しくは 1、又はベースライン値に改善した場合は減量して再開する。 ● 改善しない場合は、encorafenib を永続的に中止する。
● グレード 4 の副作用の初発	Encorafenib を最長 4 週間中断する。 ● グレード 0 若しくは 1、又はベースライン値に改善した場合は、減量して再開する。 ● 改善しない場合は、encorafenib を永続的に中止する。 又は、encorafenib を永続的に中止する。
● グレード 3 の副作用の再発	Encorafenib の永続的中止を検討する。
● グレード 4 の副作用の再発	Encorafenib を永続的に中止する。

投与期間

患者が効果を得られなくなるまで、又は許容できない毒性が発現するまで投与を継続する。

飲み忘れ

Encorafenib の服用を失念した場合は、次回投与までの時間が 12 時間を超える場合のみ服用する。

嘔吐

Encorafenib を服用後に患者が嘔吐した場合、再投与は行わず、次回投与を予定どおり行う。

特別な患者集団

高齢患者

65 歳以上の患者に対して用量調節は不要である（5.2 項を参照）。

肝機能障害

軽度から重度の肝機能障害患者では、encorafenib 曝露量が増加する可能性がある（5.2 項を参照）。

軽度肝機能障害患者（Child-Pugh 分類 A）には、encorafenib を 300 mg 1 日 1 回に減量して慎重に投与する。

中等度（Child-Pugh 分類 B）又は重度（Child-Pugh 分類 C）の肝機能障害患者に対する投与は推奨されない。

腎機能障害

母集団薬物動態（PK）解析の結果によると、軽度又は中等度の腎機能障害患者に対する用量調節は不要である。重度腎機能障害患者に encorafenib を投与した臨床データはないため、用量調節が必要かどうかを判断することはできない。重度腎機能障害患者には、encorafenib を慎重に投与すべきである（4.4 項及び 5.2 項を参照）。

小児患者

小児患者及び青年期患者における encorafenib の安全性及び有効性は確立していない。利用可能なデータはない。

用法

Braftovi は経口剤である。同剤は水と一緒にカプセルのまま嚥下する。摂食に関係なく服用できる。Encorafenib はグレープフルーツジュースと一緒に服用してはならない（4.4 項及び 4.5 項を参照）。

4.3　禁忌

有効成分又は 6.1 項に挙げる賦形剤のいずれかに対する過敏症がある患者

4.4　重大な基本的注意及び慎重投与

Encorafenib は binimetinib（BRAF V600 遺伝子変異陽性の切除不能又は遠隔転移を有する悪性黒色腫患者、及び BRAF V600E 変異陽性の進行した NSCLC 患者）と併用又はセツキシマブ（BRAF V600E 遺伝子変異陽性の遠隔転移を有する CRC 患者）との併用で投与する。Binimetinib 又はセツキシマブ投与時の警告及び注意に関する詳細情報は、binimetinib SmPC 又はセツキシマブ SmPC の 4.4 項を参照のこと。

BRAF 阻害剤の投与後に疾患進行が認められた患者に対する encorafenib と binimetinib の併用投与

BRAF V600 遺伝子変異陽性の切除不能又は遠隔転移を有する悪性黒色腫に対して過去に BRAF 阻害剤を投与し、疾患進行が認められた患者については、encorafenib と binimetinib を併用投与したデータは限られている。これらのデータによると、このような患者では encorafenib と binimetinib の併用療法の有効性は低い。

脳転移を有する患者に対する encorafenib と binimetinib の併用投与

脳転移を有する BRAF V600 遺伝子変異陽性の悪性黒色腫患者又は BRAF V600E 遺伝子変異陽性の NSCLC 患者については、encorafenib と binimetinib を併用投与した場合の有効性に関するデータは限られている（5.1 項を参照）。

左室機能不全（LVD）

Encorafenib と binimetinib の併用投与によって、症候性又は無症候性の駆出率低下と定義される LVD が報告されている。左室駆出率（LVEF）評価を実施する際は心エコー又はマルチゲート（MUGA）スキャンを用い、encorafenib と binimetinib の投与開始前、投与開始後 1 カ月、以降の投与期間中は約 3 カ月ごと、ただし臨床的に必要な場合は更に高頻度で行うことが推奨される。治療期間中に LVD が発現した場合は、binimetinib SmPC の 4.2 項を参照のこと。

ベースライン時の LVEF が 50%未満又は施設基準値下限を下回る患者については、encorafenib と binimetinib を併用投与した場合の安全性は確立されていない。したがって、これらの患者には binimetinib を慎重に投与し、左室機能不全の症状、グレード 3～4 の LVEF 低下又はベースラインから 10%以上の LVEF の絶対的低下が認められた場合は binimetinib と encorafenib の投与を中止し、回復するまで 2 週ごとに LVEF を評価する。

出血

Encorafenib 投与によって、重大な出血性事象などの出血を生じる可能性がある（4.8 項を参照）。抗凝固剤及び抗血小板剤を併用した場合、出血リスクが上昇する可能性がある。グレード 3 以上の出血性事象が発現した場合及び臨床的に必要と考えられる場合は、投与中断又は投与中止によって対処する（4.2 項の表 4 を参照）。

眼毒性

Encorafenib 投与によって、ぶどう膜炎、虹彩炎及び虹彩毛様体炎などの眼毒性が発現する可能性がある。Encorafenib と binimetinib を併用投与した患者では RPED の発現も報告されている（4.8 項を参照）。

各来院時に視覚障害の新規発症又は増悪について評価する。中心視野狭窄、霧視、視力喪失など視覚障害の新規発症又は増悪が認められた場合は、眼科学的検査を速やかに実施することが推奨される。

治療期間中に虹彩毛様体炎及び虹彩炎を含むぶどう膜炎が発現した場合は、4.2 項を参照のこと。

治療期間中に患者が RPED 又は RVO を発現した場合は、指針として binimetinib SmPC の 4.2 項を参考にすること。

QT 延長

BRAF 阻害剤を投与した患者で QT 延長が観察されている。Encorafenib 投与時の QT 延長を詳細に評価した QT 試験は実施していない。

総じて、encorafenib を単剤投与した場合、心拍数の軽度上昇が認められる可能性がある。Encorafenib と binimetinib を推奨用量で投与した複数の併用投与試験及び encorafenib の単剤投与試験の結果から、encorafenib 投与によって QTc 間隔がわずかに延長する可能性が示唆される（5.1 項を参照）。

臨床的に重要な曝露量依存性の QT 延長を否定するにはデータが十分ではない。QT 延長のリスクがあるため、治療開始前及び治療期間中にはマグネシウムやカリウムなどの血清電解質異常を補正し、QT 延長のリスク因子（うっ血性心不全、徐脈性不整脈など）を制御することが推奨される。

心電図（ECG）による評価は、encorafenib の投与開始前、投与開始後 1 カ月、以降の投与期間中は約 3 カ月間隔、ただし臨床的に必要な場合は更に高頻度で実施することが推奨される。QTc 延長が認められた場合は、encorafenib を減量、投与中断又は投与中止するとともに、電解質異常の補正及びリスク因子の制御により対処することができる（4.2 項を参照）。

新たな原発性悪性腫瘍

BRAF 阻害剤を投与した患者では新たな原発性悪性腫瘍（皮膚悪性腫瘍及び非皮膚悪性腫瘍）が認められており、encorafenib を投与した場合にも発現する可能性がある（4.8 項を参照）。

皮膚悪性腫瘍

Encorafenib などの BRAF 阻害剤を投与した患者で、ケラトアカントーマなどの皮膚扁平上皮癌（cuSCC）をはじめとする皮膚悪性腫瘍が観察されている。Encorafenib などの BRAF 阻害剤を投与した患者で、新規の原発性悪性黒色腫が観察されている（4.8 項を参照）。

Encorafenib を投与する際は、治療開始前に皮膚科学的評価を実施し、治療期間中及び治療中止後 6 カ月までは 2 カ月間隔で皮膚科学的評価を実施する。疑わしい皮膚病変が認められる場合は、皮膚科学的に切除して皮膚病理学的検査を実施する。

新たな皮膚病変が出現した場合は直ちに医師に連絡するよう、患者を指導する。Encorafenib

は用量調節せずに継続する。

非皮膚悪性腫瘍

Encorafenib はその作用機序から、遺伝子変異などの機序を介した RAS 活性化に伴い悪性腫瘍を進行させる可能性がある。患者に encorafenib を投与する場合は、臨床上の必要性に応じて、頭頸部検査、胸部／腹部コンピュータ断層撮影（CT）、肛門部及び骨盤部の検査（女性の場合）並びに全血算を、投与開始前、投与期間中及び治療終了時に実施する。患者が RAS 遺伝子変異陽性の非皮膚悪性腫瘍を発現した場合は、encorafenib の永続的中止を検討する。RAS 遺伝子変異陽性の悪性腫瘍の既往歴又は現病歴を有する患者については、encorafenib を投与する前にベネフィットとリスクを慎重に検討する。

腫瘍崩壊症候群（TLS）

TLS は致死性の可能性があり、その発現は binimetinib と併用する encorafenib の使用と関係がある（4.8 項を参照）。TLS のリスク因子には腫瘍量が多いこと、既存の慢性腎不全、乏尿、脱水、低血圧、及び酸性尿がある。このような患者は厳重に監視し、臨床的に適応がある場合は迅速に治療する必要があり、予防的な水分補給を考慮する必要がある。

肝機能検査値異常

Encorafenib 投与によって、AST 及び ALT の増加を含む肝機能検査値異常が観察されている（4.8 項を参照）。Encorafenib を投与する場合は、投与開始前、投与開始後最初の 6 カ月間は月 1 回以上、その後は臨床上の必要性に応じて、肝機能検査値をモニタリングすること。肝機能検査値異常が認められた場合は、投与中断、減量又は投与中止によって対処する（4.2 項を参照）。

肝機能障害

Encorafenib は主に肝臓において代謝及び排泄されるため、軽度から重度の肝機能障害患者では、患者間でばらつきがみられるものの、encorafenib の曝露量が増加する可能性がある（5.2 項を参照）。

臨床データが存在しないため、中等度又は重度の肝機能障害患者への encorafenib 投与は推奨されない。

軽度肝機能障害の患者には、encorafenib を 300 mg 1 日 1 回にして慎重に投与する（4.2 項を参照）。

軽度肝機能障害の患者では、encorafenib に関連する毒性をより注意深くモニタリングするこ

とが推奨されるため、治療期間中は臨床検査や肝機能検査などを行い、また臨床的に必要な場合は ECG を実施する。

腎機能障害

重度腎機能障害患者に関するデータはない（4.2 項及び 5.2 項を参照）。重度腎機能障害患者には encorafenib を慎重に投与する。Encorafenib を単剤投与した場合及び binimetinib 又はセツキシマブと併用投与した場合に、クレアチニン増加が多数報告されている。急性腎障害や腎機能障害などの腎不全症例では、嘔吐や脱水を伴うことが多い。その他の要因として糖尿病や高血圧などが挙げられる。臨床上の必要性に応じて血中クレアチニンをモニタリングし、クレアチニン増加が認められた場合は用量調節又は投与中止によって対処する（4.2 項の表 4 を参照）。治療期間中は必ず十分な水分補給を行う。

Encorafenib に対する他の薬剤の影響

Encorafenib の投与期間中は強力な CYP3A 阻害剤の併用を避けるべきである。強力な CYP3A 阻害剤を併用する必要がある場合は、患者の安全性を注意深くモニタリングする（4.5 項を参照）。

中程度の CYP3A 阻害剤を encorafenib と併用する際は注意が必要である。

4.5　他剤との相互作用及びその機序

Encorafenib に対する他剤の影響

Encorafenib は主に CYP3A4 によって代謝される。

CYP3A4 阻害剤

健康被験者に中程度の CYP3A4 阻害剤（ジルチアゼム）及び強力な CYP3A4 阻害剤（ポサコナゾール）を encorafenib 単剤と併用投与した結果、血中濃度−時間曲線下面積（AUC）はそれぞれ 2 倍及び 3 倍に増加し、encorafenib の最高血中濃度（Cmax）はそれぞれ 44.6%及び 68.3%上昇した。

モデルに基づいた予測では、ポサコナゾールを反復投与した場合の AUC は同程度（3 倍に増加）で、Cmax はわずかに上昇する（2.7 倍の上昇）ことが示唆される。ケトコナゾールを投与した場合は、encorafenib 450 mg 又は 300 mg を 1 日 1 回投与した時に、AUC は約 5 倍に増加し、Cmax は 3～4 倍に上昇すると予測された。

したがって、encorafenib と強力な CYP3A4 阻害剤の併用は避けるべきである（encorafenib の曝露量が増加し、毒性が発現する可能性が高まるため。5.2 項を参照）。強力な CYP3A4 阻害剤の例としては、リトナビル、イトラコナゾール、クラリスロマイシン、テリスロマイシ

ン、ポサコナゾール、グレープフルーツジュースなどが挙げられるが、これらに限定されない。やむを得ず強力な CYP3A 阻害剤を併用する場合は、患者の安全性を注意深くモニタリングする。
中程度の CYP3A4 阻害剤を併用する場合は注意が必要である。中程度の CYP3A4 阻害剤の例としては、アミオダロン、エリスロマイシン、フルコナゾール、ジルチアゼム、アンプレナビル、イマチニブなどが挙げられるが、これらに限定されない。Encorafenib を中程度の CYP3A 阻害剤と併用する場合は、患者の安全性を注意深くモニタリングする。

CYP3A4 誘導剤
Encorafenib と強力な CYP3A4 誘導剤との併用は臨床試験で評価されなかったが、encorafenib への曝露はおそらく低下し、その結果、encorafenib の有効性が損なわれる可能性がある。強力な CYP3A4 誘導剤の例としては、カルバマゼピン、リファンピシン、フェニトイン、セントジョーンズワートなどが挙げられるが、これらに限定されない。CYP3A の誘導作用がゼロから中程度の他の薬剤への代替を検討する。

<u>他の薬剤に対する encorafenib の影響</u>
CYP 基質
Encorafenib は CYP3A4 の強力な誘導剤である。CYP3A4 の基質（ホルモン避妊薬など）と併用した場合、基質となる薬剤の効力が低下する可能性がある。治療指数が狭い CYP3A4 基質の併用が避けられない場合は、承認された SmPC に従い、これらの基質の用量を調節する。
Encorafenib は UGT1A1 阻害剤である。UGT1A1 の基質となる薬剤（ラルテグラビル、アトルバスタチン、ドルテグラビルなど）と併用する場合は、これらの薬剤の曝露量が増加する可能性があるため、注意が必要である。

Binimetinib に対する encorafenib の影響
Encorafenib は比較的強力な UGT1A1 の可逆的阻害剤であるが、binimetinib と encorafenib を併用投与しても binimetinib の曝露量に臨床的な差は認められなかった。

トランスポーター基質
In vivo において、encorafenib は OATP1B1、OATP1B3 及び／又は BCRP の阻害剤である。Encorafenib を OATP1B1、OATP1B3 又は BCRP の基質（ロスバスタチン、アトルバスタチン、メトトレキサートなど）と併用すると、濃度が上昇する可能性がある（5.2 項参照）。

In vitro では、encorafenib は他の複数のトランスポーターを阻害する可能性がある。腎臓トランスポーターOAT1、OAT3、OCT2 の基質となる薬剤（フロセミド、ペニシリンなど）、肝臓トランスポーターOCT1 の基質となる薬剤（ボセンタンなど）、及び P-gp の基質となる薬剤（ポサコナゾールなど）も曝露量が増加する可能性がある。
したがって、トランスポーターの基質であるこれらの薬剤の併用時には注意が必要である。

4.6　受精能、妊娠及び授乳

妊娠の可能性がある女性／女性の避妊

妊娠の可能性がある女性は、encorafenib の投与期間中及び最終投与から 1 カ月以上、効果的な避妊法を実施しなければならない。Encorafenib 投与によってホルモン避妊薬の効果が低下する可能性がある（4.5 項を参照）。このため、ホルモン避妊薬を使用している女性患者に対しては、encorafenib の投与期間中及び最終投与から 1 カ月以上は、バリア法（コンドームなど）などの避妊法を追加する又は別の避妊法に切り替えるよう助言する。

妊娠

妊娠女性に encorafenib を投与したデータはない。動物実験では生殖毒性が認められている（5.3 項を参照）。
妊婦及び避妊法を実施していない妊娠する可能性のある女性には、encorafenib 投与は推奨されない。妊娠中に encorafenib を投与する場合、又は encorafenib の投与期間中に患者が妊娠した場合は、胎児への危険性について患者に説明すること。

授乳

ヒトにおいて encorafenib 又はその代謝物が乳汁中に移行するかどうかは不明である。授乳期の新生児／乳児に対するリスクは否定できない。子に対する授乳のベネフィットと母に対する治療のベネフィットを考慮して、授乳を中止するか encorafenib 療法を中止するか判断しなければならない。

受精能

ヒトの受精能に対する encorafenib の影響に関するデータはない。動物実験によると、encorafenib は雄の生殖能に影響する可能性がある（5.3 項を参照）。この知見の臨床的関連性は不明であるため、精子形成障害の潜在的リスクについて男性患者に伝えること。

4.7　自動車運転及び機械操作に対する影響

Encorafenib が自動車運転及び機械操作に及ぼす影響は少ない。臨床試験では、encorafenib を投与した患者に視覚障害が報告されている。視覚障害又は自動車運転若しくは機械操作に影響を及ぼす可能性があるその他の副作用が認められた場合は、自動車運転又は機械操作を行わないよう患者に助言する（4.4 項及び 4.8 項を参照）。

4.8　好ましくない作用

安全性プロファイルの要約

BRAF V600 遺伝子変異陽性の切除不能又は遠隔転移を有する悪性黒色腫患者及び BRAF V600E 遺伝子変異陽性の進行した NSCLC 患者を含む 372 例の統合安全性集団（ISP）（以下、Combo 450 ISP と呼ぶ）に encorafenib（450 mg、1 日 1 回内服）と binimetinib（45 mg、1 日 2 回内服）を併用投与した場合の安全性を評価した。Combo 450 ISP では 274 例が BRAF V600 遺伝子変異陽性の切除不能又は遠隔転移を有する悪性黒色腫治療のため（第 II 相試験（CMEK162X2110 及び CLGX818X2109）2 件と第 III 相試験（CMEK162B2301、Part 1）1 件において）、98 例が BRAF V600E 遺伝子変異陽性の進行した NSCLC 治療のため（第 II 相試験（ARRAY-818-202）1 件において）、この併用療法を受けた（5.1 項を参照）。

Encorafenib を binimetinib と併用した場合に最も高頻度（25%以上）に発現した副作用は、疲労、悪心、下痢、嘔吐、腹痛、ミオパチー／筋疾患、及び関節痛であった。

第Ⅲ相試験（CMEK162B2301、Part 2）を基に、BRAF V600 遺伝子変異陽性の切除不能又は遠隔転移を有する悪性黒色腫患者 257 例（以下、Combo 300 群と呼ぶ）に encorafenib（300 mg、1 日 1 回内服）と binimetinib（45 mg、1 日 2 回内服）を併用投与した場合の安全性を評価した。Encorafenib 300 mg を binimetinib と併用した場合に最も高頻度（25%以上）に発現した副作用は、疲労、悪心及び下痢であった。

Encorafenib（300 mg、1 日 1 回内服）単剤投与の安全性プロファイルは、BRAF V600 遺伝子変異陽性の切除不能又は遠隔転移を有する悪性黒色腫患者 217 例（以下、併合 encorafenib 300 集団と呼ぶ）のデータに基づいている。併合 encorafenib 300 集団で最も高頻度（25%以上）に発現した副作用は、過角化、脱毛症、PPES、疲労、発疹、関節痛、皮膚乾燥、悪心、筋肉痛、頭痛、嘔吐及びそう痒症であった。

第III相試験（ARRAY-818-302）を基に、BRAF V600E 遺伝子変異陽性の遠隔転移を有する CRC 患者 216 例に encorafenib（300 mg、1 日 1 回内服）とセツキシマブ（SmPC に従って投与）を併用投与した場合の安全性を評価した。この集団で最も高頻度（25%以上）に発現した副作用は、疲労、悪心、下痢、ざ瘡様皮膚炎、腹痛、関節痛／筋骨格痛、食欲減退、発疹及び嘔吐であった。

いずれかの副作用によるすべての治験薬の投与中止率は、encorafenib 300 mg とセツキシマブを併用投与した患者の 1.9%であった。

副作用の一覧表

下表に MedDRA 器官別大分類による副作用一覧を示す。発現頻度は極めて高頻度（1/10 以上）、高頻度（1/100 以上 1/10 未満）、低頻度（1/1,000 以上 1/100 未満）、まれ（1/10,000 以上 1/1,000 未満）、極めてまれ（1/10,000 未満）及び不明（入手データからは推定不能）で表した。

各頻度の分類内では、重症度が高い順に副作用を挙げた。

表 5：副作用

頻度	**Encorafenib 300 mg 単剤投与（n=217）**	**Encorafenib 450 mg と binimetinib の併用投与（n=372）**	**Encorafenib 300 mg とセツキシマブの併用投与（n=216）**
良性、悪性および詳細不明の新生物			
極めて高頻度	皮膚乳頭腫* メラノサイト性母斑		メラノサイト性母斑
高頻度	cuSCC[a] 新規の原発性悪性黒色腫*	cuSCC[a] 皮膚乳頭腫*	cuSCC[a] 皮膚乳頭腫* 新規の原発性悪性黒色腫*
低頻度	基底細胞癌	基底細胞癌*	基底細胞癌*
血液およびリンパ系障害			
極めて高頻度		貧血	
免疫系障害			
高頻度	過敏症 [b]	過敏症 [b]	過敏症 [b]
代謝および栄養障害			
極めて高頻度	食欲減退		食欲減退
不明		腫瘍崩壊症候群	
精神障害			
極めて高頻度	不眠症		不眠症
神経系障害			
極めて高頻度	頭痛* 末梢性ニューロパチー* 味覚異常*	末梢性ニューロパチー* 浮動性めまい* 頭痛*	末梢性ニューロパチー* 頭痛*
高頻度	顔面不全麻痺 [c]	味覚不全*	浮動性めまい* 味覚不全
低頻度		顔面不全麻痺 [c]	
眼障害			

極めて高頻度		視力障害* RPED*	
高頻度		ぶどう膜炎 *	
低頻度	ぶどう膜炎*		
心臓障害			
高頻度	上室性頻脈 d	LVD[h]	上室性頻脈 d
血管障害			
極めて高頻度		出血 i 高血圧 *	出血 i
高頻度		VTE[j]	
胃腸障害			
極めて高頻度	悪心 嘔吐* 便秘	悪心 嘔吐* 便秘 腹痛* 下痢*	悪心 嘔吐* 便秘 腹痛* 下痢*
高頻度		大腸炎 k	
低頻度	膵炎*	膵炎*	膵炎*
皮膚および皮下組織障害			
極めて高頻度	PPES 過角化* 発疹* 皮膚乾燥* そう痒症* 脱毛症* 紅斑 e 皮膚色素過剰*	過角化* 発疹* 皮膚乾燥* そう痒症* 脱毛症*	ざ瘡様皮膚炎* 発疹* 皮膚乾燥* そう痒症*
高頻度	ざ瘡様皮膚炎* 皮膚剥脱 f 光線過敏症*	ざ瘡様皮膚炎* PPES 紅斑* 脂肪織炎* 光線過敏症*	皮膚色素過剰 PPES 過角化* 脱毛症 紅斑 e
低頻度			皮膚剥脱 f
筋骨格系および結合組織障害			
極めて高頻度	関節痛* 筋肉痛 g 四肢痛 背部痛	関節痛* ミオパチー／筋障害 l 四肢痛 背部痛	関節痛/筋骨格痛* ミオパチー／筋障害* 四肢痛 背部痛
高頻度	関節炎 *		
低頻度		横紋筋融解症	
腎および尿路障害			
高頻度	腎不全 *	腎不全*	腎不全*

一般・全身障害および投与部位の状態			
極めて高頻度	疲労 * 発熱*	疲労* 発熱* 末梢性浮腫 m	疲労* 発熱*
臨床検査			
極めて高頻度	γ－グルタミルトランスフェラーゼ（GGT）増加*	血中クレアチンホスホキナーゼ増加 γ－グルタミルトランスフェラーゼ（GGT）増加* トランスアミナーゼ上昇*	
高頻度	トランスアミナーゼ上昇* 血中クレアチニン増加* リパーゼ増加	血中アルカリホスファターゼ増加 血中クレアチニン増加* アミラーゼ増加 リパーゼ増加	血中クレアチニン増加* トランスアミナーゼ上昇*
低頻度	アミラーゼ増加		アミラーゼ増加 リパーゼ増加

* 2 つ以上の基本語を統合した用語
a ケラトアカントーマ、扁平上皮癌を含む。
b 血管浮腫、薬物過敏症、過敏症、過敏性血管炎、蕁麻疹、アナフィラキシー反応を含む。
c 顔面神経障害、顔面麻痺、顔面不全麻痺を含む。
d 期外収縮及び洞性頻脈を含む。
e 紅斑、全身紅斑、足底紅斑を含む。
f 剥脱性皮膚炎、皮膚剥脱、剥脱性発疹を含む。
g 筋肉痛、筋肉疲労、筋損傷、筋痙縮、筋力低下を含む。
h 左室機能不全、駆出率減少、心不全、駆出率異常を含む。
i 脳出血など様々な部位の出血を含む。
j 肺塞栓症、深部静脈血栓症、塞栓症、血栓性静脈炎、表在性血栓性静脈炎及び血栓症を含む。
k 大腸炎、潰瘍性大腸炎、腸炎及び直腸炎を含む。
l 筋肉痛、筋力低下、筋痙縮、筋損傷、ミオパチー、筋炎を含む。
m 体液貯留、末梢性浮腫、限局性浮腫を含む。

CMEK162B2301 試験の Part 2 で encorafenib 300 mg 1 日 1 回と binimetinib 45 mg 1 日 2 回（Combo 300）を併用投与した結果、併合 Combo 450 集団と比較して、貧血、末梢性ニューロパチー、出血、高血圧及びそう痒症（高頻度）、並びに大腸炎、アミラーゼ増加及びリパーゼ増加（低頻度）の副作用発現頻度が低かった。

特定の副作用の説明

皮膚悪性腫瘍

皮膚扁平上皮癌

悪性黒色腫及びNSCLC

Combo 450 ISP では、ケラトアカントーマなどの cuSCC が 3.0%（11/372）で観察された。cuSCC（全グレード）の初回発現までの期間の中央値は 6.5 カ月であった（1.0～22.8 カ月）。

併合 encorafenib 300 集団の 7.4%（16/217）で cuSCC が報告された。第Ⅲ相試験（CMEK162B2301）で cuSCC を発現した患者では、cuSCC（全グレード）初回発現までの期間の中央値は 2.3 カ月であった（0.3～12.0 カ月）。

CRC

Encorafenib 300 mg とセツキシマブの併用投与を受けた患者では、ケラトアカントーマを含む cuSCC が患者の 1.4%（3/216）に認められた。これら 3 名の患者における cuSCC（全グレード）初回発現までの期間の中央値は 0.5、0.6 及び 3.6 カ月であった。

新規の原発性悪性黒色腫

悪性黒色腫

併合 encorafenib 300 集団の 4.1%（9/217）で新たな原発性悪性黒色腫が認められ、このうちグレード 1 が 1.4%（3/217）、グレード 2 が 2.1%（4/217）、グレード 3 が 0.5%（1/217）、グレード 4 が 0.5%（1/217）であった。

CRC

Encorafenib 300 mg とセツキシマブの併用投与を受けた患者では、患者の 1.9%（4/216）に新たな原発性悪性黒色腫が発現し、グレード 2 が患者の 0.9%（2/216）に、グレード 3 が患者の 0.9%（2/216）であった。

眼に関する事象

悪性黒色腫及びNSCLC

Combo 450 集団の 3.5%（13/372）でぶどう膜炎が報告され、このうちグレード 1 が 0.5%（2/372）、グレード 2 が 2.7%（10/372）、グレード 3 が 0.3%（1/372）であった。霧視、視力低下などの視覚障害が 23.1%（86/372）で認められた。概して、ぶどう膜炎及び視覚障害は可逆性であった。

RPED が 22.3%（83/372）で認められ、大部分はグレード 1～2 で、グレード 3 は 1.6%（6/372）であった。

CMEK162B2301 試験の Part 2 では、Combo 300 群の 12.5%（32/257）で RPED が観察され、0.4%（1/257）がグレード 4 であった。

左室機能不全

悪性黒色腫及び NSCLC 患者への encorafenib と binimetinib の併用投与では、LVD の発現が

報告された（binimetinib SmPC の 4.8 項を参照）。

出血

悪性黒色腫及びNSCLC

Combo 450 ISP の 16.7%（62/372）で出血性事象が観察された。このうち大部分である 13.2%（49/372）はグレード 1 又は 2 であり、3.5%（13/372）はグレード 3 以上であった。投与中断又は減量の必要が生じた患者はほとんどいなかった（2.4%、9/372）。投与中止に至る出血性事象が 0.8%（3/372）で認められた。最も高頻度に発現した出血性事象は血尿 2.7%（10/372）、血便排泄 2.7%（10/372）及び直腸出血 2.2%（8/372）であった。死亡原因となる多臓器不全を伴う致死的な出血性胃潰瘍が 1 例に認められた。脳出血／頭蓋内出血が 1.3%（5/372）で報告され、このうち 4 例は致死的転帰に至った。いずれの事象も脳転移の新たな発現又は増悪に伴って発現した。

CMEK162B2301 試験の Part 2 では、Combo 300 群の 6.6%（17/257）で出血性事象が観察され、このうち 1.6%（4/257）はグレード 3～4 であった。

CRC

Encorafenib 300 mg とセツキシマブの併用投与を受けた患者の 21.3%（46/216）で出血性事象が観察され、1.4%（3/216）がグレード 3 であり、1 名の死亡が報告された。1.9%（4/216）の患者は投与中断又は減量となった。投与中止に至る出血性事象は 1 名（0.5%）に認められた。

最も高頻度に発現した出血性事象は、鼻出血 6.9%（15/216）、血便排泄 2.8%（6/216）、直腸出血 2.8%（6/216）及び血尿 2.8%（6/216）であった。

高血圧

悪性黒色腫及び NSCLC 患者への encorafenib と binimetinib の併用投与では、高血圧の発現が報告された（binimetinib SmPC の 4.8 項を参照）。

静脈血栓塞栓症

悪性黒色腫及び NSCLC 患者への encorafenib と binimetinib の併用投与では、VTE の発現が報告された（binimetinib SmPC の 4.8 項を参照）。

膵炎

悪性黒色腫及びNSCLC

Combo 450 ISP では膵酵素増加が報告されたが、大部分は無症候性であった。アミラーゼ増加及びリパーゼ増加がそれぞれ 4.0%（15/372）及び 7.8%（29/372）で報告された。膵炎が 0.8%（3/372）で報告された。3 例ともグレード 3 の事象が発現した。
投与中断に至った膵炎は 0.3%（1/372）であった。

CRC
Encorafenib 300 mg とセツキシマブの併用投与を受けた集団では、リパーゼ及びアミラーゼ増加を伴うグレード 3 の膵炎が 1 名（0.5%）に報告され、投与中断に至った。

皮膚反応
発疹
悪性黒色腫及びNSCLC
Combo 450 ISP では発疹が 20.4%（76/372）に発現した。大部分の事象は軽度で、グレード 3 又は 4 の事象は 1.1%（4/372）であった。発疹のため投与中止した患者は 0.8%（3/372）、投与中断又は用量調節した患者は 2.4%（9/372）であった。
併合 encorafenib 300 集団の 43.3%（94/217）で発疹が報告された。大部分の事象は軽度で、グレード 3 又は 4 の患者は 4.6%（10/217）であった。発疹のため投与中止した患者は 0.5%（1/217）、投与中断又は用量調節した患者は 7.4%（16/217）であった。

CRC
Encorafenib 300 mg とセツキシマブの併用投与を受けた患者の 30.6%（66/216）に発疹が発現した。ほとんどの事象は軽度であり、グレード 3 の事象は 0.5%（1/216）に報告された。休薬に至った発疹は 0.5%（1/216）であった。

手掌・足底発赤知覚不全症候群（PPES）
悪性黒色腫及びNSCLC
Combo 450 ISP の 5.1%（19/372）で PPES が報告された。PPES の副作用はいずれもグレード 1（2.7%）又はグレード 2（2.4%）であった。投与中断又は用量調節した患者は 1.1%（4/372）であった。
CMEK162B2301 試験の Part 2 では、Combo 300 群の 3.9%（10/257）で PPES が観察され、このうちグレード 3 は 0.4%（1/257）であった。
併合 encorafenib 300 集団の 51.6%（112/217）で PPES が報告された。大部分の事象は軽度から中等度で、グレード 1 が 12.4%（27/217）、グレード 2 が 26.7%（58/217）、グレード 3

が 12.4%（27/217）であった。PPES のため投与中止した患者は 4.1%（9/217）、投与中断又は用量調節した患者は 23.0%（50/217）であった。

CRC

Encorafenib 300 mg とセツキシマブの併用投与を受けた患者の 5.1%（11/216）に PPES が報告された。患者の 3.7%（8/216）に認められた PPES はグレード 1 であった。グレード 2 の事象は患者の 0.9%（2/216）、グレード 3 の事象は患者の 0.5%（1/216）に認められた。投与中断、用量調節又は投与中止に至った事象はなかった。

ざ瘡様皮膚炎

悪性黒色腫及びNSCLC

Encorafenib と binimetinib の併用投与では、ざ瘡様皮膚炎の発現が報告された（binimetinib SmPC の 4.8 項を参照）。

CRC

Encorafenib 300 mg とセツキシマブの併用投与を受けた患者の 33.3%（72/216）にざ瘡様皮膚炎が発現し、そのほとんどがグレード 1：25.5%（55/216）又は 2：6.9%（15/216）であった。減量又は投与中断に至った患者は 2.3%（5/216）であり、投与中止に至った例はなかった。ざ瘡様皮膚炎はおおむね可逆性であった。

光線過敏症

悪性黒色腫及びNSCLC

Combo 450 ISP の 4.3%（16/372）で光線過敏症が認められた。大部分の事象はグレード 1～2 で、グレード 3 は 0.3%（1/372）であった。投与中止に至った事象はなかった。投与中断又は用量調節に至った事象は 0.3%（1/372）であった。

併合 encorafenib 300 集団の 4.1%（9/217）で光線過敏症が報告された。いずれもグレードは 1～2 であった。投与中止、用量調節又は投与中断に至った事象はなかった。

顔面不全麻痺

悪性黒色腫及びNSCLC

Combo 450 ISP の 0.8%（3/372）で顔面不全麻痺が認められ、このうち 0.3%（1/372）がグレード 3 であった。事象は可逆性で、投与中止に至る事象は発現しなかった。投与中断又は用量調節した患者は 0.3%（1/372）であった。

併合 encorafenib 300 集団の 7.4%（16/217）で顔面不全麻痺が観察された。大部分の事象は軽度から中等度で、グレード 1 は 2.3%（5/217）、グレード 2 は 3.7%（8/217）、グレード 3 は 1.4%（3/217）であった。顔面不全麻痺の初回発現までの期間の中央値は 0.3 カ月であった（0.1～12.1 カ月）。概して、顔面不全麻痺は可逆性で、投与中止した患者は 0.9%（2/217）であった。投与中断又は用量調節した患者は 3.7%（8/217）で、コルチコステロイド投与などの対症療法を施行した患者は 5.1%（11/217）であった。

CK 増加及び横紋筋融解症

悪性黒色腫及び NSCLC 患者への encorafenib と binimetinib の併用投与では、CK 増加及び横紋筋融解症が認められた（binimetinib SmPC の 4.8 項を参照）。

腎機能障害

悪性黒色腫及びNSCLC

Combo 450 ISP の 9.4%（35/372）で軽度かつ無症候性の血中クレアチニン増加が認められ、大部分がグレード 1 であった。グレードが 3 又は 4 の患者は 0.8%（3/372）であった。Encorafenib と binimetinib を併用投与した患者の 3.5%（13/372）で急性腎障害、腎不全、及び腎機能障害を含む腎不全事象が報告され、グレード 3 又は 4 の患者は 1.9%（7/372）であった。概して、腎不全は可逆性で、投与中断、補水及びその他の全身支持療法によって回復した。

CRC

Encorafenib 300 mg とセツキシマブの併用投与を受けた患者の 2.8%（6/216）に血中クレアチニン増加が認められ、グレード 4 の 1 件を除き、すべて軽度であった。腎不全事象はグレード 3 又は 4 であり、1.9%（4/216）が急性腎障害、0.5%（1/216）が腎不全として報告された。

肝機能検査値異常

悪性黒色腫及びNSCLC

Combo 450 ISP における肝機能検査値異常の発現率は以下のとおりである。

- トランスアミナーゼ上昇：全体 16.4%（61/372）、グレード 3：6.5%（24/372）
- GGT 増加：全体 11.3%（42/372）、グレード 3～4：6.7%（25/372）

CMEK162B2301 試験 Part 2 の Combo 300 群における肝機能検査値異常の発現率は以下のとおりである。

- トランスアミナーゼ上昇：全体 13.2%（34/257）、グレード 3～4：5.4%（14/257）
- GGT 増加：全体 14.0%（36/257）、グレード 3～4：4.7%（12/257）

CRC

Encorafenib 300 mg とセツキシマブの併用投与を受けた患者の 8.8%（19/216）にトランスアミナーゼ上昇が認められ、1.4%（3/216）はグレード 3 であった。

胃腸障害

悪性黒色腫及びNSCLC

Combo 450 ISP の 41.7%（155/372）で下痢が観察され、このうち 3.8%（14/372）がグレード 3 又は 4 であった。投与中止に至った下痢は 0.8%、投与中断又は用量調節に至った下痢は 8.1%に認められた。

便秘は 24.7%（92/372）に発現し、グレードは 1 又は 2 であった。腹痛が 28.5%（106/372）で認められ、このうち 2.2%（8/372）がグレード 3 であった。悪心が 46.0%（171/372）で認められ、このうち 3.0%（11/372）がグレード 3 であった。嘔吐が 31.2%（116/372）で認められ、このうち 1.9%（7/372）がグレード 3 であった。

CMEK162B2301 試験 Part 2 の Combo 300 群では悪心が 27.2%（70/257）で認められ、このうち 1.6%（4/257）がグレード 3 であった。嘔吐が 15.2%（39/257）で認められ、このうち 0.4%（1/257）がグレード 3 であった。下痢が 28.4%（73/257）で認められ、このうち 1.6%（4/257）がグレード 3 であった。

CRC

Encorafenib 300 mg とセツキシマブの併用投与を受けた患者の 38.4%（83/216）に下痢が認められ、2.8%（6/216）がグレード 3 であった。投与中止に至った下痢は 0.5%（1/216）、投与中断又は用量調節に至った下痢は 3.7%（8/216）に認められた。

腹痛は 36.6%（79/216）に報告され、5.1%（11/216）がグレード 3 であった。悪心は 38.0%（82/216）に発現し、0.5%（1/216）がグレード 3 であった。嘔吐は 27.3%（59/216）に発現し、1.4%（3/216）がグレード 3 であった。便秘は 18.1%（39/216）に発現し、グレードは 1 又は 2 であった。

胃腸障害の多くは標準的な治療で管理が可能であった。

貧血

悪性黒色腫及びNSCLC

Combo 450 ISP の 23.1%（86/372）で貧血が報告され、このうち 7.0%（26/372）がグレード 3 又は 4 であった。貧血による投与中止例はなく、3.2%（12/372）で投与中断又は用量調節が必要となった。
CMEK162B2301 試験 Part 2 の Combo 300 群では貧血が 9.7%（25/257）で認められ、このうち 2.7%（7/257）がグレード 3～4 であった。

頭痛
悪性黒色腫及びNSCLC
Combo 450 ISP の 18.8%（70/372）で頭痛が認められ、このうち 1.1%（4/372）がグレード 3 であった。
CMEK162B2301 試験 Part 2 の Combo 300 群では頭痛が 12.1%（31/257）で認められ、このうち 0.4%（1/257）がグレード 3 であった。

CRC
Encorafenib 300 mg とセツキシマブの併用投与を受けた患者では、グレード 1 又は 2 の頭痛が 20.4%（44/216）に認められた。

疲労
悪性黒色腫及びNSCLC
Combo 450 ISP の 48.1%（179/372）で疲労が認められ、このうち 4.3%（16/372）がグレード 3 又は 4 であった。
CMEK162B2301 試験 Part 2 の Combo 300 群では疲労が 33.5%（86/257）で認められ、このうち 1.6%（4/257）がグレード 3～4 であった。

CRC
Encorafenib 300 mg とセツキシマブの併用投与を受けた患者の 56.9%（123/216）に疲労が認められ、7.9%（17/216）がグレード 3 であった。

特別な患者集団
高齢者
悪性黒色腫及びNSCLC
Combo 450 ISP（n=372）のうち 65 歳未満が 230 例（61.8%）、65～74 歳は 107 例（28.8%）、75 歳超は 35 例（9.4%）であった。高齢患者（65 歳以上）と若齢患者との間で

は、高齢患者の方が報告の頻度が高かった下痢及びそう痒症を除き、安全性及び有効性に全体的な差は認められなかった。
75 歳以上の患者の年齢サブグループでは、グレード 3 以上の副作用（62.9% vs 47.5%）、治験薬の用量調節を必要とする副作用（全グレード）（60.0% vs 48.1%）又は治療中止に至る副作用（全グレード）（25.7% vs 7.4%）が 75 歳未満よりも報告される頻度が高かった。75 歳未満の患者と比べて、75 歳以上の患者での発現が高かった主な副作用は、疲労、悪心、下痢、嘔吐、及び貧血であった。

CRC
Encorafenib 300 mg とセツキシマブの併用投与を受けた患者（216 例）のうち、134 例（62%）が 65 歳未満、62 例（28.7%）が 65～74 歳、及び 20 例（9.3%）が 75 歳以上であった。65 歳未満の患者と比べて、65 歳以上の患者での発現が高かった主な副作用は、疲労、食欲減退、及び出血であった。
CRC の集団において、75 歳以上の患者集団は非常に少数例であったため、75 歳未満の患者と比較した副作用の発現率の差は評価できなかった。

副作用が疑われる症例の報告
医薬品承認後に、副作用が疑われる症例を報告することが重要である。この報告により、医薬品のベネフィット／リスク比のモニタリングが継続できる。医療従事者は、Appendix V に記載する国の報告システムを用いて副作用が疑われる症例を報告することが求められる。

4.9　過量投与

症状
Encorafenib 600～800 mg の 1 日 1 回投与によって、14 名中 3 名で腎機能障害（グレード 3 の高クレアチン血症）が観察された。最も高用量を投与された 1 名は投薬過誤によるものであり、encorafenib 600 mg を 1 日 2 回（総量 1200 mg）服用した。当該患者で報告された副作用はグレード 1 の悪心、嘔吐及び霧視で、いずれも回復した。

管理
過量投与に対する明確な治療法はない。
Encorafenib は血漿蛋白と中程度の結合性を示すため、encorafenib の過量投与に対する治療として血液透析は無効であると考えられる。Encorafenib の既知の解毒剤はない。過量投与が生じた場合は encorafenib 投与を中断し、副作用発現と併せて腎機能をモニタリングする。必

要に応じて対症療法及び支持療法を施行する。

1.6.2　　米国の添付文書

以下に、米国添付文書の原文を添付する。

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BRAFTOVI safely and effectively. See full prescribing information for BRAFTOVI.

BRAFTOVI® (encorafenib) capsules, for oral use
Initial U.S. Approval: 2018

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2)	12/2024
Dosage and Administration (2.1, 2.3)	12/2024
Warnings and Precautions (5.1, 5.4, 5.5, 5.7, 5.10)	12/2024

----------INDICATIONS AND USAGE----------

BRAFTOVI is a kinase inhibitor indicated:

Melanoma

- in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a *BRAF V600E* or *V600K* mutation, as detected by an FDA-approved test. (1.1, 2.1)

Colorectal Cancer (CRC)

- in combination with cetuximab and mFOLFOX6, for the treatment of patients with metastatic colorectal cancer (mCRC) with a *BRAF V600E* mutation, as detected by an FDA-approved test. (1.2, 2.1)
  This indication is approved under accelerated approval based on response rate and durability of response *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
- in combination with cetuximab, for the treatment of adult patients with metastatic CRC with a *BRAF V600E* mutation, as detected by an FDA-approved test, after prior therapy. (1.2, 2.1)

Non-Small Cell Lung Cancer (NSCLC)

- in combination with binimetinib, for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with *a BRAF V600E* mutation, as detected by an FDA-approved test. (1.3, 2.1)

Limitations of Use

BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF CRC, or wild-type BRAF NSCLC. (1.4, 5.2)

----------DOSAGE AND ADMINISTRATION----------

Melanoma

- Confirm the presence of *BRAF V600E* or *V600K* mutation in tumor specimens prior to the initiation of BRAFTOVI. (2.1)
- The recommended dose is 450 mg orally once daily in combination with binimetinib. (2.2)

CRC

- Confirm the presence of *BRAF V600E* mutation in plasma or tumor specimens prior to the initiation of BRAFTOVI. (2.1)
- The recommended dose is 300 mg orally once daily in combination with cetuximab. (2.3)

NSCLC

- Confirm the presence of *BRAF V600E* mutation in tumor or plasma specimens prior to initiating BRAFTOVI. (2.1)
- The recommended dose is 450 mg orally once daily in combination with binimetinib. (2.2)

Take BRAFTOVI with or without food. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 75 mg. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- New Primary Malignancies, cutaneous and noncutaneous: Can occur. Monitor for malignancies and perform dermatologic evaluations prior to, while on therapy, and following discontinuation of treatment. (5.1)
- Tumor Promotion in BRAF Wild-Type Tumors: Increased cell proliferation can occur with BRAF inhibitors. (5.2)
- Cardiomyopathy: Assess left ventricular ejection fraction (LVEF) before initiating treatment with BRAFTOVI and binimetinib, and after one month of treatment, then every 2 to 3 months thereafter. The safety of BRAFTOVI in combination with binimetinib has not been established in patients with LVEF below 50%. (5.3)
- Hepatotoxicity: Monitor liver function tests before and during treatment with BRAFTOVI and binimetinib and as clinically indicated. (5.4)
- Hemorrhage: Major hemorrhagic events can occur in patients receiving BRAFTOVI and binimetinib. (5.5)
- Uveitis: Perform ophthalmologic evaluation at regular intervals and for any visual disturbances. (5.6)
- QT Prolongation: Monitor electrolytes before and during treatment. Correct electrolyte abnormalities and control for cardiac risk factors for QT prolongation. Withhold BRAFTOVI for QTc of 500 ms or greater. (5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females with reproductive potential of potential risk to the fetus and to use effective nonhormonal method of contraception. (5.8, 8.1, 8.3)
- Risks Associated with BRAFTOVI as a Single Agent: If binimetinib is temporarily interrupted or permanently discontinued, reduce the dose of BRAFTOVI as recommended. (5.9)
- Risks Associated with Combination Treatment: BRAFTOVI is indicated for use as part of a regimen in combination with binimetinib or cetuximab. (5.10)

----------ADVERSE REACTIONS----------

- Melanoma: Most common adverse reactions (≥25%) for BRAFTOVI, in combination with binimetinib, are fatigue, nausea, vomiting, abdominal pain, and arthralgia. (6.1)
- CRC: Most common adverse reactions (≥25%) for BRAFTOVI, in combination with cetuximab and mFOLFOX6, are peripheral neuropathy, nausea, fatigue, rash, diarrhea, decreased appetite, vomiting, hemorrhage, abdominal pain, and pyrexia. (6.1)
  Most common adverse reactions (≥25%) for BRAFTOVI, in combination with cetuximab, are fatigue, nausea, diarrhea, dermatitis acneiform, abdominal pain, decreased appetite, arthralgia, and rash. (6.1)
- NSCLC: Most common adverse reactions (≥25%) for BRAFTOVI, in combination with binimetinib, are fatigue, nausea, diarrhea, musculoskeletal pain, vomiting, abdominal pain, visual impairment, constipation, dyspnea, rash, and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong or moderate CYP3A4 inhibitors: Avoid coadministration. If unavoidable, reduce BRAFTOVI dosage. (2.6, 7.1)
- Strong CYP3A4 inducers: Avoid coadministration. (7.1)
- Sensitive CYP3A4 substrates: Avoid coadministration with CYP3A4 substrates (including hormonal contraceptives) for which a decrease in plasma concentration may lead to reduced efficacy of the substrate. (7.2)
- Transporters: Dose reductions of drugs that are substrates of OATP1B1, OATP1B3, or BCRP may be required when used concomitantly with BRAFTOVI. (7.2, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)
- Males of Reproductive Potential: BRAFTOVI may impair fertility. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2025

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Reference ID: 5548023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 *BRAF V600E* or *V600K* Mutation-Positive Unresectable or Metastatic Melanoma

BRAFTOVI is indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a *BRAF V600E* or *V600K* mutation, as detected by an FDA-approved test *[see Dosage and Administration (2.1)]*.

1.2 *BRAF V600E* Mutation-Positive Metastatic Colorectal Cancer (mCRC)

- BRAFTOVI is indicated, in combination with cetuximab and mFOLFOX6, for the treatment of patients with metastatic colorectal cancer (mCRC) with a *BRAF V600E* mutation, as detected by an FDA-approved test *[see Dosage and Administration (2.1)]*.
    - This indication is approved under accelerated approval based on response rate and durability of response *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

- BRAFTOVI is indicated, in combination with cetuximab, for the treatment of adult patients with mCRC with a *BRAF V600E* mutation, as detected by an FDA-approved test, after prior therapy *[see Dosage and Administration (2.1)]*.

1.3 *BRAF V600E* Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

BRAFTOVI is indicated, in combination with binimetinib, for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with a *BRAF V600E* mutation, as detected by an FDA-approved test *[see Dosage and Administration (2.1)]*.

1.4 Limitations of Use

BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF CRC, or wild-type BRAF NSCLC *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

BRAF V600E or *V600K* Mutation-Positive Unresectable or Metastatic Melanoma

Confirm the presence of a *BRAF V600E* or *V600K* mutation in tumor specimens prior to initiating BRAFTOVI *[see Warnings and Precautions (5.2), Clinical Studies (14.1)]*. Information on FDA-approved tests for the detection of *BRAF V600E* and *V600K* mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

Confirm the presence of a *BRAF V600E* mutation in plasma or tumor tissue prior to initiating BRAFTOVI *[see Warnings and Precautions (5.2), Clinical Studies (14.2, 14.3)]*. If no mutation is detected in a plasma specimen, test tumor tissue. Information on FDA-approved tests for the detection of *BRAF V600E* mutations in CRC is available at: http://www.fda.gov/CompanionDiagnostics.

BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

Confirm the presence of a *BRAF V600E* mutation in tumor or plasma specimens prior to initiating BRAFTOVI *[see Warnings and Precautions (5.2), Clinical Studies (14.4)]*. If no mutation is detected in a plasma specimen, test tumor tissue. Information on FDA-approved tests for the detection of *BRAF V600E* mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage for *BRAF V600E* or *V600K* Mutation-Positive Unresectable or Metastatic Melanoma and for *BRAF V600E* Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

The recommended dosage of BRAFTOVI is 450 mg (six 75 mg capsules) orally once daily in combination with binimetinib until disease progression or unacceptable toxicity. Refer to the binimetinib prescribing information for recommended binimetinib dosing information.

2.3 Recommended Dosage for *BRAF V600E* Mutation-Positive Metastatic Colorectal Cancer (CRC)

The recommended dosage of BRAFTOVI is 300 mg (four 75 mg capsules) orally once daily in combination with biweekly cetuximab and mFOLFOX6 (fluorouracil, leucovorin and oxaliplatin) *[see Clinical Studies (14.2)]* or in combination with weekly cetuximab *[see Clinical Studies (14.3)]* until disease progression or unacceptable toxicity.

2.4 Administration

BRAFTOVI may be taken with or without food *[see Clinical Pharmacology (12.3)]*. Do not take a missed dose of BRAFTOVI within 12 hours of the next dose of BRAFTOVI.

Do not take an additional dose if vomiting occurs after BRAFTOVI administration but continue with the next scheduled dose.

2.5 Dosage Modifications for Adverse Reactions

BRAF V600E or *V600K* Mutation-Positive Unresectable or Metastatic Melanoma or *BRAF V600E* Mutation-Positive Metastatic NSCLC

If binimetinib is withheld, reduce BRAFTOVI to a maximum dose of 300 mg (four 75 mg capsules) once daily until binimetinib is resumed *[see Warnings and Precautions (5.9)]*.

Dose reductions for adverse reactions associated with BRAFTOVI are presented in Table 1.

Table 1: Recommended Dose Reductions for BRAFTOVI for Adverse Reactions – Melanoma or NSCLC

Action	Recommended Dose
First Dose Reduction	300 mg (four 75 mg capsules) orally once daily
Second Dose Reduction	225 mg (three 75 mg capsules) orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate BRAFTOVI 225 mg (three 75 mg capsules) once daily

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

If cetuximab is discontinued, discontinue BRAFTOVI.

Dose reductions for adverse reactions associated with BRAFTOVI are presented in Table 2.

Table 2: Recommended Dose Reductions for BRAFTOVI for Adverse Reactions – CRC

Action	Recommended Dose
First Dose Reduction	225 mg (three 75 mg capsules) orally once daily
Second Dose Reduction	150 mg (two 75 mg capsules) orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate BRAFTOVI 150 mg (two 75 mg capsules) once daily

BRAF V600E or *V600K* Mutation-Positive Unresectable or Metastatic Melanoma, *BRAF V600E* Mutation-Positive Metastatic Colorectal Cancer (CRC), or *BRAF V600E* Mutation-Positive NSCLC

Dosage modifications for adverse reactions associated with BRAFTOVI are presented in Table 3.

Reference ID: 5548023

Table 3: Recommended Dosage Modifications for BRAFTOVI for Adverse Reactions

Severity of Adverse Reaction[a]	Dose Modification for BRAFTOVI
New Primary Malignancies [see Warnings and Precautions (5.1)]	
Noncutaneous RAS Mutation-positive Malignancies	Permanently discontinue BRAFTOVI.
Cardiomyopathy [see Warnings and Precautions (5.3)]	
• Symptomatic congestive heart failure or absolute decrease in LVEF of greater than 20% from baseline that is also below LLN	Reduce BRAFTOVI by one dose level *[see Dosage and Administration (2.3)]*. • If LVEF improves to at least institutional LLN and absolute decrease to less than or equal to 10% compared to baseline, continue BRAFTOVI at the reduced dose *[see Dosage and Administration (2.3)]*. • If no improvement, withhold BRAFTOVI until improves to at least institutional LLN and absolute decrease to less than or equal to 10% compared to baseline and then resume at the reduced dose or reduce dose an additional dose level.
Hepatotoxicity [see Warnings and Precautions (5.4)]	
• Grade 2 AST or ALT increased	Maintain BRAFTOVI dose. • If no improvement within 4 weeks, withhold BRAFTOVI until improves to Grade 0-1 or to pretreatment/baseline levels and then resume at same dose.
• Grade 3 or 4 AST or ALT increased	See *Other Adverse Reactions.*
Uveitis [see Warnings and Precautions (5.6)]	
• Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold BRAFTOVI for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue BRAFTOVI.
• Grade 4	Permanently discontinue BRAFTOVI.
QTc Prolongation [see Warnings and Precautions (5.7)]	
• QTcF greater than 500 ms and less than or equal to 60 ms increase from baseline	Withhold BRAFTOVI until QTcF less than or equal to 500 ms. Resume at reduced dose. • If more than one recurrence, permanently discontinue BRAFTOVI.
• QTcF greater than 500 ms and greater than 60 ms increase from baseline	Permanently discontinue BRAFTOVI.
Dermatologic [other than Hand-foot Skin Reaction (HFSR)] [see Adverse Reactions (6.1)]	
• Grade 2	If no improvement within 2 weeks, withhold BRAFTOVI until Grade 0-1. Resume at same dose.
• Grade 3	Withhold BRAFTOVI until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
• Grade 4	Permanently discontinue BRAFTOVI.
Other Adverse Reactions (including Hemorrhage) [see Warnings and Precautions (5)] and HFSR [see Adverse Reactions (6.1)][b]	
• Recurrent Grade 2 or • First occurrence of any Grade 3	Withhold BRAFTOVI for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline level, resume at reduced dose. • If no improvement, permanently discontinue BRAFTOVI.

Severity of Adverse Reaction[a]	Dose Modification for BRAFTOVI
• First occurrence of any Grade 4	Permanently discontinue BRAFTOVI or Withhold BRAFTOVI for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline level, then resume at reduced dose. • If no improvement, permanently discontinue BRAFTOVI.
• Recurrent Grade 3	Consider permanently discontinuing BRAFTOVI.
• Recurrent Grade 4	Permanently discontinue BRAFTOVI.

a. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
b. Dose modification of BRAFTOVI when administered with binimetinib or with cetuximab is not recommended for new primary cutaneous malignancies; ocular events other than uveitis, iritis, and iridocyclitis; interstitial lung disease/pneumonitis; creatine phosphokinase (CPK) elevation; rhabdomyolysis; and venous thromboembolism.

Refer to the binimetinib or cetuximab prescribing information for dose modifications for adverse reactions associated with each product, as appropriate.

2.6 Dose Modifications for Coadministration with Strong or Moderate CYP3A4 Inhibitors

Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors. If coadministration is unavoidable, reduce the BRAFTOVI dose according to the recommendations in Table 4. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the BRAFTOVI dose that was taken prior to initiating the CYP3A4 inhibitor *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Table 4: Recommended Dose Reductions for BRAFTOVI for Coadministration with Strong or Moderate CYP3A4 Inhibitors

Current Daily Dose[a]	Dose for Coadministration with Moderate CYP3A4 Inhibitor	Dose for Coadministration with Strong CYP3A4 Inhibitor
450 mg	225 mg (three 75 mg capsules)	150 mg (two 75 mg capsules)
300 mg	150 mg (two 75 mg capsules)	75 mg
225 mg	75 mg	75 mg
150 mg	75 mg	75 mg[b]

a. Current daily dose refers to recommended dose of BRAFTOVI based on indication or reductions for adverse reactions based on dosing recommendations in Table 1 (Melanoma) and Table 2 (CRC).
b. Encorafenib exposure at the 75 mg QD BRAFTOVI dosage when coadministered with a strong CYP3A4 inhibitor is expected to be higher than at the 150 mg QD dosage in the absence of a CYP3A4 inhibitor and similar to exposure at the 225 mg QD dosage in the absence of a CYP3A4 inhibitor. Monitor patients closely for adverse reactions and use clinical judgement when using BRAFTOVI with strong CYP3A4 inhibitors at the 150 mg dose level.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 75 mg, hard gelatin, stylized “A” on beige cap and “LGX 75mg” on white body.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 New Primary Malignancies

New primary malignancies, cutaneous and noncutaneous, have been observed in patients treated with BRAF inhibitors and can occur with BRAFTOVI.

Cutaneous Malignancies

In COLUMBUS, cutaneous squamous cell carcinoma (cuSCC), including keratoacanthoma (KA), occurred in 2.6%, and basal cell carcinoma occurred in 1.6% of patients who received BRAFTOVI in combination with binimetinib. Median time to first occurrence of cuSCC/KA was 5.8 months (range 1 to 9 months) *[see Adverse Reactions (6.1)]*.

For patients who received BRAFTOVI as a single agent, cuSCC/KA was reported in 8%, basal cell carcinoma in 1%, and a new primary melanoma in 5% of patients.

In BEACON CRC, cuSCC/KA occurred in 1.4% of patients with CRC, and a new primary melanoma occurred in 1.4% of patients who received BRAFTOVI in combination with cetuximab.

In PHAROS, cuSCC and skin papilloma, each occurred in 2% of patients who received BRAFTOVI in combination with binimetinib.

In BREAKWATER, skin papilloma was reported in 2.6%, basal cell carcinoma in 1.3%, squamous cell carcinoma of skin in 0.9%, keratoacanthoma in 0.4% and malignant melanoma in situ in 0.4% of patients who received BRAFTOVI in combination with cetuximab and mFOLFOX6.

Perform dermatologic evaluations prior to initiating treatment, every 2 months during treatment, and for up to 6 months following discontinuation of treatment. Manage suspicious skin lesions with excision and dermatopathologic evaluation. Dose modification is not recommended for new primary cutaneous malignancies.

Noncutaneous Malignancies

Based on its mechanism of action, BRAFTOVI may promote malignancies associated with activation of RAS through mutation or other mechanisms *[see Warnings and Precautions (5.2)]*. Monitor patients receiving BRAFTOVI for signs and symptoms of noncutaneous malignancies. Discontinue BRAFTOVI for RAS mutation-positive noncutaneous malignancies *[see Dosage and Administration (2.5)]*.

5.2 Tumor Promotion in BRAF Wild-Type Tumors

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells, which are exposed to BRAF inhibitors. Confirm evidence of *BRAF V600E* or *V600K* mutation prior to initiating BRAFTOVI *[see Indications and Usage (1), Dosage and Administration (2.1)]*.

5.3 Cardiomyopathy

Cardiomyopathy, manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, has been reported in patients treated with BRAFTOVI in combination with binimetinib. In COLUMBUS, evidence of cardiomyopathy (decreased in LVEF below the institutional LLN with an absolute decreased in LVEF ≥10% below baseline as detected by echocardiography or MUGA) occurred in 7% of patients receiving BRAFTOVI plus binimetinib. Grade 3 left ventricular dysfunction occurred in 1.6% of patients. The median time to first occurrence of left ventricular dysfunction (any grade) in patients receiving BRAFTOVI in combination with binimetinib was 3.6 months (range 0 to 21 months). Cardiomyopathy resolved in 87% of patients receiving BRAFTOVI plus binimetinib.

In PHAROS, evidence of cardiomyopathy (decrease in LVEF below the institutional LLN with an absolute decrease in LVEF ≥10% below baseline as detected by echocardiography or MUGA) occurred in 11% of patients receiving BRAFTOVI in combination with binimetinib. Grade 3 left ventricular dysfunction occurred in 1% of patients. Cardiomyopathy resolved in 82% of patients receiving BRAFTOVI plus binimetinib.

Assess ejection fraction by echocardiogram or MUGA scan prior to initiating treatment, one month after initiating treatment, and every 2 to 3 months during treatment. The safety of BRAFTOVI in combination with binimetinib has not been established in patients with baseline ejection fraction that is either below 50% or below the institutional lower limit of normal (LLN). Patients with cardiovascular risk factors should be monitored closely when treated with BRAFTOVI.

Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.4 Hepatotoxicity

Hepatotoxicity can occur when BRAFTOVI is administered in combination with binimetinib. In COLUMBUS, the incidence of Grade 3 or 4 increases in liver function laboratory tests in patients receiving BRAFTOVI in combination with binimetinib was 6% for alanine aminotransferase (ALT), 2.6% for aspartate aminotransferase (AST), and 0.5% for alkaline phosphatase. In PHAROS, the incidence of Grade 3 or 4 increases in liver function laboratory tests in patients receiving BRAFTOVI in combination with binimetinib was 10% for AST, 9% for ALT, and 3.2% for alkaline phosphatase.

In BREAKWATER, the incidence of Grade 3 or 4 increases in liver function laboratory tests in patients receiving BRAFTOVI in combination with cetuximab and mFOLFOX6 was 2.2% for alkaline phosphatase, 1.3% for ALT, and 0.9% for AST.

Monitor liver laboratory tests before initiation of BRAFTOVI, monthly during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.5 Hemorrhage

In COLUMBUS, hemorrhage occurred in 19% of patients receiving BRAFTOVI in combination with binimetinib; Grade 3 or greater hemorrhage occurred in 3.2% of patients. The most frequent hemorrhagic events were gastrointestinal, including rectal hemorrhage (4.2%), hematochezia (3.1%), and hemorrhoidal hemorrhage (1%). Fatal intracranial hemorrhage in the setting of new or progressive brain metastases occurred in 1.6% of patients.

In BEACON CRC, hemorrhage occurred in 19% of patients receiving BRAFTOVI in combination with cetuximab; Grade 3 or higher hemorrhage occurred in 1.9% of patients, including fatal gastrointestinal hemorrhage in 0.5% of patients. The most frequent hemorrhagic events were epistaxis (6.9%), hematochezia (2.3%), and rectal hemorrhage (2.3%).

In PHAROS, hemorrhage occurred in 12% of patients receiving BRAFTOVI in combination with binimetinib including fatal hemorrhage intracranial (1%); Grade 3 or 4 hemorrhage occurred in 4.1% of patients. The most frequent hemorrhagic events were anal hemorrhage and hemothorax (2% each).

In BREAKWATER, hemorrhage occurred in 30% of patients receiving BRAFTOVI in combination with cetuximab and mFOLFOX6; Grade 3 or 4 hemorrhage occurred in 3% of patients.

Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5), Adverse Reactions (6.1)]*.

5.6 Uveitis

Uveitis, including iritis and iridocyclitis, has been reported in patients treated with BRAFTOVI in combination with binimetinib. In COLUMBUS, the incidence of uveitis among patients treated with BRAFTOVI in combination with binimetinib was 4%. In PHAROS, the incidence of uveitis among patients treated with BRAFTOVI in combination with binimetinib was 1%.

Assess for visual symptoms at each visit. Perform an ophthalmologic evaluation at regular intervals and for new or worsening visual disturbances, and to follow new or persistent ophthalmologic findings. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5), Adverse Reactions (6.1)]*.

5.7 QT Prolongation

BRAFTOVI is associated with dose-dependent QTc interval prolongation in some patients *[see Clinical Pharmacology (12.2)]*. In COLUMBUS, an increase in QTcF to >500 ms was measured in 0.5% (1/192) of patients who received BRAFTOVI in combination with binimetinib. In PHAROS, an increase in QTcF to >500 ms was measured in 2.1% (2/95) of patients who received BRAFTOVI in combination with binimetinib.

In BREAKWATER, an increase of QTcF >500 ms was measured in 3.6% (8/222) of patients receiving BRAFTOVI in combination with cetuximab and mFOLFOX6.

Monitor patients who already have or who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation. Correct hypokalemia and hypomagnesemia prior to and during BRAFTOVI administration. Withhold, reduce dose, or permanently discontinue for QTc >500 ms *[see Dosage and Administration (2.5), Adverse Reactions (6.1)]*.

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action, BRAFTOVI can cause fetal harm when administered to a pregnant woman. Encorafenib produced embryo-fetal developmental changes in rats and rabbits and was an abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 26 (in the rat) and 178 (in the rabbit) times the human exposure at the recommended dose of 450 mg, with no clear findings at lower doses.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use an effective, nonhormonal method of contraception since BRAFTOVI can render hormonal contraceptives ineffective, during treatment and for 2 weeks after the last dose of BRAFTOVI *[see Use in Specific Populations (8.1, 8.3)]*.

5.9 Risks Associated with BRAFTOVI as a Single Agent

BRAFTOVI when used as a single agent is associated with an increased risk of certain adverse reactions compared to when BRAFTOVI is used in combination with binimetinib. In COLUMBUS, Grades 3 or 4 dermatologic reactions occurred in 21% of patients treated with BRAFTOVI single agent compared to 2% of patients treated with BRAFTOVI in combination with binimetinib *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.

If binimetinib is temporarily interrupted or permanently discontinued, reduce the dose of BRAFTOVI as recommended *[see Dosage and Administration (2.5)]*.

5.10 Risks Associated with Combination Treatment

BRAFTOVI is indicated for use as part of a regimen in combination with binimetinib, in combination with cetuximab, or in combination with cetuximab and mFOLFOX6. Refer to the prescribing information for binimetinib, cetuximab and individual product components of mFOLFOX6 for additional risk information.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- New Primary Malignancies *[see Warnings and Precautions (5.1)]*
- Tumor Promotion in BRAF Wild-Type Tumors *[see Warnings and Precautions (5.2)]*
- Cardiomyopathy *[see Warnings and Precautions (5.3)]*
- Hepatotoxicity *[see Warnings and Precautions (5.4)]*
- Hemorrhage *[see Warnings and Precautions (5.5)]*
- Uveitis *[see Warnings and Precautions (5.6)]*
- QT Prolongation *[see Warnings and Precautions (5.7)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.8)]*
- Risks Associated with BRAFTOVI as a Single Agent *[see Warnings and Precautions (5.9)]*
- Risks Associated with Combination Treatment *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

BRAF V600E or *V600K* Mutation-Positive Unresectable or Metastatic Melanoma

The safety of BRAFTOVI in combination with binimetinib is described in 192 patients with *BRAF V600* mutation-positive unresectable or metastatic melanoma who received BRAFTOVI (450 mg once daily) in combination with binimetinib (45 mg twice daily) in a randomized open-label, active-controlled trial (COLUMBUS).

The COLUMBUS trial *[see Clinical Studies (14.1)]* excluded patients with a history of Gilbert's syndrome, abnormal left ventricular ejection fraction, prolonged QTc (>480 ms), uncontrolled hypertension, and history or current evidence of retinal vein occlusion. The median duration of exposure was 11.8 months for patients treated with BRAFTOVI in combination with binimetinib and 6.2 months for patients treated with vemurafenib.

The most common (≥25%) adverse reactions in patients receiving BRAFTOVI in combination with binimetinib were fatigue, nausea, vomiting, abdominal pain, and arthralgia.

Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 30% of patients receiving BRAFTOVI in combination with binimetinib; the most common were nausea (7%), vomiting (7%), and pyrexia (4%). Adverse reactions leading to dose reductions of BRAFTOVI occurred in 14% of patients receiving BRAFTOVI in combination with binimetinib; the most common were arthralgia (2%), fatigue (2%), and nausea (2%). Five percent (5%) of patients receiving BRAFTOVI in combination with binimetinib experienced an adverse reaction that resulted in permanent discontinuation of BRAFTOVI; the most common were hemorrhage in 2% and headache in 1% of patients.

Table 5 and Table 6 present adverse drug reactions and laboratory abnormalities, respectively, identified in COLUMBUS. The COLUMBUS trial was not designed to demonstrate a statistically significant difference in adverse reaction rates for BRAFTOVI in combination with binimetinib, as compared to vemurafenib, for any specific adverse reaction listed in Table 5.

Table 5: Adverse Reactions Occurring in ≥10% of Patients Receiving BRAFTOVI in Combination with Binimetinib in COLUMBUS[a]

Adverse Reaction	BRAFTOVI with binimetinib N=192		Vemurafenib N=186	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)
General Disorders and Administration Site Conditions				
Fatigue[c]	43	3	46	6
Pyrexia[c]	18	4	30	0
Gastrointestinal Disorders				
Nausea	41	2	34	2
Vomiting[c]	30	2	16	1
Abdominal pain[c]	28	4	16	1
Constipation	22	0	6	1

Table 5: Adverse Reactions Occurring in ≥10% of Patients Receiving BRAFTOVI in Combination with Binimetinib in COLUMBUS[a]

Adverse Reaction	BRAFTOVI with binimetinib N=192		Vemurafenib N=186	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia[c]	26	1	46	6
Myopathy[c]	23	0	22	1
Pain in extremity	11	1	13	1
Skin and Subcutaneous Tissue Disorders				
Hyperkeratosis[c]	23	1	49	1
Rash[c]	22	1	53	13
Dry skin[c]	16	0	26	0
Alopecia[c]	14	0	38	0
Pruritus[c]	13	1	21	1
Nervous System Disorders				
Headache[c]	22	2	20	1
Dizziness[c]	15	3	4	0
Peripheral neuropathy[c]	12	1	13	2
Vascular Disorders				
Hemorrhage[c]	19	3	9	2

a. Grades per National Cancer Institute CTCAE v4.03.
b. Grade 4 adverse reactions limited to fatigue (n=1), pruritus (n=1), and rash (n=1) in the BRAFTOVI with binimetinib arm.
c. Represents a composite of multiple, related preferred terms.

BRAFTOVI when used as a single agent increases the risk of certain adverse reactions compared to BRAFTOVI in combination with binimetinib. In patients receiving BRAFTOVI 300 mg orally once daily as a single agent, the following adverse reactions were observed at a higher rate (≥5%) compared to patients receiving BRAFTOVI in combination with binimetinib: palmar-plantar erythrodysesthesia syndrome (51% vs. 7%), hyperkeratosis (57% vs. 23%), dry skin (38% vs. 16%), erythema (16% vs. 7%), rash (41% vs. 22%), alopecia (56% vs. 14%), pruritus (31% vs. 13%), arthralgia (44% vs. 26%), myopathy (33% vs. 23%), back pain (15% vs. 9%), dysgeusia (13% vs. 6%), and acneiform dermatitis (8% vs. 3%).

Other clinically important adverse reactions occurring in <10% of patients who received BRAFTOVI in combination with binimetinib were:

Nervous system disorders: *Facial paresis*

Gastrointestinal disorders: *Pancreatitis*

Skin and subcutaneous tissue disorders: *Panniculitis, Photosensitivity*

Immune system disorders: *Drug hypersensitivity*

Table 6: Laboratory Abnormalities Occurring in ≥10% (All Grades) of Patients Receiving BRAFTOVI in Combination with Binimetinib in COLUMBUS[a]

Laboratory Abnormality	BRAFTOVI with binimetinib[a] N=192		Vemurafenib[a] N=186	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hematology				
Anemia	36	3.6	34	2.2
Leukopenia	13	0	10	0.5
Lymphopenia	13	2.1	30	7
Neutropenia	13	3.1	4.8	0.5
Chemistry				
Increased Creatinine	93	3.6	92	1.1
Increased Gamma Glutamyl Transferase	45	11	34	4.8
Increased ALT	29	6	27	2.2
Increased AST	27	2.6	24	1.6
Hyperglycemia	28	5	20	2.7
Increased Alkaline Phosphatase	21	0.5	35	2.2
Hyponatremia	18	3.6	15	0.5
Hypermagnesemia	10	1.0	26	0.5

a. Grades per National Cancer Institute CTCAE v4.03.

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (mCRC) in combination with Cetuximab and mFOLFOX6

The safety of BRAFTOVI 300 mg once daily in combination with cetuximab (500 mg/m^2 every 2 weeks) and mFOLFOX6 was evaluated in 231 patients with *BRAF V600E* mutation-positive metastatic CRC in a randomized, open-label, active-controlled trial (BREAKWATER) *[see Clinical Studies (14.2)]*. BREAKWATER excluded patients with pancreatitis, leptomeningeal disease, chronic inflammatory bowel disease requiring medical intervention, as well as clinically significant cardiovascular diseases [e.g., myocardial infarction, acute coronary syndromes, NYHA Class ≥II congestive heart failure, prolonged QTcF interval (≥480 ms), history of prolonged QT syndrome] and active infectious conditions.

Among patients who received BRAFTOVI, 54% were exposed for 6 months or longer and 18% were exposed for one year or longer.

Serious adverse reactions occurred in 38% of patients who received BRAFTOVI in combination with cetuximab and mFOLFOX6. Serious adverse reactions in >3% of patients included intestinal obstruction and pyrexia (3.5% each).

Fatal gastrointestinal perforation occurred in 0.9% of patients who received BRAFTOVI in combination with cetuximab and mFOLFOX6.

Permanent discontinuation of BRAFTOVI due to an adverse reaction occurred in 12% of patients. Adverse reactions which resulted in permanent discontinuation of BRAFTOVI in ≥1% of patients included increased lipase.

Dosage interruptions of BRAFTOVI due to an adverse reaction occurred in 57% of patients. Adverse reactions which required dosage interruption in ≥5% included decreased neutrophil count, pyrexia, and anemia.

Dose reductions of BRAFTOVI due to an adverse reaction occurred in 22% of patients. Adverse reactions leading to dose reductions of BRAFTOVI in ≥2% of patients included increased lipase, nausea, and vomiting.

The most common (≥25%) adverse reactions of BRAFTOVI when used in combination with cetuximab and mFOLFOX6 were peripheral neuropathy, nausea, fatigue, rash, diarrhea, decreased appetite, vomiting, hemorrhage, abdominal pain, and pyrexia.

The most common Grade 3 or 4 laboratory abnormalities (≥10%) of BRAFTOVI when used in combination with cetuximab and mFOLFOX6 were increased lipase, decreased neutrophil count, decreased hemoglobin, decreased white blood cell count, and increased glucose.

Table 7 and Table 8 present adverse drug reactions and laboratory abnormalities, respectively, identified in BREAKWATER.

Table 7: Adverse Reactions Occurring in ≥10% of Patients Receiving BRAFTOVI in Combination with Cetuximab and mFOLFOX6 in BREAKWATER[a]

Adverse Reaction	BRAFTOVI with cetuximab and mFOLFOX6 N=231		mFOLFOX6 ± bevacizumab or FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab N=228	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Nervous System Disorders				
Peripheral neuropathy[b]	62	15	53	6
Headache	13	<1	7	0
Dysgeusia	12	0	14	0
Neurotoxicity	11	5	8	0
Gastrointestinal Disorders				
Nausea	51	3	48	3
Diarrhea	34	1	47	4
Vomiting	33	4	21	2
Abdominal pain[b]	26	4	27	1
Constipation	20	<1	19	<1
General Disorders and Administration Site Conditions				
Fatigue[b]	49	7	38	4
Pyrexia[b]	26	2	14	<1
Metabolism and Nutrition Disorders				
Decreased appetite	33	2	25	1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia[b]	23	1	4	0
Myopathy[b]	14	0	7	<1
Skin and Subcutaneous Tissue Disorders				
Rash[b]	31	1	4	0
Alopecia	21	0	10	0
Dry skin[b]	17	0	4	0
Dermatitis acneiform[b]	17	1	1	0
Skin hyperpigmentation	17	0	2	0
Pruritus	11	0	3	<1

Table 7: Adverse Reactions Occurring in ≥10% of Patients Receiving BRAFTOVI in Combination with Cetuximab and mFOLFOX6 in BREAKWATER[a]

Adverse Reaction	BRAFTOVI with cetuximab and mFOLFOX6 N=231		mFOLFOX6 ± bevacizumab or FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab N=228	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Vascular Disorders				
Hemorrhage[b]	30	3	18	1
Psychiatric Disorder				
Insomnia[b]	11	0	7	0

a. Grades per National Cancer Institute CTCAE v4.03.
b. Represents multiple related terms.

Table 8: Laboratory Abnormalities Occurring in ≥20% (All Grades) of Patients Receiving BRAFTOVI in Combination with Cetuximab and mFOLFOX6 in BREAKWATER[a]

Laboratory Abnormality[b]	BRAFTOVI with cetuximab and mFOLFOX6		mFOLFOX6 ± bevacizumab or FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Neutrophil count decreased	63	36	60	34
White blood cell decreased	62	12	54	7
Hemoglobin decreased	60	13	47	5
Platelet count decreased	60	1	50	2
Activated partial thromboplastin time prolonged	57	3	38	1
INR increased	39	1	20	1
Chemistry				
Lipase increased	82	51	54	25
Creatinine increased	64	1	67	1
Glucose increased	49	11	35	2
Alanine aminotransferase increased	38	1	40	2
Albumin decreased	36	0	24	1
Aspartate aminotransferase increased	36	1	35	2
Potassium decreased	33	4	19	4
Alkaline phosphatase increased	31	2	31	1
Calcium decreased	24	4	16	2
Magnesium decreased	23	1	11	1

a. Grades per National Cancer Institute CTCAE v4.03.
b. The denominator used to calculate the rate varied from 220 to 227 based on the number of patients with a baseline and at least one post-treatment value.

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

The safety of BRAFTOVI 300 mg once daily in combination with cetuximab (400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly) was evaluated in 216 patients with *BRAF V600E* mutation-positive metastatic CRC in a randomized, open-label, active-controlled trial (BEACON CRC). The BEACON CRC trial *[see Clinical Studies (14.3)]* excluded patients with a history of Gilbert's syndrome, abnormal left ventricular ejection fraction, prolonged QTc (>480 ms), uncontrolled hypertension, and history or current evidence of retinal vein occlusion. The median duration of exposure was 4.4 months for patients treated with BRAFTOVI in combination with cetuximab and 1.6 months for patients treated with either irinotecan or infusional 5-fluorouracil (5-FU)/folinic acid (FA)/irinotecan (FOLFIRI) in combination with cetuximab.

The most common (≥25%) adverse reactions in patients receiving BRAFTOVI in combination with cetuximab were fatigue, nausea, diarrhea, dermatitis acneiform, abdominal pain, decreased appetite, arthralgia, and rash.

Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 33% of patients receiving BRAFTOVI in combination with cetuximab; the most common were vomiting (4%), fatigue (4%), nausea (4%), pyrexia (3%), and diarrhea (3%). Adverse reactions leading to dose reductions of BRAFTOVI occurred in 9% of patients receiving BRAFTOVI in combination with cetuximab; the most common were fatigue (2%), arthralgia (2%), and peripheral neuropathy (2%). Ten percent (10%) of patients receiving BRAFTOVI in combination with cetuximab experienced an adverse reaction that resulted in permanent discontinuation of BRAFTOVI. None of the adverse reactions leading to permanent discontinuation of BRAFTOVI occurred in more than one patient (>0.5%).

Table 9 and Table 10 present adverse drug reactions and laboratory abnormalities, respectively, identified in BEACON CRC.

Table 9: Adverse Reactions Occurring in ≥10% of Patients Receiving BRAFTOVI in Combination with Cetuximab in BEACON CRC[a]

Adverse Reaction	BRAFTOVI with cetuximab N=216		Irinotecan with cetuximab or FOLFIRI with cetuximab N=193	
	All Grades (%)	≥ Grade 3[b] (%)	All Grades (%)	≥ Grade 3 (%)
General Disorders and Administration Site Conditions				
Fatigue[c]	51	7	50	8
Pyrexia[c]	17	1	15	1
Gastrointestinal Disorders				
Nausea	34	1	41	1
Diarrhea[c]	33	2	48	10
Abdominal pain[c]	30	4	32	5
Vomiting	21	1	29	3
Constipation	15	0	18	1
Metabolism and Nutrition Disorders				
Decreased appetite	27	1	27	3
Musculoskeletal and Connective Tissue Disorders				
Arthralgia[c]	27	1	3	0
Myopathy[c]	15	1	4	0
Pain in extremity	10	0	1	0

Table 9: Adverse Reactions Occurring in ≥10% of Patients Receiving BRAFTOVI in Combination with Cetuximab in BEACON CRC[a]

Adverse Reaction	BRAFTOVI with cetuximab N=216		Irinotecan with cetuximab or FOLFIRI with cetuximab N=193	
	All Grades (%)	≥ Grade 3[b] (%)	All Grades (%)	≥ Grade 3 (%)
Skin and Subcutaneous Tissue Disorders				
Dermatitis acneiform[c]	32	1	43	3
Rash[c]	26	0	26	2
Pruritus[c]	14	0	6	0
Melanocytic nevus	14	0	0	0
Dry skin[c]	13	0	12	1
Nervous System Disorders				
Headache[c]	20	0	3	0
Peripheral neuropathy[c]	12	1	6	0
Vascular Disorders				
Hemorrhage[c]	19	2	9	0
Psychiatric Disorders				
Insomnia[c]	13	0	6	0

a. Grades per National Cancer Institute CTCAE v4.03.
b. Grade 4-5 adverse reactions in the BRAFTOVI with cetuximab arm were limited to Grade 5 hemorrhage (n=1).
c. Represents a composite of multiple, related preferred terms.

Other clinically important adverse reactions occurring in <10% of patients who received BRAFTOVI in combination with cetuximab were:

Gastrointestinal disorders: *Pancreatitis*

Table 10: Laboratory Abnormalities Occurring in ≥10% (All Grades) of Patients Receiving BRAFTOVI in Combination with Cetuximab in BEACON CRC[a]

Laboratory Abnormality[b]	BRAFTOVI with cetuximab		Irinotecan with cetuximab or FOLFIRI with cetuximab	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hematology				
Anemia	34	4	48	5
Lymphopenia	24	7	35	5
Increased Activated Partial Thromboplastin Time	13	1	7	1
Chemistry				
Hypomagnesemia	19	0	22	1
Increased Alkaline Phosphatase	18	4	30	7
Increased ALT	17	0	29	3
Increased AST	15	1	22	2
Hypokalemia	12	3	32	5
Hyponatremia	11	2	13	2

a. Grades per National Cancer Institute CTCAE v4.03.
b. Based on the number of patients with available baseline and at least one on-treatment laboratory test.

BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

The safety of BRAFTOVI in combination with binimetinib was evaluated in 98 patients with *BRAF V600E* mutation-positive metastatic NSCLC who received BRAFTOVI (450 mg once daily) in combination with binimetinib (45 mg twice daily) in an open-label, single-arm trial (PHAROS).

The PHAROS trial *[see Clinical Studies (14.4)]* excluded patients with abnormal left ventricular ejection fraction, prolonged QTc (>480 ms), uncontrolled hypertension, and history or current evidence of retinal vein occlusion. The median duration of treatment for BRAFTOVI and binimetinib was 9.2 and 8.4 months, respectively.

The most common (≥25%) adverse reactions in patients receiving BRAFTOVI were fatigue, nausea, diarrhea, musculoskeletal pain, vomiting, abdominal pain, visual impairment, constipation, dyspnea, rash, and cough.

Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 59% of patients receiving BRAFTOVI; the most common (≥5%) were diarrhea (17%); nausea (13%); musculoskeletal pain, fatigue (8% each); AST increased (7%); ALT increased, anemia, hemorrhage, vomiting (6% each); and acute kidney injury (5%). Adverse reactions leading to dose reductions of BRAFTOVI occurred in 30% of patients receiving BRAFTOVI; the most common (≥5%) were diarrhea, nausea (8% each); AST increased and fatigue (5% each). A total of 16% of patients receiving BRAFTOVI experienced an adverse reaction that resulted in permanent discontinuation of BRAFTOVI; the most common (≥2%) were diarrhea, musculoskeletal pain (3.1% each); fatigue, rash, nausea, visual impairment, and vomiting (2% each). None of the other adverse reactions leading to permanent discontinuation of BRAFTOVI occurred in more than 1 patient.

Serious adverse reactions occurred in 38% of patients who received BRAFTOVI in combination with binimetinib. Serious adverse reactions occurring in ≥2% of patients were hemorrhage (6%); diarrhea (4.1%); anemia, dyspnea, pneumonia (3.1% each); arrhythmia, device related infection, edema, myocardial infarction, and pleural effusion (2% each). Fatal adverse reactions occurred in 2% of patients who received BRAFTOVI (450 mg once daily) in combination with binimetinib, including intracranial hemorrhage and myocardial infarction (1% each).

Table 11 and Table 12 present adverse drug reactions and laboratory abnormalities, respectively, identified in PHAROS.

Table 11: Adverse Reactions Occurring in ≥10% of Patients Receiving BRAFTOVI in Combination with Binimetinib in PHAROS[a]

Adverse Reaction	BRAFTOVI with binimetinib N=98	
	All Grades (%)	Grades 3 and 4[b] (%)
General Disorders and Administration Site Conditions		
Fatigue[c]	61	8
Edema[d]	23	1
Pyrexia	22	0
Gastrointestinal Disorders		
Nausea	58	3.1
Diarrhea[e]	52	7
Vomiting	37	1
Abdominal pain[f]	32	1
Constipation	27	0
Eye Disorders		
Visual impairment[g]	29	2

Table 11: Adverse Reactions Occurring in ≥10% of Patients Receiving BRAFTOVI in Combination with Binimetinib in PHAROS[a]

Adverse Reaction	BRAFTOVI with binimetinib N=98	
	All Grades (%)	Grades 3 and 4[b] (%)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[h]	48	4.1
Skin and Subcutaneous Tissue Disorders		
Rash[i]	27	3.1
Pruritis[j]	16	0
Dry skin	13	0
Alopecia	12	0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea[k]	27	8
Cough[l]	26	0
Nervous System Disorders		
Dizziness[m]	17	1
Headache	11	0
Metabolism and Nutrition Disorders		
Decreased appetite	14	1
Vascular Disorders		
Hemorrhage[b,n]	12	4.1
Hypertension	10	5
Cardiac Disorders		
Left ventricular dysfunction/cardiomyopathy[o]	11	1
Investigations		
Weight increased	11	1
Psychiatric Disorders		
Insomnia	10	0

a. Grades per National Cancer Institute CTCAE v4.03.
b. One Grade 5 adverse reaction of hemorrhage occurred.
c. Fatigue includes fatigue, asthenia.
d. Edema includes edema peripheral, generalized edema, swelling, localized edema, face edema.
e. Diarrhea includes diarrhea, colitis.
f. Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort.
g. Visual impairment includes vision blurred, visual impairment, vitreous floaters, photophobia, visual acuity reduced, photopsia.
h. Musculoskeletal pain includes back pain, arthralgia, pain in extremity, myalgia, musculoskeletal chest pain, noncardiac chest pain, neck pain.
i. Rash includes rash, rash macular, rash maculo-papular, rash papular, rash pustular, dermatitis acneiform, palmar-plantar erythrodysesthesia syndrome, eczema, skin exfoliation.
j. Pruritis includes pruritus, pruritus genital.
k. Dyspnea includes dyspnea, dyspnea exertional.
l. Cough includes cough, productive cough.
m. Dizziness includes dizziness, balance disorder.
n. Hemorrhage includes anal hemorrhage, hemothorax, gastrointestinal hemorrhage, hematochezia, hematuria, hemoptysis, hemorrhage intracranial, hyphema, small intestinal hemorrhage, upper gastrointestinal hemorrhage, vaginal hemorrhage.
o. Left ventricular dysfunction/cardiomyopathy includes ejection fraction decreased, cardiac failure, cardiac failure congestive.

Other clinically important adverse reactions occurring in <10% of patients who received BRAFTOVI in combination with binimetinib were:

Nervous system disorders: *Peripheral neuropathy, Dysgeusia, Facial paresis*

Gastrointestinal disorders: *Pancreatitis*

Skin and subcutaneous tissue disorders: *Hyperkeratosis, Erythema, Photosensitivity*

Immune system disorders: *Drug hypersensitivity*

Table 12: Laboratory Abnormalities Occurring in ≥10% (All Grades) of Patients Receiving BRAFTOVI with Binimetinib[a]

Laboratory Abnormality[b]	BRAFTOVI with binimetinib	
	All Grades (%)	Grades 3 and 4 (%)
Hematology		
Anemia	47	11
Lymphopenia	24	6
Thrombocytopenia	20	1.1
Leukopenia	12	0
Neutropenia	12	1.1
Chemistry		
Increased creatinine	91	3.2
Hyperglycemia	48	6
Increased creatine kinase	41	3.3
Lipase increased	40	14
Increased ALT	34	9
Hypoalbuminemia	32	0
Increased AST	31	10
Increased alkaline phosphatase	31	3.2
Hyperkalemia	31	2.1
Hyponatremia	26	11
Serum amylase increased	22	1.1
Hypocalcemia	12	2.1

a. Grades per National Cancer Institute CTCAE v4.03.
b. Based on the number of patients with available baseline and at least one on-treatment laboratory test.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRAFTOVI

Strong or Moderate CYP3A4 Inhibitors

Coadministration of BRAFTOVI with a strong or moderate CYP3A4 inhibitor increases encorafenib plasma concentrations *[see Clinical Pharmacology (12.3)]* and may increase encorafenib adverse reactions. Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors, including grapefruit juice. If coadministration is unavoidable, reduce the BRAFTOVI dose *[see Dosage and Administration (2.6)]*.

Strong CYP3A4 Inducers

Coadministration of BRAFTOVI with a strong CYP3A4 inducer may decrease encorafenib plasma concentrations *[see Clinical Pharmacology (12.3)]* and may decrease encorafenib efficacy. Avoid coadministration of BRAFTOVI with strong CYP3A4 inducers.

7.2 Effect of BRAFTOVI on Other Drugs

Sensitive CYP3A4 Substrates

BRAFTOVI is a strong CYP3A4 inducer at steady-state. Concomitant use of BRAFTOVI may decrease the plasma concentrations of CYP3A4 substrates (including hormonal contraceptives), *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of these substrates. Avoid the coadministration of BRAFTOVI with CYP3A4 substrates for which a decrease in plasma concentration may lead to reduced efficacy of the substrate. If the coadministration cannot be avoided, see the CYP3A4 substrate product labeling for recommendations.

OATP1B1, OATP1B3, or BCRP Substrates

Coadministration of BRAFTOVI with OATP1B1, OATP1B3, or BCRP substrates can result in increased concentrations of the substrates, and may increase toxicity of these agents. When used in combination, monitor patients closely for signs and symptoms of increased exposure and consider adjusting the dose of these substrates *[see Clinical Pharmacology (12.3)]*.

7.3 Drugs That Prolong the QT Interval

BRAFTOVI is associated with dose-dependent QTc interval prolongation *[see Warnings and Precautions (5.7), Clinical Pharmacology (12.2)]*. Avoid coadministration of BRAFTOVI with drugs known to prolong the QT/QTc interval.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BRAFTOVI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available clinical data on the use of BRAFTOVI during pregnancy. In animal reproduction studies, encorafenib produced embryo-fetal developmental changes in rats and rabbits and was an abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 26 (in the rat) and 178 (in the rabbit) times the human exposure at the clinical dose of 450 mg, with no clear findings at lower doses *(see Data)*. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In reproductive toxicity studies, administration of encorafenib to rats during the period of organogenesis resulted in maternal toxicity, decreased fetal weights, and increased incidence of total skeletal variations at a dose of 20 mg/kg/day (approximately 26 times the human exposure based on area under the concentration-time curve [AUC] at the recommended clinical dose of 450 mg once daily). In pregnant rabbits, administration of encorafenib during the period of organogenesis resulted in maternal toxicity, decreased fetal body weights, increased incidence of total skeletal variations and increased post-implantation loss, including total loss of pregnancy at a dose of 75 mg/kg/day (approximately 178 times the human exposure based on AUC at the recommended clinical dose of 450 mg once daily). While formal placental transfer studies have not been performed, encorafenib exposure in the fetal plasma of both rats and rabbits was up to 1.7% and 0.8%, respectively, of maternal exposure.

8.2 Lactation

Risk Summary

There are no data on the presence of encorafenib or its metabolites in human milk or the effects of encorafenib on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child from BRAFTOVI, advise women not to breastfeed during treatment with BRAFTOVI and for 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

BRAFTOVI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating BRAFTOVI *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with BRAFTOVI and for 2 weeks after the last dose. Counsel patients to use a nonhormonal method of contraception since BRAFTOVI has the potential to render hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Infertility

Males

Based on findings in male rats at doses approximately 13 times the human exposure at the 450 mg clinical dose, use of BRAFTOVI may impact fertility in males *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of BRAFTOVI have not been established in pediatric patients.

8.5 Geriatric Use

Of the 690 patients with BRAF mutation-positive melanoma who received BRAFTOVI in combination with binimetinib across multiple clinical trials, 20% were aged 65 to 74 years and 8% were aged 75 years and older *[see Clinical Studies (14.1)]*.

Of the 231 patients with *BRAF V600E* mutation-positive metastatic CRC who received BRAFTOVI in combination with cetuximab and mFOLFOX6, 83 (36%) were 65 years of age and over and 16 (7%) were 75 years of age and over *[see Clinical Studies (14.2)]*.

Of the 216 patients with *BRAF V600E* mutation-positive metastatic CRC who received BRAFTOVI in combination with cetuximab, 62 (29%) were 65 years of age to up to 75 years of age, while 20 (9%) were 75 years of age and over *[see Clinical Studies (14.3)]*.

Of the 98 patients with BRAF *V600E* mutation-positive metastatic NSCLC who received BRAFTOVI with binimetinib, 62 (63%) were 65 years of age and over and 20 (20%) were 75 years and over *[see Clinical Studies (14.4)]*.

No overall differences in the safety or effectiveness of BRAFTOVI plus binimetinib, BRAFTOVI plus cetuximab, or BRAFTOVI plus cetuximab and mFOLFOX6 were observed in older patients as compared to younger patients.

Reference ID: 5548023

8.6 Hepatic Impairment

No BRAFTOVI dosage adjustment is recommended in patients with mild hepatic impairment (Child-Pugh Class A) *[see Clinical Pharmacology (12.3)]*. A recommended dosage has not been established in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

8.7 Renal Impairment

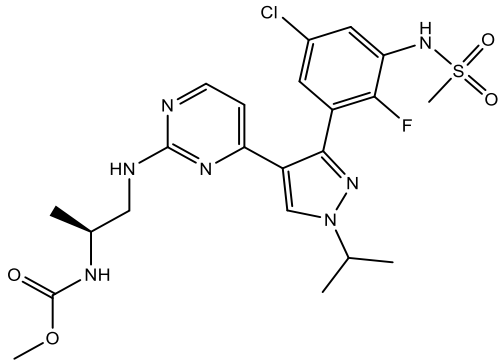
No BRAFTOVI dosage adjustment is recommended in patients with mild to moderate renal impairment (CLcr 30 to <90 mL/min) *[see Clinical Pharmacology (12.3)]*. A recommended dosage has not been established in patients with severe renal impairment (CLcr <30 mL/min).

10 OVERDOSAGE

Since encorafenib is 86% bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with BRAFTOVI.

11 DESCRIPTION

Encorafenib is a kinase inhibitor. The chemical name is methyl *N*-{(2*S*)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1*H*-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate. The molecular formula is $C_{22}H_{27}ClFN_7O_4S$ and the molecular weight is 540 daltons. The chemical structure of encorafenib is shown below:



Encorafenib is a white to almost white powder. In aqueous media, encorafenib is slightly soluble at pH 1, very slightly soluble at pH 2, and insoluble at pH 3 and higher.

BRAFTOVI (encorafenib) capsules for oral use contain 75 mg of encorafenib with the following inactive ingredients: copovidone, poloxamer 188, microcrystalline cellulose, succinic acid, crospovidone, colloidal silicon dioxide, magnesium stearate (vegetable origin). The capsule shell contains gelatin, titanium dioxide, iron oxide red, iron oxide yellow, ferrosoferric oxide, monogramming ink (pharmaceutical glaze, ferrosoferric oxide, propylene glycol).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Encorafenib is a kinase inhibitor that targets *BRAF V600E*, as well as wild-type BRAF and CRAF in in vitro cell-free assays with IC_{50} values of 0.35, 0.47, and 0.3 nM, respectively. Mutations in the BRAF gene, such as *BRAF V600E*, can result in constitutively activated BRAF kinases that may stimulate tumor cell growth. Encorafenib was also able to bind to other kinases in vitro including JNK1, JNK2, JNK3, LIMK1, LIMK2, MEK4, and STK36 and reduce ligand binding to these kinases at clinically achievable concentrations (≤0.9 µM).

Encorafenib inhibited in vitro growth of tumor cell lines expressing *BRAF V600* E, D, and K mutations. In mice implanted with tumor cells expressing *BRAF V600E,* encorafenib induced tumor regressions associated with RAF/MEK/ERK pathway suppression.

Encorafenib and binimetinib target two different kinases in the RAS/RAF/MEK/ERK pathway. Compared with either drug alone, coadministration of encorafenib and binimetinib resulted in greater anti-proliferative activity in vitro in BRAF mutation-positive cell lines and greater anti-tumor activity with respect to tumor growth inhibition in *BRAF V600E* mutant human melanoma xenograft studies in mice. Additionally, the combination of encorafenib and binimetinib delayed the emergence of resistance in *BRAF V600E* mutant human melanoma xenografts in mice compared to either drug alone. In a *BRAF V600E* mutant NSCLC patient-derived xenograft model in mice, coadministration of encorafenib and binimetinib resulted in greater anti-tumor activity compared to binimetinib alone, with respect to tumor growth inhibition. Increased tumor growth delay after dosing cessation was also observed with the coadministration compared to either drug alone.

In the setting of BRAF-mutant CRC, induction of EGFR-mediated MAPK pathway activation has been identified as a mechanism of resistance to BRAF inhibitors. Combinations of a BRAF inhibitor and agents targeting EGFR have been shown to overcome this resistance mechanism in nonclinical models. Coadministration of encorafenib and cetuximab had an anti-tumor effect greater than either drug alone, in a mouse model of colorectal cancer with mutated *BRAF V600E*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

A dedicated study to evaluate the QT prolongation potential of BRAFTOVI has not been conducted. BRAFTOVI is associated with dose-dependent QTc interval prolongation. Based on a central tendency analysis of QTc in a study of adult patients with melanoma who received the recommended dose of BRAFTOVI in combination with binimetinib, the largest mean (90% CI) QTcF change from baseline (ΔQTcF) was 18 (14 to 22) ms *[see Warnings and Precautions (5.7)]*.

12.3 Pharmacokinetics

The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumors, including advanced and unresectable or metastatic cutaneous melanoma harboring a *BRAF V600E* or *V600K* mutation, *BRAF V600E* mutation-positive metastatic CRC. After a single dose, systemic exposure of encorafenib was dose proportional over the dose range of 50 mg to 700 mg (0.1 to 1.6 times the maximum recommended dose of 450 mg). After once-daily dosing, systemic exposure of encorafenib was less than dose proportional over the dose range of 50 mg to 800 mg (0.1 to 1.8 times the maximum recommended dose of 450 mg). Steady-state was reached within 15 days, with exposure being 50% lower compared to Day 1; intersubject variability (CV%) of AUC ranged from 12% to 69%.

Absorption

The median T_{max} of encorafenib is 2 hours. At least 86% of the dose is absorbed.

Effect of Food

Following administration of a single dose of BRAFTOVI 100 mg (0.2 times the maximum recommended dose of 450 mg) with a high-fat, high-calorie meal (consisting of approximately 150 calories from protein, 350 calories from carbohydrates, and 500 calories from fat) the mean maximum encorafenib concentration (C_{max}) decreased by 36% and there was no effect on AUC.

Distribution

The geometric mean (CV%) of apparent volume of distribution is 164 L (70%). The protein binding of encorafenib is 86% in vitro. The blood-to-plasma concentration ratio is 0.58.

Elimination

The mean (CV%) terminal half-life ($t_{1/2}$) of encorafenib is 3.5 hours (17%), and the apparent clearance is 14 L/h (54%) at day 1, increasing to 32 L/h (59%) at steady-state at the maximum recommended dose of 450 mg.

Reference ID: 5548023

Metabolism

Encorafenib is primarily metabolized by CYP3A4 (83%) and to a lesser extent by CYP2C19 (16%) and CYP2D6 (1%).

Excretion

Following a single radiolabeled dose of 100 mg encorafenib, 47% (5% unchanged) of the administered dose was recovered in feces and 47% (2% unchanged) in urine.

Specific Populations

No clinically significant differences in the pharmacokinetics of encorafenib were observed based on age (19 to 94 years), sex, body weight (34 to 168 kg), mild hepatic impairment (Child-Pugh Class A), and mild or moderate renal impairment (CLcr 30 to <90 mL/min). The effect of race or ethnicity, moderate or severe hepatic impairment (Child-Pugh Class B or C), and severe renal impairment (CLcr <30 mL/min) on encorafenib pharmacokinetics have not been studied.

Drug Interaction Studies

Clinical Studies

CYP3A4 Inhibitors: Coadministration of posaconazole (strong CYP3A4 inhibitor) or diltiazem (moderate CYP3A4 inhibitor) increased AUC of encorafenib by 3- and 2-fold, respectively, and increased C_{max} by 68% and 45%, respectively, after a single dose of 50 mg BRAFTOVI (0.1 times the maximum recommended dose of 450 mg).

Strong CYP3A4 Inducers: The effect of a strong CYP3A4 inducer on encorafenib exposure has not been studied *[see Drug Interactions (7.1)]*.

Moderate CYP3A4 Inducers: Repeat dose administration of BRAFTOVI 450 mg once daily and binimetinib 45 mg twice daily with modafinil, a moderate CYP3A4 inducer, decreased encorafenib steady-state AUC by 24% and C_{max} by 20%, compared to BRAFTOVI alone.

Effect of encorafenib on CYP3A4 Substrates: Repeat dose administration of BRAFTOVI 450 mg once daily and binimetinib 45 mg twice daily with a single dose of midazolam 2 mg, a sensitive CYP3A4 substrate, decreased midazolam AUC by 82% and C_{max} by 74% relative to midazolam 2 mg alone.

Effect of encorafenib on Other CYP Substrates: There was no clinically significant effect of repeat dose administration of BRAFTOVI 450 mg once daily and binimetinib 45 mg twice daily on the exposure of substrates of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP2D6.

Proton Pump Inhibitors: No clinically significant differences in encorafenib pharmacokinetics were observed when coadministered with rabeprazole.

Binimetinib: No clinically significant differences in the pharmacokinetics of binimetinib (UGT1A1 substrate) were observed when coadministered with BRAFTOVI (UGT1A1 inhibitor).

Cetuximab: No clinically significant differences in the pharmacokinetics of encorafenib or cetuximab were observed when the recommended BRAFTOVI dose of 300 mg was coadministered with cetuximab.

Transporters: Repeat dose administration of BRAFTOVI 450 mg once daily and binimetinib 45 mg twice daily with a single dose of rosuvastatin (a sensitive *substrate for* OATP1B1, OATP1B3, and BCRP) increased rosuvastatin C_{max} by 2.7-fold and AUC by 1.6-fold.

In Vitro Studies

CYP/UGT Enzymes: Encorafenib is a reversible inhibitor of UGT1A1.

Transporters: Encorafenib is a substrate of P-glycoprotein (P-gp) but not of breast cancer resistance protein (BCRP), multidrug resistance-associated protein 2 (MRP2), organic anion transporting polypeptide (OATP1B1, OATP1B3) or organic cation transporter (OCT1) at clinically relevant plasma concentrations.

Encorafenib is an inhibitor of P-gp, BCRP, OCT2, organic anion transporter (OAT1, OAT3), OATP1B1, and OATP1B3, but not of OCT1 or MRP2 at clinically relevant plasma concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with encorafenib have not been conducted. Encorafenib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, or micronuclei in bone marrow of rats.

No dedicated fertility studies were performed with encorafenib in animals. In a general toxicology study in rats, decreased testes and epididymis weights, tubular degeneration in testes, and oligospermia in epididymides were observed at doses approximately 13 times the human exposure at the 450 mg clinical dose based on AUC. No effects on reproductive organs were observed in either sex in any of the nonhuman primate toxicity studies.

13.2 Animal Toxicology and/or Pharmacology

Adverse histopathology findings of hyperplasia and hyperkeratosis occurred in the stomach of rats at encorafenib doses of 20 mg/kg/day (approximately 14 times the human exposure at the 450 mg clinical dose based on AUC) or greater, in both 4 and 13-week studies.

14 CLINICAL STUDIES

14.1 *BRAF V600E* or *V600K* Mutation-Positive Unresectable or Metastatic Melanoma

BRAFTOVI in combination with binimetinib was evaluated in a randomized, active-controlled, open-label, multicenter trial (COLUMBUS; NCT01909453). Eligible patients were required to have *BRAF V600E* or *V600K* mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux THxID™ BRAF assay. Patients were permitted to have received immunotherapy in the adjuvant setting and one prior line of immunotherapy for unresectable locally advanced or metastatic disease. Prior use of BRAF inhibitors or MEK inhibitors was prohibited. Randomization was stratified by American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), and prior immunotherapy for unresectable or metastatic disease (yes versus no).

Patients were randomized (1:1:1) to receive BRAFTOVI 450 mg once daily in combination with binimetinib 45 mg twice daily (BRAFTOVI in combination with binimetinib), BRAFTOVI 300 mg once daily, or vemurafenib 960 mg twice daily. Treatment continued until disease progression or unacceptable toxicity. Only the results of the approved dosing (BRAFTOVI 450 mg in combination with binimetinib 45 mg) are described below.

The major efficacy outcome measure was progression-free survival (PFS), as assessed by a blinded independent central review, to compare BRAFTOVI in combination with binimetinib with vemurafenib. Additional efficacy outcome measures included overall survival (OS), as well as objective response rate (ORR) and duration of response (DoR) which were assessed by central review.

A total of 577 patients were randomized, 192 to the BRAFTOVI in combination with binimetinib arm, 194 to the BRAFTOVI arm, and 191 to the vemurafenib arm. Of the 383 patients randomized to either the BRAFTOVI in combination with binimetinib or the vemurafenib arms, the median age was 56 years (20 to 89 years), 59% were male, 91% were White, and 72% had baseline ECOG performance status of 0. Ninety-five percent (95%) had metastatic disease, 65% were Stage IVM1c, and 4% received prior CTLA-4, PD-1, or PD-L1 directed antibodies. Twenty-eight percent (28%) had elevated baseline serum lactate dehydrogenase (LDH), 45% had ≥3 organs with tumor involvement at baseline, and 3% had brain metastases. Based on centralized testing, 100% of patients' tumors tested positive for BRAF mutations; *BRAF V600E* (88%), *BRAF V600K* (11%), or both (<1%).

BRAFTOVI in combination with binimetinib demonstrated a statistically significant improvement in PFS compared to vemurafenib. Efficacy results are summarized in Table 13 and Figure 1.

Table 13: Efficacy Results for COLUMBUS

	BRAFTOVI with binimetinib N=192	**Vemurafenib N=191**
Progression-Free Survival		
Number of events (%)	98 (51)	106 (55)
Progressive disease	88 (46)	104 (54)
Death	10 (5)	2 (1)
Median PFS, months (95% CI)	14.9 (11.0, 18.5)	7.3 (5.6, 8.2)
HR (95% CI)[a]	0.54 (0.41, 0.71)	
P-value[b]	<0.0001	
Overall Survival[c]		
Number of events (%)	139 (72)	147 (77)
Median OS, months (95% CI)	33.6 (24.4, 39.2)	16.9 (14.0, 24.5)
HR (95% CI)[a]	0.67 (0.53, 0.84)	
Overall Response Rate		
ORR (95% CI)	63% (56%, 70%)	40% (33%, 48%)
CR	8%	6%
PR	55%	35%
Duration of Response		
Median DoR, months (95% CI)	16.6 (12.2, 20.4)	12.3 (6.9, 16.9)

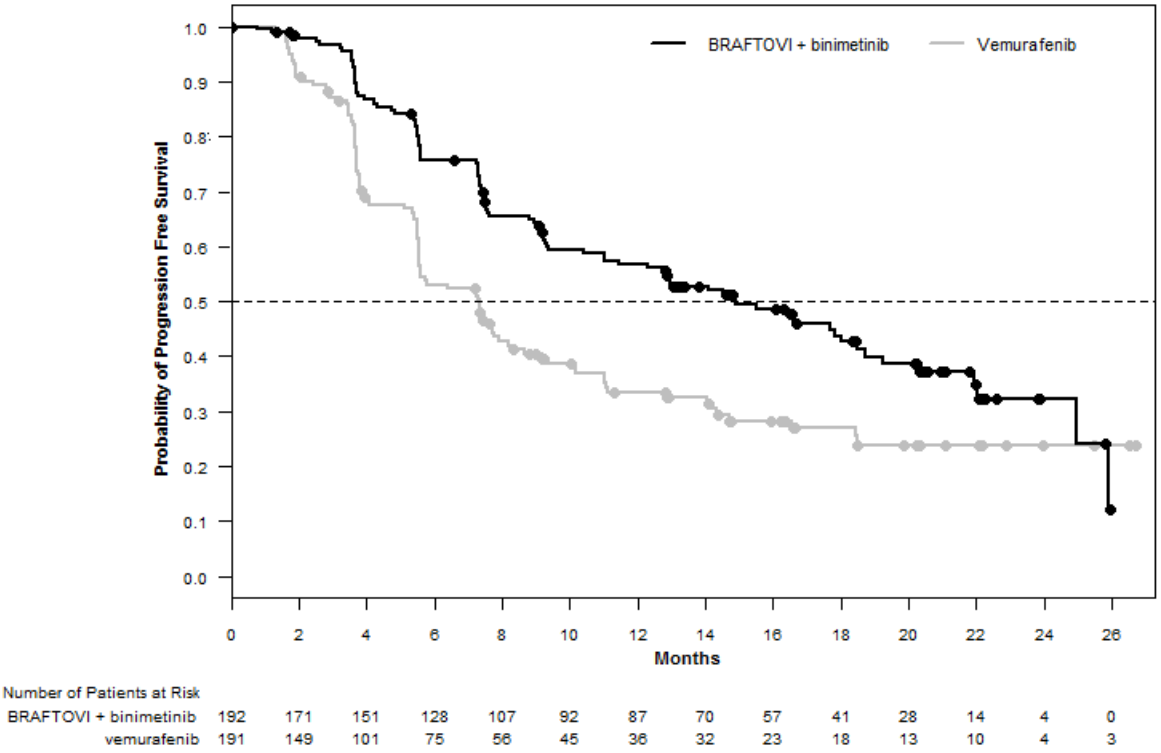
CI = Confidence interval; CR = Complete response; DoR = Duration of response; HR = Hazard ratio; NE = Not estimable; ORR = Overall response rate; OS = Overall survival; PFS = Progression-free survival; PR = Partial response.

a. Estimated with Cox proportional hazard model adjusted by the following stratification factors: American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1).

b. Log-rank test adjusted by the same stratification factors.

c. Based on a cutoff date of 82.4 months after the date of the PFS analysis.

Figure 1: Kaplan-Meier Curves for Progression-Free Survival in COLUMBUS



14.2 *BRAF V600E* Mutation-Positive Metastatic Colorectal Cancer (mCRC)-BRAFTOVI with Cetuximab and mFOLFOX6

BRAFTOVI in combination with cetuximab and mFOLFOX6 was evaluated in a randomized, active-controlled, open-label, multicenter trial (BREAKWATER CRC; NCT04607421). Eligible patients were required to have *BRAF V600E* mutation-positive metastatic colorectal cancer (CRC), as detected using the Qiagen therascreen *BRAF V600E* RGQ polymerase chain reaction (PCR) Kit. Other key eligibility criteria included no prior systemic treatment in the metastatic setting, absence of prior treatment with any selective BRAF inhibitor or EGFR inhibitor, tumor that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) unless the patient is ineligible to receive immune checkpoint inhibitors, tumor that is not RAS-mutated or for which RAS mutation status is unknown, and Eastern Cooperative Oncology Group (ECOG) performance status 0-1. Randomization was stratified by ECOG performance status (0 versus 1) and region (US/Canada versus Europe versus Rest of World).

Patients were initially randomized 1:1:1 to one of the following treatment arms, and then 1:1 after discontinuation of enrollment of the BRAFTOVI+cetuximab arm (158 patients):

- BRAFTOVI 300 mg orally once daily in combination with cetuximab 500 mg/m^2 IV infusion every 2 weeks (BRAFTOVI+cetuximab arm)
- BRAFTOVI 300 mg orally once daily in combination with cetuximab 500 mg/m^2 IV infusion every 2 weeks and mFOLFOX6 every 2 weeks (BRAFTOVI+cetuximab+mFOLFOX6 arm)
- mFOLFOX6 (every 2 weeks), or FOLFOXIRI (every 2 weeks), or CAPOX (every 3 weeks), each with or without bevacizumab (administered per prescribing instructions)

mFOLFOX6 consisted of oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, 5-FU 400 mg/m^2 IV bolus, then 5-FU 2400 mg/m^2 continuous IV infusion over 46-48 hours; CAPOX consisted of oxaliplatin 130 mg/m^2 IV infusion

and capecitabine 1000 mg/m^2 oral tablet twice daily on Days 1-14; FOLFOXIRI consisted of irinotecan 165 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, 5-FU 2400 or 3200 mg/m^2 (per local standard of care) continuous IV infusion over 46-48 hours.

Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, lost to follow-up, or death. Only the results of the approved regimen (BRAFTOVI in combination with cetuximab and mFOLFOX6) are described below.

The major efficacy outcome measure was confirmed objective response rate (ORR) as assessed by BICR and was evaluated in the first 110 participants randomized in each arm. An additional efficacy outcome measure included duration of response (DoR) as assessed by BICR.

A total of 236 patients were randomized to the BRAFTOVI+cetuximab+mFOLFOX6 arm and 243 to the control arm. Of these patients, the median age was 61 years, 50% were female, 60% were White, 37% were Asian, 0.4% were Multiracial, 0.2% were Black or African American, and 2.5% were not reported. Twelve percent (12%) were Hispanic or Latino, 81% were not Hispanic or Latino, and 7% were not reported. Fifty-four percent (54%) had baseline ECOG performance status of 0.

BRAFTOVI in combination with cetuximab and mFOLFOX6 demonstrated a statistically significant improvement in ORR compared to the active comparator. Efficacy results are summarized in Table 14 below.

Table 14: Efficacy Results for BREAKWATER

Efficacy Parameter	**BRAFTOVI with cetuximab and mFOLFOX6 N=110**	**mFOLFOX6 ± bevacizumab or FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab N=110**
Objective Response Rate (per BICR)		
ORR (95% CI)	61% (52%, 70%)	40% (31%, 49%)
CR	2.7%	1.8%
PR	58%	38%
P-value[a]	0.0008	
Duration of Response (per BICR)		
Median DoR, months (95% CI)	13.9 (8.5, NE)	11.1 (6.7, 12.7)
% with DoR ≥6 months	69%	34%
% with DoR ≥12 months	22%	11%

CI = Confidence interval; CR = Complete response; DoR = Duration of response; N = Number of patients; NE = Not estimable; ORR = Objective response rate; PR = Partial response.

a. Stratified by ECOG performance status and geographic region at randomization. Cochran-Mantel-Haenszel test; tested at 1-sided alpha level of 0.001.

14.3 *BRAF V600E* Mutation-Positive Metastatic Colorectal Cancer (CRC)

BRAFTOVI in combination with cetuximab was evaluated in a randomized, active-controlled, open-label, multicenter trial (BEACON CRC; NCT02928224). Eligible patients were required to have *BRAF V600E* mutation-positive metastatic colorectal cancer (CRC), as detected using the Qiagen therascreen *BRAF V600E* RGQ polymerase chain reaction (PCR) Kit, with disease progression after 1 or 2 prior regimens. Other key eligibility criteria included absence of prior treatment with a RAF, MEK, or EGFR inhibitor, eligibility to receive cetuximab per local labeling with respect to tumor RAS status, and ECOG performance status (PS) 0-1. Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), prior use of irinotecan (yes versus no), and cetuximab product used (US-licensed versus EU-approved).

Patients were randomized 1:1:1 to one of the following treatment arms:

- BRAFTOVI 300 mg orally once daily in combination with cetuximab (BRAFTOVI/cetuximab arm)
- BRAFTOVI 300 mg orally once daily in combination with binimetinib and cetuximab
- Irinotecan with cetuximab or FOLFIRI with cetuximab (control arm)

The dosage of cetuximab in all patients was 400 mg/m^2 intravenously for the first dose followed by 250 mg/m^2 weekly.

Patients in the control arm received cetuximab with either irinotecan 180 mg/m^2 intravenously on Days 1 and 15 of each 28-day cycle or FOLFIRI intravenously (irinotecan 180 mg/m^2 on Days 1 and 15; folinic acid 400 mg/m^2 on Days 1 and 15; then fluorouracil 400 mg/m^2 bolus on Days 1 and 15 followed by fluorouracil 2400 mg/m^2/day by continuous infusion over 2 days).

Treatment continued until disease progression or unacceptable toxicity. Only the results of the approved regimen (BRAFTOVI in combination with cetuximab) are described below.

The major efficacy outcome measure was overall survival (OS). Additional efficacy outcome measures included progression-free survival (PFS), overall response rate (ORR), and duration of response (DoR) as assessed by blinded independent central review (BICR). OS and PFS were assessed in all randomized patients. ORR and DoR were assessed in the subset of the first 220 patients included in the randomized portion of the BRAFTOVI/cetuximab and control arm of the study.

A total of 220 patients were randomized to the BRAFTOVI/cetuximab arm and 221 to the control arm. Of these 441 patients, the median age was 61 years; 53% were female; 80% were White, 15% were Asian, and 5% were other or not reported. Four percent (4%) were Hispanic or Latino, 90% were not Hispanic or Latino, and 6% were not reported or unknown. Fifty percent (50%) had baseline ECOG performance status of 0; 66% received 1 prior therapy and 34% received 2; 93% received prior oxaliplatin and 52% received prior irinotecan.

BRAFTOVI in combination with cetuximab demonstrated a statistically significant improvement in OS, ORR, and PFS compared to the active comparator. Efficacy results are summarized in Table 15 and Figure 2.

Table 15: Efficacy Results From BEACON CRC

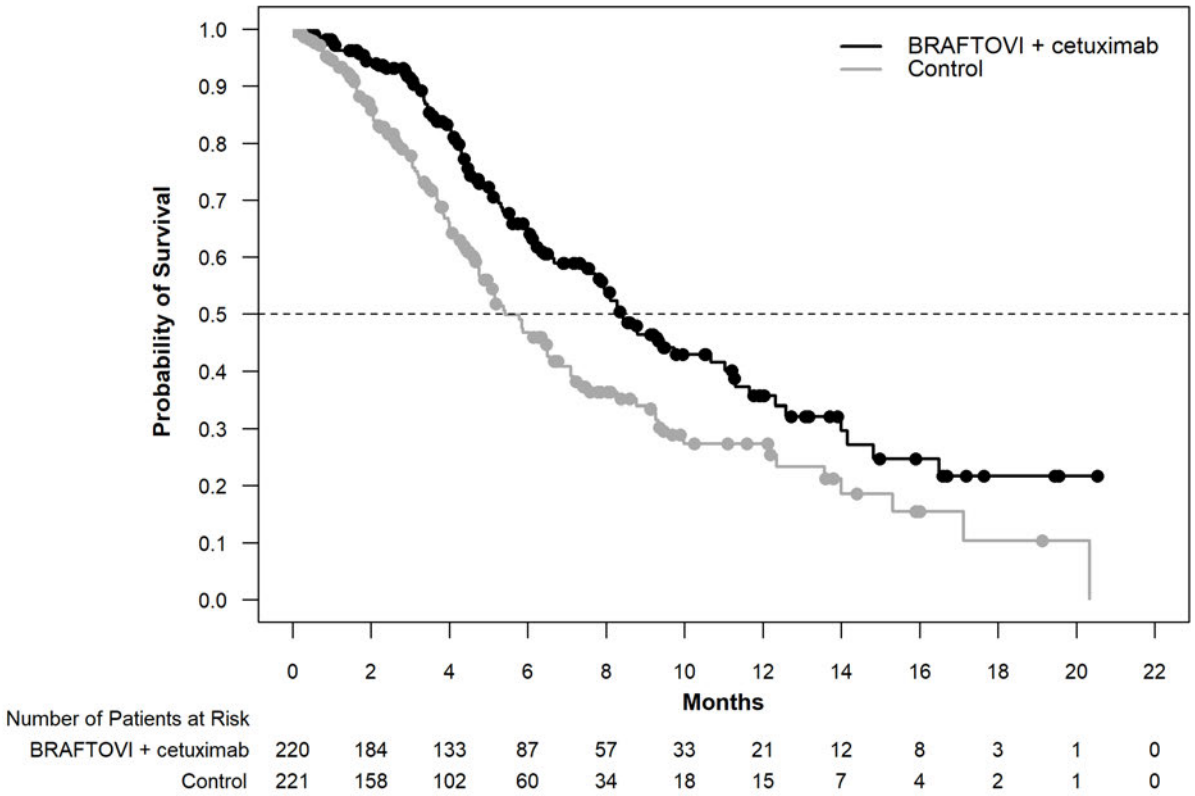
	BRAFTOVI with cetuximab N=220	**Irinotecan with cetuximab or FOLFIRI with cetuximab N=221**
Overall Survival		
Number of Events (%)	93 (42)	114 (52)
Median OS, months (95% CI)	8.4 (7.5, 11.0)	5.4 (4.8, 6.6)
HR (95% CI)[a,b]	0.60 (0.45, 0.79)	
P-value[a,c]	0.0003	

	BRAFTOVI with cetuximab N=220	Irinotecan with cetuximab or FOLFIRI with cetuximab N=221
Overall Response Rate (per BICR)		
ORR (95% CI)[d]	20% (13%, 29%)	2% (0%, 7%)
CR	5%	0%
PR	15%	2%
P-value[a,e]	<0.0001	
Median DoR, months (95% CI)	6.1 (4.1, 8.3)	NR (2.6, NR)
Progression Free Survival (per BICR)		
Number of events (%)	133 (60)	128 (58)
Progressive disease	110 (50)	101 (46)
Death	23 (10)	27 (12)
Median PFS, months (95% CI)	4.2 (3.7, 5.4)	1.5 (1.4, 1.7)
HR (95% CI)[a,b]	0.40 (0.31, 0.52)	
P-value[a,f]	<0.0001	

CI = Confidence interval; CR = Complete response; DoR = Duration of response; HR = Hazard ratio; NR = Not reached; ORR = Overall response rate; OS = Overall survival; PFS = Progression-free survival; PR = Partial response.

a. Stratified by ECOG PS, source of cetuximab (US-licensed versus EU-approved) and prior irinotecan use at randomization.
b. Stratified Cox proportional hazard model.
c. Stratified log-rank test, tested at alpha level of 0.0084.
d. BRAFTOVI/cetuximab arm (n=113) and control arm (n=107).
e. Cochran-Mantel-Haenszel test; tested at alpha level of 0.05.
f. Stratified log-rank test, tested at alpha level of 0.0234.

Figure 2: Kaplan-Meier Curves for Overall Survival in BEACON CRC



14.4 *BRAF V600E* Mutation-Positive Metastatic Non-Small Cell Lung Cancer

BRAFTOVI in combination with binimetinib was evaluated in an open-label, multicenter, single-arm study in patients with *BRAF V600E* mutation-positive metastatic non-small cell lung cancer (NSCLC) (PHAROS; NCT03915951). Eligible patients had a diagnosis of histologically-confirmed metastatic NSCLC with *BRAF V600E* mutation that was treatment-naïve or had been previously treated with 1 prior line of systemic therapy in the metastatic setting (platinum-based chemotherapy and/or anti-PD-1/PD-L1 therapies), age 18 years or older, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Prior use of BRAF inhibitors or MEK inhibitors was not allowed.

Patients received BRAFTOVI 450 mg once daily and binimetinib 45 mg orally twice daily until disease progression or unacceptable toxicity. The major efficacy outcome measures were objective response rate (ORR) per RECIST v1.1 and duration of response (DoR) as assessed by independent review committee (IRC).

In the efficacy population, *BRAF V600E* mutation status was determined by prospective local testing using tumor tissue (78%) or blood (22%) specimens. Of the 98 patients with *BRAF V600E* mutation, 6 patients were enrolled into the trial based on testing of their tumor tissue specimens with the FoundationOne CDx tissue test. Of the remaining 92 patients enrolled based on local testing, 68 patients had their tumor tissue specimens retrospectively confirmed as having *BRAF V600E* positive status by the FoundationOne CDx tissue test. The remaining patients had either *BRAF V600E* negative status (n=5) or had unevaluable results (n=19) by the FoundationOne CDx tissue test. In addition, plasma samples from 81 out of 98 patients were retrospectively tested using the FoundationOne Liquid CDx assay. Of the 81 patients, 48 were confirmed positive for *BRAF V600E*, while 33 patients were *BRAF V600E* mutation negative by FoundationOne Liquid CDx assay. The remaining 17 samples had unevaluable results with FoundationOne Liquid CDx assay.

The efficacy population included 59 treatment-naïve patients and 39 previously-treated patients. Among these 98 patients, the median age was 70 years (range: 47 to 86); 53% female; 88% White, 7% Asian, 3% Black or African American, and 1% American Indian or Alaska Native; 99% were not Hispanic or Latino; 13% were

current smokers and 57% were former smokers; 73% had ECOG PS of 1; and 97% had adenocarcinoma. All patients had metastatic disease, and 8% had brain metastases at baseline.

Efficacy results for patients with *BRAF V600E* mutation-positive metastatic NSCLC are summarized in Table 16.

Table 16: Efficacy Results for PHAROS

	BRAFTOVI with binimetinib	
Efficacy Parameter	**Treatment naïve (N=59)**	**Previously treated (N=39)**
Objective Response Rate[a]		
ORR (95% CI)	75% (62, 85)	46% (30, 63)
CR	15%	10%
PR	59%	36%
Duration of Response[a,b]	N=44	N=18
Range in months	1.4, 51.6+	3.8, 45.8+
% with DoR ≥12 months	64%	44%
% with DoR ≥24 months	43%	22%

CI = Confidence interval; CR = Complete response; DoR = Duration of response; N = Number of patients; NE = Not estimable; ORR = Objective response rate; PR = Partial response.

a. Assessed by Independent Central Review (ICR).

b. Based on observed duration of response.

16 HOW SUPPLIED/STORAGE AND HANDLING

BRAFTOVI (encorafenib) is supplied as 75 mg hard gelatin capsules.

75 mg: stylized "A" on beige cap and "LGX 75mg" on white body, available in cartons (NDC 70255-025-01) containing two bottles of 90 capsules each (NDC 70255-025-02) and cartons (NDC 70255-025-03) containing two bottles of 60 capsules each (NDC 70255-025-04).

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Do not use if safety seal under cap is broken or missing. Dispense in original bottle. Do not remove desiccant. Protect from moisture. Keep container tightly closed.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the following:

New Primary Malignancies

Advise patients that BRAFTOVI increases the risk of developing new primary cutaneous and noncutaneous malignancies. Advise patients to contact their healthcare provider immediately for change in or development of new skin lesions *[see Warnings and Precautions (5.1)]*.

Tumor Promotion in BRAF Wild-Type Tumors

Advise patients of the need to confirm *BRAF V600E* or *V600K* mutation prior to initiating BRAFTOVI *[see Warnings and Precautions (5.2)]*.

Cardiomyopathy

Advise patients to report any symptoms of heart failure to their healthcare provider *[see Warnings and Precautions (5.3)]*.

Hepatotoxicity

Advise patients that serial testing of serum liver tests (ALT, AST, bilirubin) is recommended during treatment with BRAFTOVI. Instruct patients to report symptoms of liver dysfunction including jaundice, dark urine, nausea, vomiting, loss of appetite, fatigue, bruising, or bleeding *[see Warnings and Precautions (5.4)]*.

Hemorrhage

Advise patients to notify their healthcare provider immediately with any symptoms suggestive of hemorrhage, such as unusual bleeding *[see Warnings and Precautions (5.5)]*.

Uveitis

Advise patients to contact their healthcare provider if they experience any changes in their vision *[see Warnings and Precautions (5.6)]*.

QT Prolongation

Advise patients that BRAFTOVI can cause QTc interval prolongation and to inform their physician if they have any QTc interval prolongation symptoms, such as syncope *[see Warnings and Precautions (5.7)]*.

Embryo-Fetal Toxicity

- Advise females with reproductive potential of the potential risk to a fetus. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with BRAFTOVI *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective nonhormonal contraception during treatment with BRAFTOVI and for 2 weeks after the last dose *[Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with BRAFTOVI and for 2 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males of reproductive potential that BRAFTOVI may impair fertility *[see Use in Specific Populations (8.3)]*.

Drug Interactions

Coadministration of BRAFTOVI with a strong or moderate CYP3A inhibitor may increase encorafenib concentrations; coadministration of BRAFTOVI with a strong CYP3A inducer may decrease encorafenib concentrations. Advise patients that they may need to avoid certain medications while taking BRAFTOVI and to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Advise patients to avoid grapefruit and grapefruit juice while taking BRAFTOVI *[see Drug Interactions (7.1)]*.

Storage

BRAFTOVI is moisture sensitive. Advise patients to store BRAFTOVI in the original bottle with desiccant and to keep the cap of the bottle tightly closed. Do not remove the desiccants from the bottle.

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

Distributed by:

Array BioPharma Inc., a wholly owned subsidiary of Pfizer Inc.
3200 Walnut Street
Boulder, CO 80301

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LAB-1428-6.0

MEDICATION GUIDE

BRAFTOVI® (braf-TOE-vee)

(encorafenib)

capsules

Important information: BRAFTOVI is used in combination with other medicines, including binimetinib, cetuximab, or cetuximab and mFOLFOX6 (fluorouracil, leucovorin and oxaliplatin). Read the Medication Guide that comes with binimetinib if BRAFTOVI is used with binimetinib. Talk to your healthcare provider about cetuximab, or cetuximab and mFOLFOX 6 if used with BRAFTOVI.

What is the most important information I should know about BRAFTOVI?

BRAFTOVI may cause serious side effects, including:

Risk of new skin cancers. BRAFTOVI when used alone, or with binimetinib or cetuximab, may cause skin cancers called cutaneous squamous cell carcinoma or basal cell carcinoma.

Talk to your healthcare provider about your risk for these cancers.

Check your skin and tell your healthcare provider right away about any skin changes, including a:

- new wart
- skin sore or reddish bump that bleeds or does not heal
- change in size or color of a mole

Your healthcare provider should check your skin before treatment with BRAFTOVI, every 2 months during treatment, and for up to 6 months after you stop treatment with BRAFTOVI to look for any new skin cancers.

Your healthcare provider should also check for cancers that may not occur on the skin. Tell your healthcare provider about any new symptoms that develop during treatment with BRAFTOVI.

See "**What are the possible side effects of BRAFTOVI?**" for more information about side effects.

What is BRAFTOVI?

BRAFTOVI is a prescription medicine used:

- in combination with a medicine called binimetinib to treat people with a type of skin cancer called melanoma:
  - that has spread to other parts of the body or cannot be removed by surgery, **and**
  - that has a certain type of abnormal "BRAF" gene
- in combination with a medicine called cetuximab and mFOLFOX6 (fluorouracil, leucovorin and oxaliplatin) to treat people with cancer of the colon or rectum (colorectal cancer):
  - that has spread to other parts of the body, **and**
  - that has a certain type of abnormal “BRAF” gene
- in combination with a medicine called cetuximab to treat adults with cancer of the colon or rectum (colorectal cancer) after past treatment:
  - that has spread to other parts of the body, **and**
  - that has a certain type of abnormal “BRAF” gene
- in combination with a medicine called binimetinib to treat adults with a type of lung cancer called non-small cell lung cancer (NSCLC):
  - that has spread to other parts of the body, **and**
  - that has a certain type of abnormal “BRAF” gene

BRAFTOVI should not be used to treat people with wild-type BRAF melanoma, wild-type BRAF colorectal cancer, or wild-type BRAF NSCLC. Your healthcare provider will perform a test to make sure that BRAFTOVI is right for you.

It is not known if BRAFTOVI is safe and effective in children.

Before taking BRAFTOVI, tell your healthcare provider about all of your medical conditions, including if you:

- have had bleeding problems
- have eye problems
- have heart problems, including a condition called long QT syndrome
- have been told that you have low blood levels of potassium, calcium, or magnesium
- have liver or kidney problems
- are pregnant or plan to become pregnant. BRAFTOVI can harm your unborn baby.
  - Females who are able to become pregnant should use effective non-hormonal birth control (contraception) during treatment with BRAFTOVI and for 2 weeks after the last dose of BRAFTOVI. Birth control methods that

contain hormones (such as birth control pills, injections or transdermal systems) may not work as well during treatment with BRAFTOVI.
    - Talk to your healthcare provider about birth control methods that may be right for you during this time.
    - Your healthcare provider will do a pregnancy test before you start taking BRAFTOVI. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with BRAFTOVI.
- are breastfeeding or plan to breastfeed. It is not known if BRAFTOVI passes into your breast milk. Do not breastfeed during treatment with BRAFTOVI and for 2 weeks after the last dose of BRAFTOVI. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

BRAFTOVI and certain other medicines can affect each other, causing side effects or affecting how BRAFTOVI or the other medicines work.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take BRAFTOVI?

- Take BRAFTOVI exactly as your healthcare provider tells you. Do not change your dose or stop taking BRAFTOVI unless your healthcare provider tells you to.
- Take BRAFTOVI by mouth 1 time each day.
- BRAFTOVI may be taken with or without food.
- Avoid grapefruit during treatment with BRAFTOVI. Grapefruit products may increase the amount of BRAFTOVI in your body.
- If you miss a dose of BRAFTOVI, take it as soon as you remember. If it is within 12 hours of your next scheduled dose, take your next dose at your regular time. Do not make up for the missed dose.
- Do not take an extra dose if you vomit after taking your scheduled dose. Take your next dose at your regular time.
- If you stop treatment with binimetinib or cetuximab, talk to your healthcare provider about your BRAFTOVI treatment. Your BRAFTOVI dose may need to be changed or stopped.

What are the possible side effects of BRAFTOVI?

BRAFTOVI may cause serious side effects, including:

- See "**What is the most important information I should know about BRAFTOVI?**"
- **Heart problems, including heart failure.** BRAFTOVI, when taken with binimetinib, can cause heart problems. Your healthcare provider will check your heart function before and during treatment with BRAFTOVI. Tell your healthcare provider right away if you get any of the following signs and symptoms of a heart problem:
    - feeling like your heart is pounding or racing
    - shortness of breath
    - swelling in your hands, ankles legs or feet
    - feeling faint or lightheaded
- **Liver problems**. BRAFTOVI, when taken with binimetinib, can cause liver problems. Your healthcare provider will perform blood tests to check your liver function before and during treatment with BRAFTOVI. Tell your healthcare provider if you get any of the following signs and symptoms of a liver problem:
    - yellowing of your skin or your eyes
    - dark or brown (tea-colored) urine
    - nausea or vomiting
    - loss of appetite
    - tiredness
    - bruising
    - bleeding
- **Bleeding problems.** BRAFTOVI, when taken with binimetinib or cetuximab, can cause serious bleeding problems, including in your stomach or brain, that can lead to death. Tell your healthcare provider and get medical help right away if you develop any signs of bleeding, including:
    - headaches, dizziness, or feeling weak
    - cough up blood or blood clots
    - vomit blood or your vomit looks like "coffee grounds"
    - red or black stools that look like tar
    - nose bleeds

- **Eye problems.** BRAFTOVI, when taken with binimetinib, can cause eye problems. Your healthcare provider should perform an eye exam regularly. Tell your healthcare provider right away if you develop any new or worsening symptoms of eye problems, including:
  - blurred vision, loss of vision, or other vision changes
  - see colored dots
  - see halos (blurred outline around objects)
  - eye pain, swelling, or redness

- **Changes in the electrical activity of your heart called QT prolongation.** QT prolongation can cause irregular heartbeats that can be life threatening. Your healthcare provider should do tests before you start taking BRAFTOVI with binimetinib or cetuximab and during your treatment to check your body salts (electrolytes). Tell your healthcare provider right away if you feel faint, lightheaded, dizzy or if you feel your heart beating irregularly or fast during treatment with BRAFTOVI and binimetinib or cetuximab. These symptoms may be related to QT prolongation.

Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with BRAFTOVI if you have certain side effects.

The most common side effects of BRAFTOVI when taken in combination with binimetinib for melanoma include:

- fatigue
- nausea
- vomiting
- abdominal pain
- pain or swelling of your joints (arthralgia)

The most common side effects of BRAFTOVI when taken in combination with cetuximab and mFOLFOX6 for colorectal cancer include:

- numbness, tingling or burning in your hands or feet (peripheral neuropathy)
- nausea
- fatigue
- rash
- diarrhea
- decreased appetite
- vomiting
- bleeding (hemorrhage)
- stomach-area (abdominal) pain
- fever

The most common side effects of BRAFTOVI when taken in combination with cetuximab for colorectal cancer include:

- fatigue
- nausea
- diarrhea
- acne-like rash (dermatitis acneiform)
- stomach-area (abdominal) pain
- decreased appetite
- pain or swelling of your joints (arthralgia)
- rash

The most common side effects of BRAFTOVI when taken in combination with binimetinib for NSCLC include:

- fatigue
- nausea
- diarrhea
- muscle or joint pain
- vomiting
- stomach-area (abdominal) pain
- blurred vision, loss of vision, or other vision changes
- constipation
- shortness of breath
- rash
- cough

BRAFTOVI may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of BRAFTOVI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Pfizer Inc. at 1-800-438-1985.

How should I store BRAFTOVI?

- Store BRAFTOVI at room temperature between 68°F to 77°F (20°C to 25°C).
- Store BRAFTOVI in the original bottle.
- Keep the BRAFTOVI bottle tightly closed and protect it from moisture.
- BRAFTOVI comes with a desiccant packet in the bottle to help protect your medicine from moisture. Do not remove the desiccant packet from the bottle.

Keep BRAFTOVI and all medicines out of the reach of children.

General information about the safe and effective use of BRAFTOVI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BRAFTOVI for a condition for which it was not prescribed. Do not give BRAFTOVI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about BRAFTOVI that is written for health professionals.

What are the ingredients in BRAFTOVI?

Active ingredient: encorafenib

Inactive ingredients: copovidone, poloxamer 188, microcrystalline cellulose, succinic acid, crospovidone, colloidal silicon dioxide, and magnesium stearate of vegetable origin

Capsule shell: gelatin, titanium dioxide, iron oxide red, iron oxide yellow, ferrosoferric oxide, monogramming ink (pharmaceutical glaze, ferrosoferric oxide, propylene glycol)

Distributed by: Array BioPharma Inc., a wholly owned subsidiary of Pfizer Inc. Boulder, Colorado 80301.

BRAFTOVI® is a registered trademark of Array BioPharma Inc. in the United States and various other countries.

LAB-1429-4.0

For more information, go to www.BRAFTOVIMEKTOVI.com or call 1-844-792-7729.

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This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 12/2024

1.6.3　　欧州の添付文書

以下に、欧州添付文書の原文を添付する。

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Braftovi 50 mg hard capsules
Braftovi 75 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Braftovi 50 mg hard capsules
Each hard capsule contains 50 mg of encorafenib.

Braftovi 75 mg hard capsules
Each hard capsule contains 75 mg of encorafenib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Braftovi 50 mg hard capsules
Orange opaque cap and flesh opaque body, printed with a stylised "A" on the cap and "LGX 50mg" on the body. The length of the capsule is approximately 22 mm.

Braftovi 75 mg hard capsules
Flesh coloured opaque cap and white opaque body, printed with a stylised "A" on the cap and "LGX 75mg" on the body. The length of the capsule is approximately 23 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

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

Colorectal cancer (CRC)

Encorafenib in combination with cetuximab is indicated for the treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation, who have received prior systemic therapy.

Non-small cell lung cancer (NSCLC)

Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600E mutation.

4.2 Posology and method of administration

Encorafenib treatment should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.

BRAF mutation testing

Before taking encorafenib, patients must have confirmation of BRAF V600E mutation assessed by a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used.

The efficacy and safety of encorafenib have been established only in patients with melanoma tumours expressing BRAF V600E and V600K mutations, colorectal tumours expressing a BRAF V600E mutation or NSCLC expressing a BRAF V600E mutation. Encorafenib should not be used in patients with wild type BRAF malignant melanoma, wild type BRAF colorectal cancer or wild-type BRAF NSCLC.

Posology

Melanoma and NSCLC
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.

Dose modification

Melanoma and NSCLC
The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation of encorafenib (see Tables 1, 3 and 4).
For information on the posology and recommended dose modifications of binimetinib, see section 4.2 of binimetinib Summary of Product Characteristics (SmPC).

Dose reduction recommendations for encorafenib are presented in Table 1.

Table 1: Recommended dose modifications for encorafenib when used in combination with binimetinib in melanoma or NSCLC indications

Dose level	**Encorafenib dose** when used in combination with binimetinib
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	For melanoma indication: 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. For NSCLC indication: Encorafenib should be permanently discontinued if patient is unable to tolerate 225 mg (three 75 mg capsules) once daily.

Administration of encorafenib at a dose of 450 mg once daily as a single agent is not recommended. If binimetinib is temporarily interrupted, encorafenib should be reduced to 300 mg once daily during the time of binimetinib dose interruption (see section 4.2 of binimetinib SmPC) as encorafenib is not well-tolerated at the dose of 450 mg as a single agent. If binimetinib is permanently discontinued, encorafenib should be discontinued.

If encorafenib is temporarily interrupted (see Tables 3 and 4), binimetinib should be interrupted. If encorafenib is permanently discontinued, then binimetinib should be discontinued.

If treatment-related toxicities occur, then encorafenib and binimetinib should be dose reduced, interrupted or discontinued. Dose modifications are necessary for binimetinib only (adverse reactions primarily related to binimetinib) for the following: retinal pigment epithelial detachment (RPED), retinal vein occlusion (RVO), interstitial lung disease/pneumonitis, cardiac dysfunction, creatine phosphokinase (CK) elevation and rhabdomyolysis, and venous thromboembolism (VTE).
If one of these toxicities occurs, see section 4.2 of binimetinib SmPC for dose modification instructions for binimetinib.

Colorectal cancer
The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation of encorafenib (see Tables 2, 3 and 4).
For information on the posology and recommended dose modifications of cetuximab, see section 4.2 of cetuximab SmPC.

Dose reduction recommendations for encorafenib are presented in Table 2.

Table 2: Recommended dose modifications for encorafenib when used in combination with cetuximab in CRC indication

Dose level	**Encorafenib dose** when used in combination with cetuximab
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.

Melanoma, colorectal cancer and NSCLC
Dose modifications in case of adverse reactions are provided below and in Tables 3 and 4.

For new primary cutaneous malignancies: No dose modifications are required for encorafenib.

For new primary non-cutaneous RAS mutation-positive malignancies: it should be considered to discontinue encorafenib permanently.

Table 3: Recommended dose modifications for encorafenib when used in combination with binimetinib or in combination with cetuximab for selected adverse reactions

Severity of adverse reaction[a]	**Encorafenib**
Cutaneous reactions	
• Grade 2	Encorafenib should be maintained. If rash worsens or does not improve within 2 weeks with treatment, encorafenib should be withheld until Grade 0 or 1 and then resumed at the same dose.
• Grade 3	Encorafenib should be withheld until improved to Grade 0 or 1 and resumed at the same dose if first occurrence, or resumed at a reduced dose if recurrent Grade 3.
• Grade 4	Encorafenib should be permanently discontinued.

Severity of adverse reaction[a]	Encorafenib
Palmar-plantar erythrodysaesthesia syndrome (PPES)	
• Grade 2	Encorafenib should be maintained and supportive measures such as topical therapy should be instituted. If not improved despite supportive therapy within 2 weeks, encorafenib should be withheld until improved to Grade 0 or 1 and treatment should be resumed at same dose level or at a reduced dose.
• Grade 3	Encorafenib should be withheld, supportive measures such as topical therapy should be instituted, and the patient should be reassessed weekly. Encorafenib should be resumed at same dose level or at a reduced dose level when improved to Grade 0 or 1.
Uveitis including iritis and iridocyclitis	
• Grade 1-3	If Grade 1 or 2 uveitis does not respond to specific (*e.g.* topical) ocular therapy or for Grade 3 uveitis, encorafenib should be withheld and ophthalmic monitoring should be repeated within 2 weeks. If uveitis is Grade 1 and it improves to Grade 0, then treatment should be resumed at the same dose. If uveitis is Grade 2 or 3 and it improves to Grade 0 or 1, then treatment should be resumed at a reduced dose. If not improved within 6 weeks, ophthalmic monitoring should be repeated and encorafenib should be permanently discontinued.
• Grade 4	Encorafenib should be permanently discontinued and a follow up with ophthalmologic monitoring should be performed.
QTc Prolongation	
• QTcF > 500 ms and change ≤ 60 ms from pre-treatment value	Encorafenib should be withheld (see monitoring in section 4.4). Encorafenib should be resumed at a reduced dose when QTcF ≤500 ms. Encorafenib should be discontinued if more than one recurrence.
• QTcF>500 ms and increased by >60 ms from pre-treatment values	Encorafenib should be permanently discontinued (see monitoring in section 4.4).
Liver laboratory abnormalities	
• Grade 2 (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3x ≤5x upper limit of normal (ULN))	Encorafenib should be maintained. If no improvement within 4 weeks, encorafenib should be withheld until improved to Grade 0 or 1 or to pre-treatment/baseline levels and then resumed at the same dose.
• First occurrence of Grade 3 (AST or ALT >5x ULN and blood bilirubin >2x ULN)	Encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or to baseline levels, it should be resumed at a reduced dose. • If not improved, encorafenib should be permanently discontinued

Severity of adverse reaction[a]	Encorafenib
• First occurrence of Grade 4 (AST or ALT >20 ULN)	Encorafenib should be withheld for up to 4 weeks • If improved to Grade 0 or 1 or to baseline levels, then it should be resumed at a reduced dose level. • If not improved, encorafenib should be permanently discontinued. Or, encorafenib should be permanently discontinued.
• Recurrent Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	It should be considered to permanently discontinue encorafenib.
• Recurrent Grade 4 (AST or ALT > 20 ULN)	Encorafenib should be permanently discontinued.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03

Table 4: Recommended dose modifications for encorafenib when used in combination with binimetinib or in combination with cetuximab for other adverse reactions

Severity of adverse reaction	Encorafenib
• Recurrent or intolerable Grade 2 adverse reactions • First occurrence of Grade 3 adverse reactions	Encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or to baseline levels, It should be resumed at a reduced dose. • If not improved, encorafenib should be permanently discontinued
• First occurrence of any Grade 4 adverse reaction	Encorafenib should be withheld for up to 4 weeks • If improved to Grade 0 or 1 or to baseline levels, then it should be resumed at a reduced dose level. • If not improved, encorafenib should be permanently discontinued. Or, encorafenib should be permanently discontinued.
• Recurrent Grade 3 adverse reactions	Permanent discontinuation of encorafenib should be considered.
• Recurrent Grade 4 adverse reactions	Encorafenib should be permanently discontinued.

Duration of treatment
Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity.

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.

Vomiting
In case of vomiting after administration of encorafenib, the patient should not take an additional dose and should take the next scheduled dose.

Special populations

Elderly patients
No dose adjustment is required for patients aged 65 years and older (see section 5.2).

Hepatic impairment
Patients with mild to severe hepatic impairment may have increased encorafenib exposure (see section 5.2).
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 (see sections 4.4 and 5.2).

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

Method of administration

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 (see sections 4.4 and 4.5)

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Encorafenib is to be given in combination with binimetinib (for patients with BRAF V600 mutant unresectable or metastatic melanoma, and for patients with BRAF V600E mutant advanced NSCLC), or in combination with cetuximab (for patients with BRAF V600E mutant metastatic colorectal cancer). For additional information on warnings and precautions associated with binimetinib or cetuximab treatment, see section 4.4 of binimetinib SmPC or cetuximab SmPC.

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 or BRAF V600E mutant NSCLC which have metastasised to the brain (see section 5.1).

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, see section 4.2 of binimetinib SmPC.
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 haemorrhagic events, can occur with encorafenib (see section 4.8). The risk of haemorrhage may be increased with concomitant use of anticoagulant and antiplatelet therapy. The occurrence of Grade ≥3 haemorrhagic events should be managed with dose interruption or treatment discontinuation (see Table 4 in section 4.2) 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 (see section 4.8).
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, see section 4.2.
If during treatment patient develops RPED or RVO, see section 4.2 of binimetinib SmPC for guidance.

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 (see section 5.1).
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, bradyarrhythmias) 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 (see section 4.2).

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 (see section 4.8).

Cutaneous malignancies
Cutaneous malignancies such as cutaneous squamous cell carcinoma (cuSCC) including kerathoacanthoma 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 (see section 4.8).
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 dermatological 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.

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.

Tumour lysis syndrome (TLS)

The occurrence of TLS, which may be fatal, has been associated with the use of encorafenib in association with binimetinib (see section 4.8). Risk factors for TLS include high tumour burden, preexisting chronic renal insufficiency, oliguria, dehydration, hypotension and acidic urine. These patients should be monitored closely and treated promptly as clinically indicated, and prophylactic hydration should be considered.

Liver laboratory abnormalities

Liver laboratory abnormalities including AST and ALT elevations have been observed with encorafenib (see section 4.8). 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. Liver laboratory abnormalities should be managed with dose interruption, reduction or treatment discontinuation (see section 4.2).

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 exposure (see section 5.2).
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 (see section 4.2).
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 (see sections 4.2 and 5.2). 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 (see Table 4 in section 4.2). 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 (see section 4.5).
Caution should be exercised if a moderate CYP3A inhibitor is co-administered with encorafenib.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on encorafenib

Encorafenib is primarily metabolised by CYP3A4.

CYP3A4 inhibitors
Co-administration of moderate (diltiazem) and strong (posaconazole) CYP3A4 inhibitors with single doses of encorafenib in healthy volunteers resulted in a 2 and 3-fold increase in the area under the concentration-time curve (AUC), respectively and in 44.6% and 68.3% increase in maximum encorafenib concentration (C_{max}) respectively.
Model based predictions indicate that the effect of posaconazole after repeated administrations could be similar for AUC (3-fold increase) and slightly greater for C_{max} (2.7-fold increase). Model-based predictions for ketoconazole suggest an increase of approx. 5-fold for encorafenib AUC and 3 to 4-fold for encorafenib C_{max} after administration of encorafenib 450 and 300 mg QD, respectively.
Therefore, concomitant administration of encorafenib with strong CYP3A4 inhibitors should be avoided (due to increased encorafenib exposure and potential increase in toxicity, see section 5.2). 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.

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

Effects of encorafenib on other medicinal products

CYP substrates
Encorafenib is a strong inducer of CYP3A4. Concomitant use with agents that are substrates of CYP3A4 (*e.g.*, hormonal contraceptives) may result in loss of efficacy of these agents. If the coadministration of narrow therapeutic index CYP3A4 substrates cannot be avoided, adjust the dose of these substrates in accordance with their approved SmPC.
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 concentrations (see section 5.2).
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.

4.6 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 (see section 4.5). 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 (see section 5.3).
Encorafenib is not recommended during pregnancy and in women of childbearing 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 breastfed 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 (see section 5.3). As the clinical relevance of this is unknown, male patients should be informed of the potential risk for impaired spermatogenesis.

4.7 Effects 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 (see sections 4.4 and 4.8).

4.8 Undesirable effects

Summary of safety profile

The safety of encorafenib (450 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) has been evaluated in the integrated safety population (ISP) of 372 patients including patients with BRAF V600 mutant unresectable or metastatic melanoma and BRAF V600E mutant advanced NSCLC (hereafter referred to as the Combo 450 ISP). In Combo 450 ISP, 274 patients

received the combination for the treatment of BRAF V600 mutant unresectable or metastatic melanoma (in two Phase II studies (CMEK162X2110 and CLGX818X2109) and one Phase III study (CMEK162B2301, Part 1)), and 98 patients received the combination for the treatment of BRAF V600E mutant advanced NSCLC (in one Phase II study (ARRAY-818-202)) (see section 5.1).
The most common adverse reactions (≥25%) occurring in patients treated with encorafenib administered with binimetinib were fatigue, nausea, diarrhoea, vomiting, abdominal pain, myopathy/muscular disorders, and arthralgia.

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, arthralgia, 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, diarrhoea, dermatitis acneiform, abdominal pain, arthralgia/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.

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA body system organ class and the following frequency convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 5: Adverse reactions

Frequency	Encorafenib single agent 300 mg (n = 217)	Encorafenib 450 mg in combination with binimetinib (n = 372)	Encorafenib 300 mg in combination with cetuximab (n = 216)
Neoplasms benign, malignant and unspecified			
Very common	Skin papilloma* Melanocytic naevus		Melanocytic naevus
Common	cuSCC [a] New Primary Melanoma*	cuSCC[a] Skin papilloma*	cuSCC[a] Skin papilloma* New Primary Melanoma*
Uncommon	Basal cell carcinoma	Basal cell carcinoma*	Basal cell carcinoma*
Blood and lymphatic system disorders			
Very common		Anaemia	
Immune system disorders			
Common	Hypersensitivity[b]	Hypersensitivity[b]	Hypersensitivity[b]
Metabolism and nutrition disorders			
Very common	Decreased appetite		Decreased appetite
Not known		Tumour lysis syndrome	

Psychiatric disorders			
Very common	Insomnia		Insomnia
Nervous system disorders			
Very common	Headache* Neuropathy peripheral* Dysgeusia*	Neuropathy peripheral* Dizziness* Headache*	Neuropathy peripheral* Headache*
Common	Facial paresis[c]	Dysgeusia*	Dizziness* Dysgeusia
Uncommon		Facial paresis[c]	
Eye disorders			
Very common		Visual impairment* RPED *	
Common		Uveitis *	
Uncommon	Uveitis*		
Cardiac disorders			
Common	Supraventricular tachycardia[d]	LVD[h]	Supraventricular tachycardia[d]
Vascular disorders			
Very common		Haemorrhage[i] Hypertension *	Haemorrhage[i]
Common		VTE[j]	
Gastrointestinal disorders			
Very common	Nausea Vomiting* Constipation	Nausea Vomiting* Constipation Abdominal pain* Diarrhoea*	Nausea Vomiting* Constipation Abdominal pain* Diarrhoea*
Common		Colitis [k]	
Uncommon	Pancreatitis*	Pancreatitis*	Pancreatitis*
Skin and subcutaneous tissue disorders			
Very common	PPES Hyperkeratosis* Rash* Dry skin* Pruritus* Alopecia* Erythema [e] Skin hyperpigmentation*	Hyperkeratosis* Rash* Dry skin* Pruritus* Alopecia*	Dermatitis acneiform* Rash* Dry skin* Pruritus*
Common	Dermatitis acneiform* Skin exfoliation[f] Photosensitivity*	Dermatitis acneiform* PPES Erythema* Panniculitis* Photosensitivity*	Skin hyperpigmentation PPES Hyperkeratosis* Alopecia Erythema[e]
Uncommon			Skin exfoliation[f]
Musculoskeletal and connective tissue disorders			
Very common	Arthralgia* Myalgia[g] Pain in extremity Back pain	Arthralgia* Myopathy/Muscular disorder[l] Pain in extremity Back pain*	Arthralgia/Musculoskeletal pain* Myopathy/Muscular disorder* Pain in extremity Back pain
Common	Arthritis *		

Uncommon		Rhabdomyolysis	
Renal and urinary disorders			
Common	Renal failure *	Renal failure*	Renal failure*
General disorders and administration site conditions			
Very common	Fatigue * Pyrexia*	Fatigue* Pyrexia* Peripheral oedema[m]	Fatigue* Pyrexia*
Investigations			
Very common	Gamma-glutamyl transferase (GGT) increased*	Blood creatine phosphokinase increased Gamma-glutamyl transferase (GGT) increased* Transaminase increased*	
Common	Transaminase increased* Blood creatinine increased* Lipase increased	Blood alkaline phosphatase increased Blood creatinine increased* Amylase increased Lipase increased	Blood creatinine increased* Transaminase increased*
Uncommon	Amylase increased		Amylase increased Lipase increased

*composite terms which included more than one preferred term
[a] includes keratoacanthoma, squamous cell carcinoma and squamous cell carcinoma of skin
[b] includes, but not limited to, angioedema, drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis and urticaria
[c] includes facial nerve disorder, facial paralysis, facial paresis, Bell's palsy
[d] includes but not limited to extrasystoles and sinus tachycardia
[e] includes erythema, generalised erythema, plantar erythema
[f] includes dermatitis exfoliative, skin exfoliation, exfoliative rash
[g] includes myalgia, muscle fatigue, muscle injury, muscle spasm, muscle weakness
[h] includes left ventricular dysfunction, ejection fraction decreased, cardiac failure and ejection fraction abnormal
[i] includes haemorrhage at various sites including, but not limited to, cerebral haemorrhage, intracranial haemorrhage, vaginal haemorrhage, heavy menstrual bleeding, intermenstrual bleeding, haematochezia, haemoptysis, haemothorax, gastrointestinal haemorrhage and haematuria
[j] includes, but not limited to, pulmonary embolism, deep vein thrombosis, embolism, thrombophlebitis, thrombophlebitis superficial, thrombosis, phlebitis, superior vena cava syndrome, mesenteric vein thrombosis and vena cava thrombosis
[k] includes colitis, colitis ulcerative, enterocolitis and proctitis
[l] includes myalgia, muscular weakness, muscle spasm, muscle injury, myopathy, myositis
[m] includes, but not limited to, fluid retention, peripheral oedema, localised oedema, generalised oedema and swelling

When encorafenib was used at a dose of 300 mg once daily in combination with binimetinib 45 mg twice daily (Combo 300) in study CMEK162B2301-Part 2, the frequency category was lower compared to the pooled Combo 450 population for the following adverse reactions: anaemia, peripheral neuropathy, haemorrhage, hypertension, pruritus (common); and colitis, increased amylase and increased lipase (uncommon).

Description of selected adverse reactions

Cutaneous malignancies
Cutaneous squamous cell carcinoma
Melanoma and NSCLC
In the Combo 450 ISP, cuSCC including keratoacanthomas was observed in 3.0% (11/372) of patients. The median time to onset of the first event of cuSCC (all grades) was 6.5 months (range 1.0 to 22.8 months).

In the pooled encorafenib 300 population, cuSCC was reported in 7.4% (16/217) patients. For patients in the Phase III study (CMEK162B2301) who developed cuSCC, the median time to onset of the first event of cuSCC (all grades) was 2.3 months (range 0.3 to 12.0 months).

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab, cuSCC including keratoacanthoma was observed in 1.4% (3/216) of patients. The times to first event of cuSCC (all grades) were 0.5, 0.6 and 3.6 months for these 3 patients.

New primary melanoma
Melanoma
In the pooled encorafenib 300 population, new primary melanoma events occurred in 4.1% of patients (9 /217) and was reported as Grade 1 in 1.4% (3/217) of patients, Grade 2 in 2.1% (4/217) of patients, Grade 3 in 0.5% (1/217) of patients and Grade 4 in 0.5% (1/217) of patients.

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab, new primary melanoma events occurred in 1.9% of patients (4/216) and were reported as Grade 2 in 0.9% (2/216) of patients and Grade 3 in 0.9% (2/216) of patients.

Ocular events
Melanoma and NSCLC
In the Combo 450 population, uveitis was reported in 3.5% (13/372) of patients, and was Grade 1 in 0.5% (2/372), Grade 2 in 2.7% (10/372) and Grade 3 in 0.3% (1/372). Visual impairment, including blurred vision and reduced visual acuity, occurred in 23.1% (86/372) of patients. Uveitis and visual impairment were generally reversible.
RPED occurred in 22.3% (83/372) of patients, most of them had Grade 1-2 and 1.6% (6/372) had Grade 3 events.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, RPED was observed in 12.5% (32/257) of patients with 0.4% (1/257) Grade 4 event.

Left ventricular dysfunction
LVD was reported when encorafenib is used in combination with binimetinib in melanoma and NSCLC patients (see section 4.8 of binimetinib SmPC).

Haemorrhage
Melanoma and NSCLC
Haemorrhagic events were observed in 16.7% (62/372) of patients in the Combo 450 ISP. Most events were Grade 1 or 2: 13.2% (49/372), and 3.5% (13/372) were Grade ≥3. Few patients required dose interruptions or dose reductions (2.4% or 9/372). Haemorrhagic events led to discontinuation of treatment in 0.8% (3/372) of patients. The most frequent haemorrhagic events were haematuria in 2.7% (10/372) of patients, haematochezia in 2.7% (10/372) and rectal haemorrhage in 2.2% (8/372) of patients. Fatal gastric ulcer haemorrhage, with multiple organ failure as a concurrent cause of death, occurred in one patient. Cerebral haemorrhage/intracranial haemorrhage was reported in 1.3% (5/372) of patients, with fatal outcome in 4 patients. All events occurred in the setting of new or progressive brain metastases.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, haemorrhagic events were observed in 6.6% (17/257) of patients and were Grade 3-4 in 1.6% (4/257) of patients.

Colorectal cancer
Haemorrhagic events were observed in 21.3% (46/216) of patients treated with encorafenib 300 mg in combination with cetuximab; 1.4% (3/216) of patients were Grade 3 events and one fatal case was reported. Dose interruptions or dose reductions were required in 1.9% (4/216) of patients. Haemorrhagic events led to treatment discontinuation in 1 patient (0.5%).
The most frequent haemorrhagic events were epistaxis in 6.9% (15/216) of patients, haematochezia in 2.8% (6/216), rectal haemorrhage in 2.8% (6/216) of patients and haematuria in 2.8% (6/216) of patients.

Hypertension
Hypertension was reported when encorafenib was used in combination with binimetinib in melanoma and NSCLC patients (see section 4.8 of binimetinib SmPC).

Venous thromboembolism
VTE was reported when encorafenib is used in combination with binimetinib in melanoma and NSCLC patients (see section 4.8 of binimetinib SmPC).

Pancreatitis
Melanoma and NSCLC
In the Combo 450 ISP, pancreatic enzyme elevation, mostly asymptomatic, was reported. Amylase and lipase elevations were reported in 4.0% (15/372) and 7.8% (29/372) of patients, respectively. Pancreatitis was reported in 0.8% (3/372) of patients. All 3 patients experienced Grade 3 events. Pancreatitis led to dose interruption in 0.3% (1/372) of patients.

Colorectal cancer
In the population treated with encorafenib 300 mg in combination with cetuximab, pancreatitis grade 3 with lipase and amylase increased events were reported in 1 patient (0.5%) and led to dose interruption.

Dermatologic reactions
Rash
Melanoma and NSCLC
In the Combo 450 ISP, rash occurred in 20.4% (76/372) of patients. Most events were mild, with Grade 3 or 4 events reported in 1.1 (4/372) of patients. Rash led to discontinuation in 0.8% (3/372) patients and to dose interruption or dose modification in 2.4% (9/372) of patients.

In the pooled encorafenib 300 population, rash was reported in 43.3% (94/217) of patients. Most events were mild, with Grade 3 or 4 events reported in 4.6% (10/217) of patients. Rash led to discontinuation in 0.5% (1/217) of patients and to dose interruption or dose modification in 7.4% (16/217) of patients.

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab, rash occurred in 30.6% (66/216) of patients. Most events were mild, with Grade 3 event reported in 0.5% (1/216) of patients. Rash led to dose interruption in 0.5% (1/216) of patients.

Palmar-plantar erythrodysaesthesia syndrome (PPES)
Melanoma and NSCLC
PPES was reported in 5.1% (19/372) of patients in the Combo 450 ISP. All the PPES adverse reactions were either Grade 1 (2.7%) or Grade 2 (2.4%). Dose interruption or dose modification occurred in 1.1% (4/372) of patients.

In the Combo 300 arm in Part 2 of the pivotal study, PPES was observed in 3.9% (10/257) of patients with Grade 3 reported in 0.4% (1/257) of patients.

In the pooled encorafenib 300 population, PPES was reported in 51.6% (112/217) of patients. Most events were mild-moderate: Grade 1 in 12.4% (27/217) of patients, Grade 2 in 26.7% (58/217) and Grade 3 in 12.4% (27/217) of patients. PPES led to discontinuation in 4.1% (9/217) of patients and to dose interruption or dose modification in 23.0% (50/217) of patients.

Colorectal cancer
In the population treated with encorafenib 300 mg in combination with cetuximab, PPES was reported in 5.1% (11/216) of patients. Most of PPES adverse reactions were Grade 1 in 3.7 % (8/216). Grade 2 events were reported in 0.9% (2/216) of patients, and Grade 3 in 0.5% (1/216) of patients. No dose interruption, dose modification or treatment discontinuation was required.

Dermatitis acneiform
Melanoma and NSCLC
Dermatitis acneiform was reported when encorafenib is used in combination with binimetinib (see section 4.8 of binimetinib SmPC).

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab, dermatitis acneiform occurred in 33.3% (72/216) of patients and was mostly Grade 1 (25.5% (55/216) of patients), or 2 (6.9% (15/216) of patients). Dose reduction or interruption was reported in 2.3 % (5/216) of patients. No treatment discontinuation was reported. Dermatitis acneiform was generally reversible.

Photosensitivity
Melanoma and NSCLC
In the Combo 450 ISP, photosensitivity was observed in 4.3% (16/372) of patients. Most events were Grade 1-2, with Grade 3 reported in 0.3% (1/372) of patients and no event led to discontinuation. Dose interruption or dose modification was reported in 0.3% (1/372) of patients.

In the pooled encorafenib 300 population, photosensitivity was reported in 4.1% (9/217) of patients. All events were Grade 1-2. No event required discontinuation, dose modification or interruption.

Facial paresis
Melanoma and NSCLC
In the Combo 450 ISP, facial paresis occurred in 0.8% (3/372) of patients including Grade 3 in 0.3% (1/372) of patients. The events were reversible, and no event led to treatment discontinuation. Dose interruption or modification was reported in 0.3% (1/372) of patients.

In the pooled encorafenib 300 population, facial paresis was observed in 7.4% (16/217) of patients. Most events were mild-moderate: Grade 1 in 2.3% (5/217); Grade 2 in 3.7% (8/217) and Grade 3 in 1.4% (3/217) of patients. The median time to onset of the first event of facial paresis was 0.3 months (range 0.1 to 12.1 months). Facial paresis was generally reversible and led to treatment discontinuation in 0.9% (2/217). Dose interruption or modification was reported in 3.7% (8/217) and symptomatic treatment including corticosteroids was reported in 5.1% (11/217) of patients.

CK elevation and rhabdomyolysis
CK elevation and rhabdomyolysis occurred when encorafenib is used in combination with binimetinib in melanoma and NSCLC patients (see section 4.8 of binimetinib SmPC).

Renal dysfunction
Melanoma and NSCLC
In the Combo 450 ISP, mild, mostly Grade 1, asymptomatic blood creatinine elevation was noted in 9.4% (35/372) of patients treated with the Combo 450. The incidence of Grade 3 or 4 elevation was 0.8% (3/372). Renal failure events, including acute kidney injury, renal failure and renal impairment, were reported in 3.5% (13/372) patients treated with encorafenib and binimetinib with Grade 3 or 4

events in 1.9% (7/372) of patients. Renal failure was generally reversible with dose interruption, rehydration and other general supportive measures.

Colorectal cancer
Blood creatinine elevation was reported in 2.8% (6/216) of patients treated with encorafenib 300 mg in combination with cetuximab. All were mild except one event of Grade 4. Renal failure events were Grade 3 or 4 and reported as acute kidney injury in 1.9 % (4/216) of patients and renal failure in 0.5% (1/216) of patients.

Liver laboratory abnormality
Melanoma and NSCLC
The incidences of liver laboratory abnormalities reported in the Combo 450 ISP are listed below:

- Increased transaminases: 16.4% (61/372) overall – 6.5% (24/372) Grade 3
- Increased GGT: 11.3% (42/372) overall – 6.7% (25/372) Grade 3-4

In Study CMEK162B2301-Part 2, in the Combo 300 arm, the incidence of liver laboratory abnormalities was:

- Increased transaminases: 13.2% (34/257) overall – 5.4% (14/257) Grade 3-4
- Increased GGT: 14.0% (36/257) overall – 4.7% (12/257) Grade 3-4

Colorectal cancer
The incidence of increased transaminases in patients treated with encorafenib 300 mg in combination with cetuximab was 8.8% (19/216) of patients, with Grade 3 in 1.4% (3/216) of patients.

Gastrointestinal disorders
Melanoma and NSCLC
In the Combo 450 ISP, diarrhoea was observed in 41.7% (155/372) of patients and was Grade 3-4 in 3.8% (14/372) patients. Diarrhoea led to treatment discontinuation in 0.8% of patients and to dose interruption or dose modification in 8.1% of patients.
Constipation occurred in 24.7% (92/372) of patients and was Grade 1 or 2. Abdominal pain was reported in 28.5% (106/372) of patients and was Grade 3 in 2.2% (8/372) patients. Nausea occurred in 46.0% (171/372) with Grade 3 observed in 3.0% (11/372) of patients. Vomiting occurred in 31.2% (116/372) of patients with Grade 3 reported in 1.9% (7/372) of patients.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, nausea was observed in 27.2% (70/257) of patients and was Grade 3 in 1.6% (4/257) of patients. Vomiting occurred in 15.2% (39/257) of patients with Grade 3 reported in 0.4% (1/257) of patients. Diarrhoea occurred in 28.4% (73/257) of patients with Grade 3 reported in 1.6% (4/257) of patients.

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab, diarrhoea was observed in 38.4% (83/216) of patients and was Grade 3 in 2.8% (6/216) of patients. Diarrhoea led to treatment discontinuation in 0.5% (1/216) of patients and to dose interruption or dose modification in 3.7% (8/216) of patients.

Abdominal pain was reported in 36.6% (79/216) of patients and was Grade 3 in 5.1% (11/216) of patients. Nausea occurred in 38.0% (82/216) of patients with Grade 3 observed in 0.5% (1/216) of patients. Vomiting occurred in 27.3% (59/216) of patients with Grade 3 reported in 1.4 % (3/216) of patients. Constipation occurred in 18.1% (39/216) of patients and was Grade 1 or 2.

Gastrointestinal disorders were typically managed with standard therapy.

Anaemia
Melanoma and NSCLC
In the Combo 450 ISP, anaemia was reported in 23.1% (86/372) of patients; 7.0% (26/372) patients had a Grade 3 or 4. No patients discontinued treatment due to anaemia, 3.2% (12/372) required dose interruption or dose modification.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, anaemia was observed in 9.7% (25/257) of patients with Grade 3-4 reported in 2.7% (7/257) patients.

Headache
Melanoma and NSCLC
In the Combo 450 ISP, headache occurred in 18.8% (70/372) of patients, including Grade 3 in 1.1% (4/372) of patients.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, headache was reported in 12.1% (31/257) of patients and was Grade 3 in 0.4% (1/257) of patients.

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab, headache occurred in 20.4% (44/216) of patients and was Grade 1 or 2.

Fatigue
Melanoma and NSCLC
In the Combo 450 ISP, fatigue occurred in 48.1% (179/372) of patients including Grade 3 or 4 in 4.3% (16/372) of patients.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, fatigue was observed in 33.5% (86/257) of patients with 1.6% (4/257) Grade 3-4 events.

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab, fatigue was reported in 56.9% (123/216) of patients including Grade 3 in 7.9% (17/216) of patients.

Special populations

Elderly
Melanoma and NSCLC
In patients treated with Combo 450 ISP (n = 372), 230 patients (61.8%) were <65 years old, 107 patients (28.8%) were 65 -74 years old and 35 patients (9.4%) were aged > 75. No overall differences in safety or efficacy were observed between elderly patients (≥ 65) and younger patients except diarrhoea and pruritus that were more frequently reported in elderly patients.
In the age subgroup of patients aged ≥ 75 years, Grade ≥3 adverse reactions (62.9% vs 47.5%), adverse reactions (all grades) requiring dose modification of any study drug (60.0% vs 48.1%) or leading to treatment discontinuation (25.7% vs 7.4%) were more frequently reported than in patients <75 years. The most common adverse reactions reported with a higher incidence in patients aged ≥ 75 years compared to patients aged < 75 years included fatigue, nausea, diarrhoea, vomiting and anaemia.

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab (n=216), 134 patients (62 %) were < 65 years old, 62 patients (28.7%) were 65-74 years old, and 20 patients (9.3%) were aged ≥ 75. The most common adverse reactions reported with a higher incidence in patients aged ≥ 65 years compared to patients aged < 65 years included fatigue, decreased appetite, and haemorrhage.

In the colorectal cancer population, due to a very small number of patients treated in the age subgroup of patients aged ≥ 75 years, differences in the incidence of adverse reactions compared to patients aged < 75 years could not be assessed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

At doses of encorafenib between 600 to 800 mg once daily, renal dysfunction (Grade 3 hypercreatinaemia) 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EC03

Mechanism of action

Encorafenib is a potent and highly selective ATP-competitive small molecule RAF kinase inhibitor. The half maximal inhibitory concentration (IC_{50}) of encorafenib against BRAF V600E, BRAF and CRAF enzymes was determined to be 0.35, 0.47 and 0.30 nM, respectively. The encorafenib dissociation half-life was >30 hours and resulted in prolonged pERK inhibition. Encorafenib suppresses the RAF/MEK/ERK pathway in tumour cells expressing several mutated forms of BRAF kinase (V600E, D and K). Specifically, encorafenib inhibits *in vitro* and *in vivo* BRAF V600E, D and K mutant melanoma cell growth and BRAF V600E mutant colorectal cancer cell growth. Encorafenib does not inhibit RAF/MEK/ERK signalling in cells expressing wild-type BRAF.

Combination with binimetinib
Encorafenib and binimetinib (a MEK inhibitor, see section 5.1 of binimetinib SmPC) both inhibit the MAPK pathway, resulting in higher anti-tumour activity, compared to treatment with either drug alone.

Combination with cetuximab
One of the main mechanisms of resistance of BRAF-mutant CRC to RAF inhibitors has been identified as the re-activation of EGFR with bypassing signal transduction via BRAF. Combinations of a BRAF inhibitor, *e.g.* encorafenib and agents targeting EGFR, *e.g*. cetuximab have shown to improve anti-tumour efficacy in non-clinical models.

Clinical efficacy and safety

BRAF V600 Mutant Unresectable or Metastatic Melanoma
The safety and efficacy of encorafenib in combination with binimetinib were evaluated in a 2-part Phase III, randomised (1:1:1) active-controlled, open-label, multicentre study in patients with unresectable or metastatic BRAF V600 E or K mutant melanoma (Study CMEK162B2301), as detected using a BRAF assay. Patients had histologically confirmed cutaneous or unknown primary melanoma but those with uveal or mucosal melanoma were excluded. Patients were permitted to receive prior adjuvant therapy and one prior line of immunotherapy for unresectable locally advanced or metastatic disease. Prior treatment with BRAF/ MEK inhibitors was not allowed.

Study CMEK162B2301, part 1
In Part 1, patients in the study were randomised to receive encorafenib 450 mg orally daily and binimetinib 45 mg orally twice daily (Combo 450, n = 192), encorafenib 300 mg orally daily (Enco 300, n = 194), or vemurafenib 960 mg orally twice daily (hereafter referred to as Vem, n = 191). Treatment continued until disease progression or unacceptable toxicity. Randomisation was stratified by American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, vs IVM1c) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1) and prior immunotherapy for unresectable or metastatic disease (yes vs no).

The primary efficacy outcome measure was progression-free survival (PFS) of Combo 450 compared with vemurafenib as assessed by a blinded independent review committee (BIRC). PFS as assessed by investigators (investigator assessment) was a supportive analysis. An additional secondary endpoint included PFS of Combo 450 compared with Enco 300. Other secondary efficacy comparisons between Combo 450 and either vemurafenib or Enco 300 included overall survival (OS), objective response rate (ORR), duration of response (DoR) and disease control rate (DCR) as assessed by BIRC and by investigator assessment.

The median age of patients was 56 years (range 20-89), 58% were male, 90% were Caucasian, and 72% of patients had baseline ECOG performance status of 0. Most patients had metastatic disease (95%) and were Stage IVM1c (64%); 27% of patients had elevated baseline serum lactate dehydrogenase (LDH), and 45% of patients had at least 3 organs with tumour involvement at baseline and 3.5% had brain metastases. 27 patients (5%) had received prior checkpoint inhibitors (anti-PD1/PDL1 or ipilimumab**)** (8 patients in Combo 450 arm (4%); 7 patients in vemurafenib arm (4%); 12 patients in Enco 300 arm (6%) including 22 patients in the metastatic setting (6 patients in Combo 450 arm; 5 patients in vemurafenib arm; 11 patients in Enco 300 arm) and 5 patients in the adjuvant setting (2 patients in Combo 450 arm; 2 patients in vemurafenib arm; 1 patient in Enco 300 arm).

The median duration of exposure was 11.7 months in patients treated with Combo 450, 7.1 months in patients treated with Enco 300 and 6.2 months in patients treated with vemurafenib. The median relative dose intensity (RDI) for Combo 450 was 100% for encorafenib and 99.6% for binimetinib; the median RDI was 86.2% for Enco 300 and 94.5% for vemurafenib.

Part 1 of Study CMEK162B2301 demonstrated a statistically significant improvement in PFS in the patients treated with Combo 450 compared with patients treated with vemurafenib. Table 6 summarises the PFS and other efficacy results based on central review of the data by a blinded independent radiology committee.

The efficacy results based on investigator assessment were consistent with the independent central assessment. Unstratified subgroup analyses demonstrated point estimates in favour of Combo 450, including LDH at baseline, ECOG performance status and AJCC stage.

Table 6: Study CMEK162B2301, Part 1: Progression-free survival and confirmed overall response results (independent central review)

	Encorafenib + binimetinib N=192 (Combo 450)	**Encorafenib N=194 (Enco300)**	**Vemurafenib N=191 (Vem)**
Cut-off date: 19 May 2016			
PFS (primary analysis)			
Number of events (%)	98 (51.0)	96 (49.5)	106 (55.5)
Median, months (95% CI)	14.9 (11.0, 18.5)	9.6 (7.5,14.8)	7.3 (5.6, 8.2)
HR[a] (95% CI) (vs Vem) p-value (stratified log-rank)[b]	0.54 (0.41, 0.71) <0.0001		
HR[a] (95% CI) (vs Vem) Nominal p-value		0.68 (0.52, 0.90) 0.007	
HR[a] (95% CI) (vs Enco 300) p-value (stratified log-rank)[b]	0.75 (0.56,1.00) 0.051		
Confirmed overall responses			
Overall response rate, n (%) (95% CI)	121 (63.0) (55.8, 69.9)	98 (50.5) (43.3, 57.8)	77 (40.3) (33.3, 47.6)
CR, n (%)	15 (7.8)	10 (5.2)	11 (5.8)
PR, n (%)	106 (55.2)	88 (45.4)	66 (34.6)
SD, n (%)	46 (24.0)	53 (27.3)	73 (38.2)
DCR, n (%) (95% CI)	177 (92.2) (87.4, 95.6)	163 (84.0) (78.1, 88.9)	156 (81.7) (75.4, 86.9)
Duration of response			
Median, months (95% CI)	16.6 (12.2, 20.4)	14.9 (11.1, NE)	12.3 (6.9, 16.9)

CI=Confidence interval; CR=Complete Response; DCR=Disease Control Rate (CR+PR+SD+Non-CR/Non-PD; Non-CR/Non-PD applies only to patients without a target lesion who did not achieve CR or have PD); HR=hazard ratio; NE=Not estimable; PFS=progression-free survival; PR=Partial response; SD=stable disease. Vem=vemurafenib.

[a] Hazard ratio based on a stratified Cox proportional hazard model

[b] Log-rank p-value (2-sided)

Quality of Life (QoL) (cut-off date: 19 May 2016)

The Functional Assessment of Cancer Therapy-Melanoma (FACT-M), the European Organisation for Research and Treatment of Cancer's core quality of life questionnaire (EORTC QLQ-C30) and the EuroQoL-5 Dimension-5 Level examination (EQ-5D-5L) were used to explore patient-reported outcomes (PRO) measures of health-related Quality of Life, functioning, melanoma symptoms, and treatment-related adverse reactions. A definitive 10% deterioration in FACT-M and in EORTC QLQ-C30 was significantly delayed in patients treated with Combo 450 relative to other treatments. The median time to definitive 10% deterioration in the FACT-M score was not reached in the Combo 450 arm and was 22.1 months (95% CI: 15.2, NE) in the vemurafenib arm with a HR for the difference of 0.46 (95% CI: 0.29, 0.72). An analysis of time to definitive 10% deterioration in EORTC QLQ-C30 score provided with similar results.

Patients receiving Combo 450 reported no change or a slight improvement in the mean change from baseline EQ-5D-5L index score at all visits, whilst patients receiving vemurafenib or encorafenib

reported decreases at all visits (with statistical significant differences). An evaluation of change over time in score yielded the same trend for EORTC QLQ-C30 and at all visit for FACT-M.

Study CMEK162B2301, part 2
Part 2 of Study CMEK162B2301 was designed to assess the contribution of binimetinib to the encorafenib and binimetinib combination.
The PFS for encorafenib 300 mg orally daily used in combination with binimetinib 45 mg orally twice daily (Combo 300, n = 258) was compared to the PFS for Enco 300 (n = 280, including 194 patients from Part 1 and 86 patients from Part 2). Enrolment in Part 2 started after all Part 1 patients were randomised.

Final efficacy analysis of Study CMEK162B2301, parts 1 and 2 (cut-off date: 31 March 2023)
The final efficacy analysis was consistent with the results of the interim analysis and showed a benefit in OS for Combo 450 over vemurafenib (HR 0.67 [95% CI:0.53,0.84] with median OS of 33.6 months *vs* 16.9 months). The PFS and ORR (per BIRC) results also confirmed a numerical benefit in favour of Combo 450, with a 7.6 months longer median PFS in the Combo 450 arm as compared to vemurafenib arm, see all detailed final efficacy results in Table 7 and Figures 1 and 2 below.

Moreover, Part 2 final analysis showed a numerical difference in OS for Combo 300 (Part 2) over Enco 300 monotherapy (Parts 1+2) (HR 0.89 [95% CI:0.72,1.09] with median OS of 27.1 months [95% CI:21.6-33.3] vs 22.7 months [95% CI: 19.3-29.3]). The median PFS remained longer in the Combo 300 (Part 2) arm than in the Enco 300 (Parts 1+2) group with median PFS estimates of 12.9 months (95% CI: 10.9, 14.9) and 9.2 months (95% CI: 7.4, 11.1), respectively. The confirmed ORR (per BIRC) was 67.8% (95% CI: 61.8, 73.5) and 51.4% (95% CI 45.4, 57.4) in the Combo 300 (Part 2) and Enco 300 (Parts 1 + 2) arms, respectively. Similar results were observed per Investigator assessment.

Table 7: Study CMEK162B2301 : Final results on PFS, OS and confirmed ORR (cut-off date: 31 March 2023)

	Encorafenib + binimetinib N=192 (Combo 450)	**Encorafenib N=194 (Enco 300)**	**Vemurafenib N=191 (Vem)**
Final analysis, cut-off date: 31 March 2023			
PFS (by BIRC)			
Number of events (%)	123 (64.1)	119 (61.3)	121 (63.4)
Median [a], months (95% CI)	14.9 (11.0, 20.2)	9.6 (7.4, 14.8)	7.3 (5.6, 7.9)
HR[c] (95% CI) (vs Vem) Log-rank p-value (1-sided)*	0.51 (0.39, 0.66) <0.0001	0.68 (0.53, 0.88) 0.0017	
HR[c] (95% CI) (vs Enco 300) Log-rank p-value (1-sided)*	0.77 (0.60, 0.99) 0.0214		

OS			
Number of events (%)	139 (72.4)	125 (64.4)	147 (77.0)
Median [a], months (95% CI)	33.6 (24.4, 39.2)	23.5 (19.6, 33.6)	16.9 (14.0, 24.5)
Survival probability [b] at 1 year % (95%CI)	75.5 (68.8, 81.0)	74.6 (67.6, 80.3)	63.1 (55.7, 69.7)
at 2 years % (95% CI)	57.7 (50.3, 64.3)	49.1 (41.5, 56.2)	43.2 (35.9, 50.2)
at 3 years % (95% CI)	46.5 (39.3, 53.4)	40.9 (33.6, 48.1)	31.4 (24.8, 38.2)
at 5 years % (95% CI)	34.7 (28.0, 41.5)	34.9 (27.9, 42.0)	21.4 (15.7, 27.8)
at 9 years % (95% CI)	26.0 (19.8, 32.5)	27.8 (21.1, 34.8)	18.2 (12.8, 24.3)
HR[c] (95% CI) (vs Vem) Log-rank p-value (1-sided)*	0.67 (0.53, 0.84) 0.0003	0.74 (0.58, 0.94) 0.0063	
HR[c] (95% CI) (vs Enco 300) Log-rank p-value (1-sided)*	0.93 (0.73, 1.19) 0.2821		
Confirmed Best Overall Response (per BIRC)			
Confirmed ORR [d], n (%) (95% CI)	123 (64.1) (56.8, 70.8)	100 (51.5) (44.3, 58.8)	78 (40.8) (33.8, 48.2)
CR, n (%)	29 (15.1)	17 (8.8)	16 (8.4)
PR, n (%)	94 (49.0)	83 (42.8)	62 (32.5)
SD, n (%)	44 (22.9)	52 (26.8)	71 (37.2)
DCR [d], n (%) (95% CI)	177 (92.2) (87.4, 95.6)	163 (84.0) (78.1, 88.9)	155 (81.2) (74.8, 86.4)
Duration of Response (per BIRC)			
Median, months (95% CI)	18.6 (12.7, 27.6)	15.5 (11.1, 29.5)	12.3 (6.9, 14.5)

CI=Confidence Interval; CR=Complete Response; PR=Partial response; SD=stable disease; DCR=Disease Control Rate (CR+PR+SD+Non-CR/Non-PD); HR=hazard ratio; ORR=objective response rate (CR+PR); PR and CR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response is first met.

[a] Median (time to event) and its 95% CIs are generated by KM estimation with Brookmeyer & Crowley method

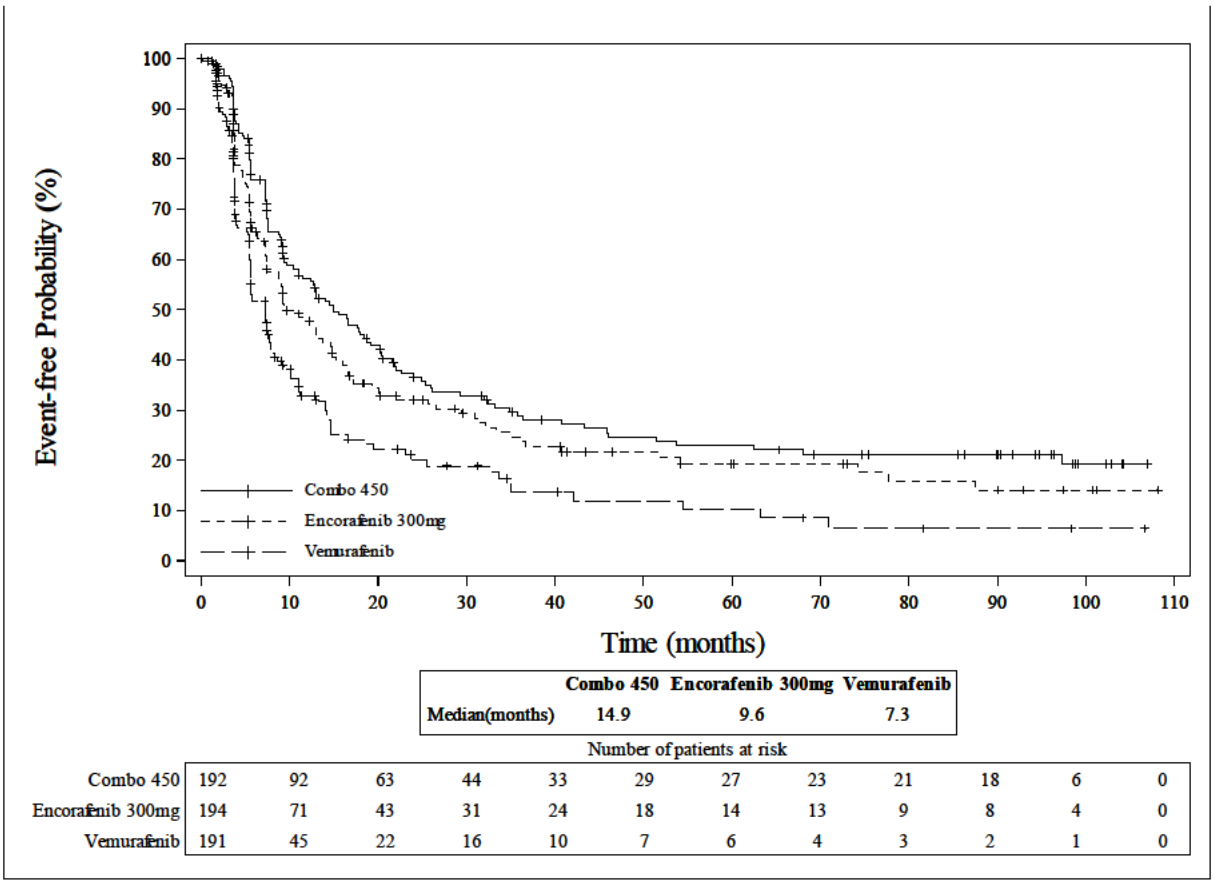
[b] Survival probability (obtained from the KM survival estimates, Greenwood formula used for CIs)

[c] Both Log-rank test and Cox PH model are stratified by IVRS AJCC stage and ECOG Performance status

[d] estimated 95% CI are obtained using the exact Clopper-Pearson method

*nominal p-value

Figure 1 Study CMEK162B2301: Kaplan-Meier plot of PFS by BIRC (cut-off date: 31 March 2023)

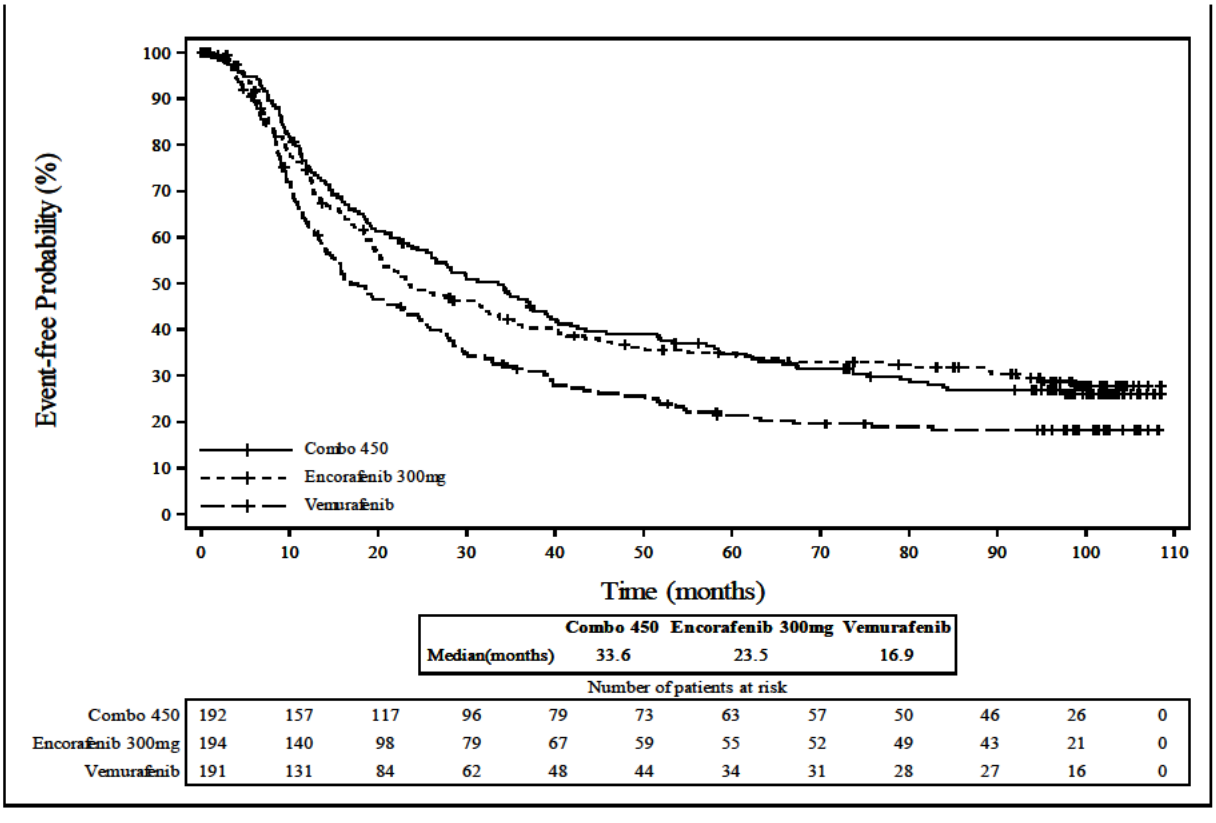


	Combo 450	Encorafenib 300mg	Vemurafenib
Median(months)	14.9	9.6	7.3

Number of patients at risk

Combo 450	192	92	63	44	33	29	27	23	21	18	6	0
Encorafenib 300mg	194	71	43	31	24	18	14	13	9	8	4	0
Vemurafenib	191	45	22	16	10	7	6	4	3	2	1	0

Figure 2 Study CMEK162B2301: Kaplan-Meier plot of OS (cut-off date: 31 March 2023)



	Combo 450	Encorafenib 300mg	Vemurafenib
Median(months)	33.6	23.5	16.9

Number of patients at risk

Combo 450	192	157	117	96	79	73	63	57	50	46	26	0
Encorafenib 300mg	194	140	98	79	67	59	55	52	49	43	21	0
Vemurafenib	191	131	84	62	48	44	34	31	28	27	16	0

BRAF V600E Mutant metastatic colorectal cancer - Study ARRAY-818-302

Encorafenib in combination with cetuximab was evaluated in a randomised, active-controlled, open-label, multicentre trial (ARRAY 818-302 BEACON CRC). Eligible patients were required to have BRAF V600E mutant metastatic colorectal cancer that had progressed after 1 or 2 prior regimens. Enrolled patients were eligible to receive cetuximab per locally approved label with regards to tumour RAS status. Prior use of RAF inhibitors, MEK inhibitors or EGFR inhibitors was prohibited. Randomisation was stratified by Eastern Cooperative Oncology Group (ECOG) performance status, prior use of irinotecan and cetuximab source.

A total of 665 patients were randomised (1:1:1) to receive encorafenib 300 mg orally daily in combination with cetuximab dosed as per its approved SmPC (n=220), or encorafenib 300 mg orally daily in combination with binimetinib 45 mg orally twice daily and cetuximab dosed as per its approved SmPC (n=224) or Control (irinotecan with cetuximab or irinotecan/5-fluorouracil/folinic acid (FOLFIRI) with cetuximab, n= 221). Treatment continued until disease progression or unacceptable toxicity.

The efficacy outcome measures were overall survival (OS) and overall response rate (ORR) as assessed by a blinded independent central review committee (BIRC), comparing encorafenib 300 mg in combination with cetuximab versus Control. Other efficacy measures are summarised in Table 8 below.

The median age of patients was 61 years (range 26-91), 47 % were male and 83% were white. 51% of patients had baseline ECOG performance status of 0, and 51% received prior irinotecan. 46.8% of patients had at least 3 organs with tumour involvement at baseline.
The median duration of exposure was 3.2-months in patients treated with encorafenib 300 mg in combination with cetuximab, and 1.4 months in patients treated with irinotecan/cetuximab or FOLFIRI/cetuximab (Control arm). In patients treated with the combination of encorafenib 300 mg and cetuximab, the median relative dose intensity (RDI) was 98% for encorafenib and 93.5% for cetuximab. In the control arm, the median RDI was 85.4% for cetuximab, 75.7% for irinotecan and in the subset of patients who received Folinic acid and 5-FU, the median RDI was 75.2% and 75% respectively.

Encorafenib 300 mg in combination with cetuximab demonstrated a statistically significant improvement in OS, ORR and PFS compared to Control. Efficacy results are summarised in Table 8 and Figures 3 and 4.

The efficacy results based on investigator assessment were consistent with the independent central assessment.

Table 8: Study ARRAY-818-302: Efficacy Results

	Encorafenib with cetuximab	**Irinotecan with cetuximab or FOLFIRI with cetuximab (Control)**
Cut-off date: 11 February 2019 (Primary analysis)		
OS		
Number of patients[a]	220	221
Number of events (%)	93 (42.3)	114 (51.6)
Median, months (95% CI)	8.4 (7.5-11.0)	5.4 (4.8, 6.6)
HR (95% CI)[b,c] (vs Control) p-value[b,c]	0.60 (0.41-0.88) 0.0002	
Median duration of follow-up, months (95% CI)	7.6 (6.4, 9.20)	7.2 (6.1, 8.1)

ORR (per BIRC)		
Number of patients[e]	113	107
ORR n (%) (95% CI)[f]	23 (20.4) (13.4, 29.0)	2 (1.9) (0.2, 6.6)
P-value[b,d,g]	<0.0001	
CR, n (%)	6 (5.3)	0
PR, n (%)	17 (15.0)	2 (1.9)
SD, n (%)	57 (50.4)	26 (24.3)
DCR, n (%) (95% CI)[f]	84 (74.3) (65.3, 82.1)	33 (30.8) (22.3, 40.5)
PFS (per BIRC)		
Number of patients[a]	220	221
Number of events (%)	133 (60.5)	128 (57.9)
Median PFS, months (95% CI)	4.2 (3.7, 5.4)	1.5 (1.5, 1.7)
HR (95% CI)[b,c] P-value[b,d]	0.40 (0.30, 0.55 < 0.0001	
Updated analysis, cut-off date: 15 August 2019		
OS		
Number of patients[a]	220	221
Number of events (%)	128 (58.2)	157 (71.0)
Median, months (95% CI)	9.3 (8.0, 11.3)	5.9 (5.1, 7.1)
HR (95% CI)[b] (vs Control) p-value[b,d,h]	0.61 (0.48, 0.77) < 0.0001	
Median duration of follow-up, months (95% CI)	12.3 (11.1, 14.1)	12.9 (10.9, 14.6)
ORR (per BIRC)		
Number of patients[a]	220	221
ORR n (%) (95% CI)[f]	43 (19.5) (14.5, 25.4)	4 (1.8) (0.5, 4.6)
p-value[b,d,g,h]	<0.0001	
CR, n (%)	7 (3.2)	0
PR, n (%)	36 (16.4)	4 (1.8)
SD, n (%)	117 (53.2)	59 (26.7)
DCR, n (%) (95% CI)[f]	167 (75.9) (69.7, 81.4)	69 (31.2) (25.2, 37.8)
PFS (per BIRC)		
Number of patients[a]	220	221
Number of events (%)	167 (75.9)	147 (66.5)
Median PFS, months (95% CI)	4.3 (4.1, 5.5)	1.5 (1.5, 1.9)
HR (95% CI)[b] P-value[b,d, h]	0.44 (0.35, 0.55) < 0.0001	

CI = Confidence interval; CR = Complete response; HR = Hazard ratio; ORR = Overall response rate; OS = Overall survival; PR = Partial response; SD = Stable disease, DCR: Disease control rate (CR+PR+SD+Non-CR/Non-PD; Non-CR/Non-PD applies only to patients with a non-measurable disease who did not achieve CR or have PD)

[a] Randomised Phase 3, Full Analysis Set

[b] Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomization
[c] Repeated CI derived using Lan DeMets O'Brien-Fleming boundaries associated with the observed information fraction at the interim analysis
[d] 1-sided
[e] Among the first 331 randomised patients
[f] Clopper-Pearson's method
[g] Cochran Mantel-Haenszel test
[h] Nominal p-value

Figure 3: Study ARRAY-818-302: Kaplan-Meier plot of Overall Survival (cut-off date: 11 February 2019)

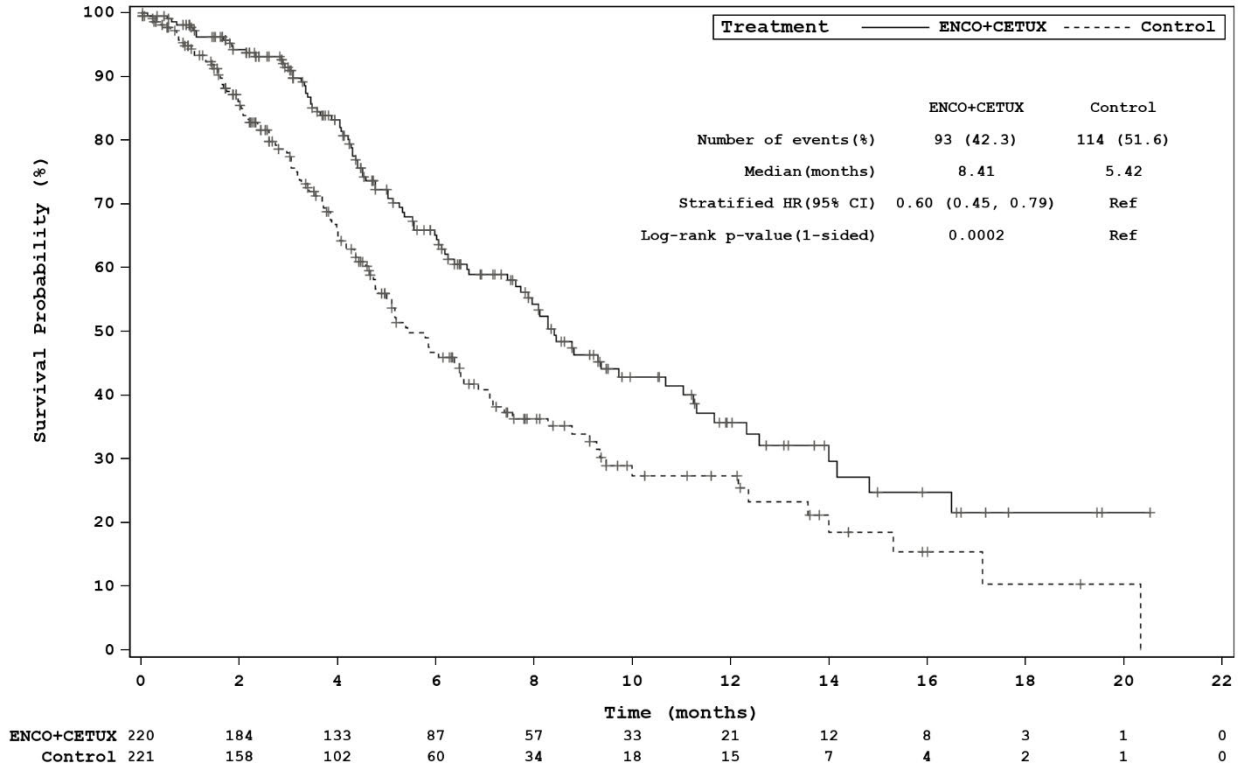
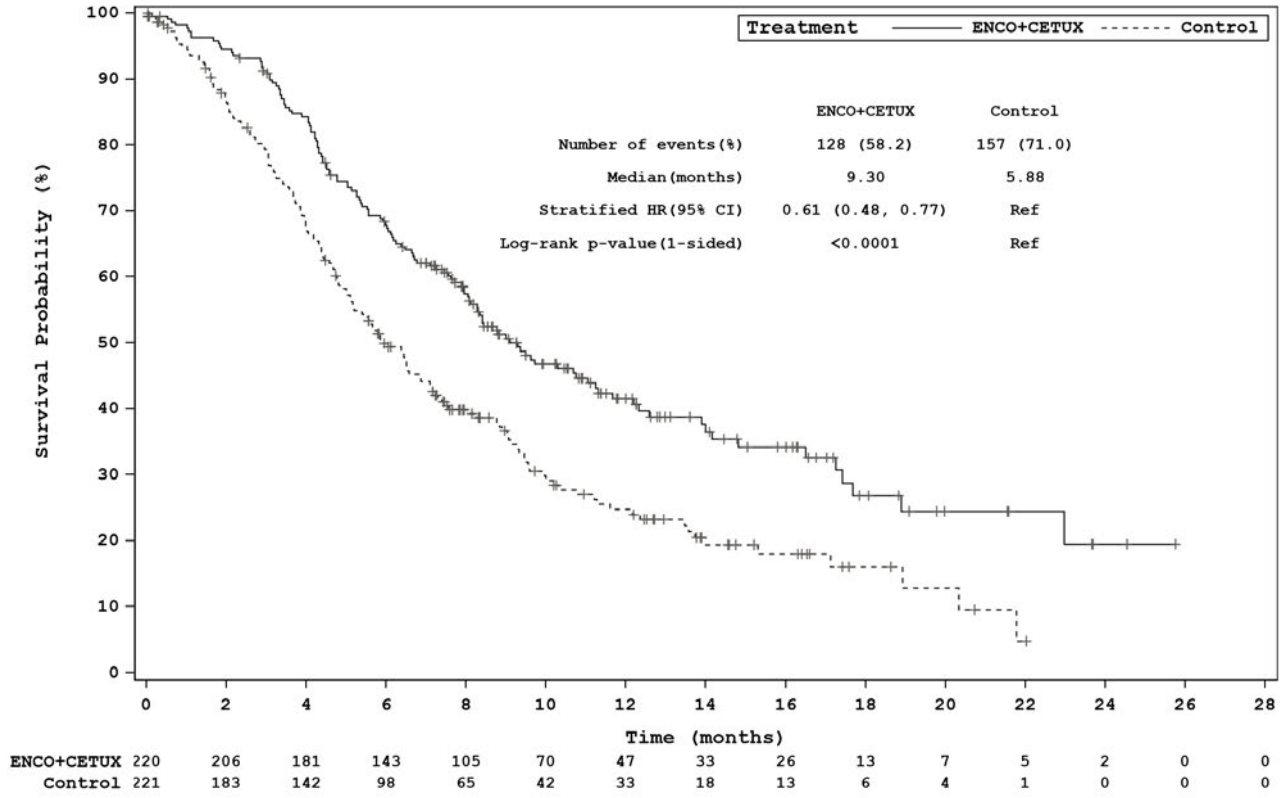


Figure 4: Study ARRAY-818-302: Kaplan-Meier plot of Overall Survival (cut-off date: 15 August 2019)



BRAF V600E Mutant advanced Non-small cell lung cancer – Study ARRAY-818-202

The safety and efficacy of encorafenib in combination with binimetinib were studied in a Phase II, open-label, multicentre, non-comparative study (Study ARRAY-818-202, PHAROS). Patients were required to have histologically-confirmed metastatic NSCLC with a BRAF V600E mutation, ECOG performance status of 0 or 1, and measurable disease. Patients had received 0 or 1 prior line of systemic therapy in the metastatic setting. Prior use of BRAF inhibitors or MEK inhibitors was prohibited.

Patients were enrolled based on the determination of a BRAF V600E mutation in tumour tissue or blood (e.g., ctDNA genetic testing) by a local laboratory assay. Central confirmation of the BRAF V600E mutation status (i.e. any short variant with protein effect V600E) was performed on archival or fresh tumour tissue collected at enrolment and utilized the FoundationOne CDx – F1CDx (tissue) assay.

The analytical sensitivity was assessed through the Limit of Detection (LoD) study for F1CDx using the hit rate method (defined as the lowest level with ≥ 95% detection) by evaluating variant allele frequency (VAF) for short variants. For F1CDx, the median LoD for substitution was determined to be 3.2% VAF.

A total of 98 patients were enrolled and treated with encorafenib 450 mg orally once daily and binimetinib 45 mg orally twice daily. Treatment continued until disease progression or unacceptable toxicity.

The primary efficacy outcome measure was objective response rate (ORR) and was according to RECIST v1.1 as evaluated by an Independent Radiology Review (IRR). Secondary endpoints included duration of response (DoR), disease control rate (DCR), PFS and OS. Results of the primary analysis

with 18.2 months for treatment naïve and 12.8 months previously treated patients are presented below.

Of the 98 patients enrolled in this study, 59 (60.2%) patients were treatment naïve. The median age of patients was 70 years (47-86), 53% were female, 88% were white and 30% had never smoked. 74% had a baseline ECOG performance status of 1 (67.8 % of participants had a baseline PS 1 in the treatment naïve population and 82.1 % in the previously treated population). All patients had metastatic disease of which 8% had brain metastases at baseline and 97% had adenocarcinoma.

At the time of the primary analysis, the median duration of exposure was 15.1 months in treatment naïve patients and 5.4 months in previously treated patients. In the overall population, the median relative dose intensity (RDI) was 99.2% for encorafenib and 95.4% for binimetinib.

At the time of the primary analysis, the primary endpoint of IRR-assessed ORR in the treatment naïve population was 74.6% (95% CI: 61.6, 85.0), including 9 (15.3%) CRs and 35 (59.3%) PRs.
The ORR by IRR in the previously treated population was 46.2% (95% CI: 30.1, 62.8), including 4 (10.3%) CRs and 14 (35.9%) PRs.

Results updated with an additional 10-month follow-up (median duration of exposure of 16.3 months in treatment naïve patients and 5.5 months in previously treated patients) are provided in Table 9.

Table 9: Study ARRAY-818-202: Efficacy Results

	Encorafenib with Binimetinib	
	Treatment Naïve (N=59)	**Previously Treated (N=39)**
ORR per IRR		
ORR, % (95% CI)	75% (62, 85)	46% (30, 63)
CR, %	15%	10%
PR, %	59%	36%
DoR per IRR	N=44	N=18
Median DoR, months (95% CI)	40.0 (23.1, NE)*	16.7 (7.4, NE)*
% with DoR ≥12 months	64%	44%

* Results from a sensitivity analysis considering new anti-cancer therapy as an event in addition to progression and death are 23.1 months in treatment naïve patients (14.8; NE) and 12.0 months (6.3; NE) in previously treated patients.
N = number of patients; ORR = Objective Response Rate; CI = Confidence Interval; CR = Complete Response; PR = Partial Response; DoR = Duration of Response; IRR= Independent Radiology Review; NE = not estimable

Cardiac electrophysiology
In the safety analysis of pooled studies, the incidence of new QTcF prolongation >500 ms was 1.1% (4/363) in the Combo 450 ISP (n = 372), and 2.5% (5/203) in the encorafenib single agent group of patients with melanoma. QTcF prolongation of >60 ms compared to pre-treatment values was observed in 6.0% (22/364) patients in the Combo 450 ISP, and in 3.4% (7/204) in the encorafenib single agent group (see sections 4.2 and 4.4).

In the safety analysis of the Phase 3 (ARRAY-818-302) safety set in colorectal indication, the incidence of new QTcF prolongation >500 ms was 3.2% (7/216) and QTcF prolongation of >60 ms compared to pre-treatment values was observed in 8.8% (19/216) of patients of the encorafenib + cetuximab arm (see sections 4.2 and 4.4).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with encorafenib in one or more subsets of the paediatric population in melanoma (see section 4.2 for information on paediatric use).

The European Medicines Agency has waived the obligation to submit the results of studies with encorafenib in all subsets of the paediatric population in colorectal carcinoma and lung cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumours. 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 T_{max} of 1.5 to 2 hours. Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, at least 86% of the encorafenib dose was absorbed. Administration of a single 100 mg dose of encorafenib with a high-fat, high-calorie meal decreased the C_{max} 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 gastric 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 [^{14}C] 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%).

Biotransformation

Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, metabolism was found to be the major clearance pathway for encorafenib (approximately 88% of the recovered radioactive dose). The predominant biotransformation reaction of encorafenib was N-dealkylation. Other major metabolic pathways involved hydroxylation, carbamate hydrolysis, indirect glucuronidation and glucose conjugate formation.

Elimination

Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, radioactivity was eliminated equally in both the faeces and urine (mean of 47.2%). In urine, 1.8% of the radioactivity was excreted as encorafenib. The mean (CV%) apparent clearance (CL/F) of encorafenib was 27.9 L/h (9.15%). The median (range) encorafenib terminal half-life ($T_{1/2}$) was 6.32 h (3.74 to 8.09 h).

Medicinal product 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).
The effect of co-administering a strong CYP3A4 inducer on encorafenib exposure has not been studied in a dedicated trial. Repeat dose administration of encorafenib 450 mg once daily and binimetinib 45 mg twice daily in melanoma patients with modafinil, a moderate CYP3A4 inducer, decreased encorafenib steady-state AUC by 24% and C_{max} by 20%, compared to encorafenib alone.

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 inhibitor of CYP3A4. Encorafenib induced CYP1A2, CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes.
Repeat dose administration of encorafenib 450 mg once daily and binimetinib 45 mg twice daily in melanoma patients with a single dose of CYP probe substrate cocktail reduced midazolam 2 mg (CYP3A4 substrate) AUC by 82% and Cmax by 74 %. It decreased omeprazole 20 mg (CYP2C19 substrate) AUC by 17 % and did not change Cmax and increased caffeine 50 mg (CYP1A2 substrate) AUC by 27 % and Cmax by 13 %. It decreased the ratio of losartan metabolite E3174 to losartan (CYP2C9 substrate) concentrations in urine by 28% and did not change the ratio of dextromethorphan metabolite (dextrorphan) to dextromethorphan (CYP2D6 substrate) concentrations in urine. These results indicate strong induction of CYP3A4, mild inhibition of CYP1A2 and no impact on pharmacokinetics of CYP2C19 substrates. From the urinary data, the inhibitory potency on CYP2C9 and CYP2D6 cannot be finally concluded. No data are available for CYP2D6 poor metabolisers.
A single dose of encorafenib 450 mg and binimetinib 45 mg reduced bupropion 75 mg (CYP2B6 substrate) AUC and Cmax by ≤ 25%. Repeated administration of encorafenib 450 mg daily and binimetinib 45 mg twice daily reduced bupropion AUC and Cmax by ≤ 26 % and increased the AUC of the active metabolite hydroxybupropion by 49% indicating mild induction.
For co-administration with 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 (OCT1, OATP1B1, OATP1B3 and OATPB1) was investigated *in vitro* using relevant transporter inhibitors. The data suggest that hepatic uptake transporters 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 OATP1B1, OATP1B3 and BCRP substrate) increased rosuvastatin Cmax by 2.7-fold and AUC by 1.6-fold indicating a mild inhibition of OATP1B1, OATP1B3 and/or BCRP transporters.
In vitro, encorafenib inhibited the hepatic transporter OCT1, but is unlikely to be an effective inhibitor clinically. Based on *in vitro* studies, there is potential for encorafenib to inhibit renal transporters OCT2, OAT1, OAT3 at clinical concentrations. In addition, encorafenib may inhibit P-gp in the gut at the expected clinical concentrations.

Special populations

Age
Based on a population pharmacokinetic analysis, age was found to be a significant covariate on encorafenib volume of distribution, but with high variability. Given the small magnitude of these

changes and high variability, these are unlikely to be clinically meaningful, and no dose adjustments are needed for elderly patients.

Gender
Based on a population pharmacokinetic analysis gender was not found to be a significant model covariate on clearance or volume of distribution. As a result, no major changes in encorafenib exposure are expected based upon gender.

Body weight
Based on a population pharmacokinetic analysis, body weight was found to be a significant model covariate on clearance and volume of distribution. However, given the small magnitude of change in clearance and the high variability in the predicted volume of distribution in the model, weight is unlikely to have a clinically relevant influence on the exposition of encorafenib.

Race
There are no clinically relevant differences in encorafenib PK between Asians and non Asians. There are insufficient data to evaluate potential differences in the exposure of encorafenib in other races or ethnicity.

Hepatic impairment
Results from a dedicated clinical study indicate a 25% higher total encorafenib exposures in patients with mild hepatic impairment (Child-Pugh Class A) compared with subjects with normal liver function. This translates into a 55% increase of the unbound encorafenib exposure.
The pharmacokinetics of encorafenib has not been evaluated clinically in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. As encorafenib is primarily metabolised and eliminated via the liver, based on PBPK modelling, patients with moderate to severe hepatic impairment may have greater increases in exposure than patients with mild hepatic impairment. No dosing recommendation can be made in patients with moderate or severe hepatic impairment (see sections 4.2 and 4.4).

Renal impairment
Encorafenib undergoes minimal renal elimination. No formal clinical study has been conducted to evaluate the effect of renal impairment on the pharmacokinetics of encorafenib.
In a population pharmacokinetic analysis, no clear trend in encorafenib CL/F was observed in patients with mild (eGFR 60 to 90 mL/min/1.73 m^2) or moderate (eGFR 30 to 59 mL/min/1.73 m^2) renal impairment compared with subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2). A small decrease in CL/F (≤5%) was predicted for patients with mild and moderate renal impairment, which is unlikely to be clinically relevant. The pharmacokinetics of encorafenib have not been studied in patients with severe renal impairment.

5.3 Preclinical safety data

In the 4-week and 13-week rat toxicity studies, clinical signs, reduced body weight reduced epididymides and prostate weights and microscopic findings in testes, epididymides, stomach and skin were noted. Partial reversibility of these findings was noted after a 4-week recovery period. No NOAEL could be established for the 4-week study. The NOAEL determined in the 13-week study was more than 10-times human therapeutic exposures.

In the 4-week and 13-week monkey toxicity study, isolated/sporadic episodes of emesis and diarrhoea as well as ophthalmic lesions were observed at slightly above human therapeutic exposures. Ophthalmic lesions were partially reversible and consisted of a separation or detachment in the retina between the outer rods and cones layer and retinal pigmented epithelium at the central macula at the fovea. This observation was similar to that described in humans as central serous-like chorioretinopathy or central serous retinopathy.

Encorafenib was not genotoxic.

Fertility studies were not conducted with encorafenib. In the 13-week rat toxicology studies, encorafenib treatment at 6 mg/kg/d (dose level more than 5 times the human exposure at the therapeutic dose) resulted in decreased testes and epididymis weights with tubular degeneration and oligospermia. In the 13-week study, partial reversibility was noted at the highest dose level (60 mg/kg/d).

The embryo-foetal development study in rats indicated that encorafenib induced foetal toxicity with lower foetal weights and delays in skeletal development.
The embryo-foetal development study in rabbits indicated that encorafenib induced foetal toxicity with lower foetal weights and transitory changes in skeletal development. Dilatation of the aortic arc was observed in some foetuses.

Encorafenib was phototoxic in an *in vitro* 3T3 Neutral Red Uptake Test. Encorafenib was not a sensitiser in the *in vivo* mouse sensitization assay. Collectively, these data indicate that encorafenib has a risk of phototoxic potential and minimal risk for sensitization at therapeutic doses in patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Copovidone (E1208)
Poloxamer 188
Cellulose microcrystalline (E460i)
Succinic acid (E363)
Crospovidone (E1202)
Silica colloidal anhydrous (E551)
Magnesium stearate (E470b)

Capsule shell

Gelatin (E441)
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)
Iron oxide black (E172)

Printing ink

Shellac (E904)
Iron oxide black (E172)
Propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Braftovi 50 mg hard capsules

Each pack contains either 28x1 or 112x1 hard capsules in polyamide/aluminium/PVC/aluminium/ PET/paper perforated unit dose blisters.
Not all pack sizes may be marketed.

Braftovi 75 mg hard capsules

Each pack contains either 42x1 or 168x1 hard capsules in polyamide/aluminium/PVC/aluminium/ PET/paper perforated unit dose blisters.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

8. MARKETING AUTHORISATION NUMBER(S)

Braftovi 50 mg hard capsules

EU/1/18/1314/001 28x1 hard capsules
EU/1/18/1314/003 112x1 hard capsules

Braftovi 75 mg hard capsules

EU/1/18/1314/002 42x1 hard capsules
EU/1/18/1314/004 168x1 hard capsules

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2018
Date of latest renewal: 23 June 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

PIERRE FABRE MEDICAMENT PRODUCTION
Site Progipharm, rue du Lycée
45500 GIEN
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Braftovi 50 mg hard capsules
encorafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg encorafenib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 x 1 hard capsules
112 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C. Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1314/001 28x1 hard capsules
EU/1/18/1314/003 112x1 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

braftovi 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Braftovi 50 mg capsules
encorafenib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pierre Fabre Médicament

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Braftovi 75 mg hard capsules
encorafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 75 mg encorafenib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

42 x 1 hard capsules
168 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C. Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1314/002 42x1 hard capsules
EU/1/18/1314/004 168x1 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

braftovi 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Braftovi 75 mg capsules
encorafenib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pierre Fabre Médicament

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Braftovi 50 mg hard capsules
Braftovi 75 mg hard capsules
encorafenib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Braftovi is and what it is used for
2. What you need to know before you take Braftovi
3. How to take Braftovi
4. Possible side effects
5. How to store Braftovi
6. Contents of the pack and other information

1. What Braftovi is and what it is used for

Braftovi is an anti-cancer medicine that contains the active substance encorafenib. Changes (mutations) in the BRAF gene can produce proteins that cause the cancer to grow. Braftovi targets proteins made from this changed BRAF gene.

It is used in combination with another medicine containing binimetinib to treat adult patients with a type of skin cancer called melanoma or a type of lung cancer called non-small cell lung cancer (NSCLC), when the cancer has
- a particular change (mutation) in a gene responsible for producing a protein called BRAF, and
- spread to other parts of the body, or cannot be removed by surgery

When Braftovi is used in combination with binimetinib, which targets another protein that stimulates cancer cell growth, the combination slows down or stops the growth of your cancer.

Braftovi is also used in combination with another medicine cetuximab, to treat adult patients with a type of large intestine cancer when it has
- a particular change (mutation) in a gene responsible for producing a protein called BRAF, and
- spread to other parts of the body of patients who have been previously treated with other anticancer medicines

When Braftovi is used in combination with cetuximab (which binds to the epidermal growth factor receptor (EGFR)), a protein on the surface of certain cancer cells), the combination slows down or stops the growth of your cancer.

2. What you need to know before you take Braftovi

Before starting treatment your doctor will check for the BRAF mutation.

As Braftovi is to be used in combination with binimetinib to treat melanoma and NSCLC, read the binimetinib leaflet carefully as well as this leaflet.

As Braftovi is to be used in combination with cetuximab to treat large intestine cancer, read the cetuximab leaflet carefully as well as this leaflet.

Do not take Braftovi
- if you are allergic to encorafenib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Braftovi, about all of your medical conditions, particularly if you have any of the following:
- heart problems including alteration of the electrical activity of your heart (QT interval prolongation)
- bleeding problems or if you are taking medicines that may cause bleeding
- eye problems
- liver or kidney problems

Tell your doctor if you have had a different type of cancer other than melanoma, large intestine cancer or NSCLC, as Braftovi may worsen certain other types of cancers.

Tell your doctor, pharmacist or nurse immediately if you get the following while you are taking this medicine:
- Heart problems: Braftovi when taken with binimetinib can make your heart work less well, alter the electrical activity of your heart called "QT interval prolongation" or make existing heart problems worse. Your doctor will check that your heart is working properly before and during your treatment with these medicines. Talk to your doctor immediately if you have any symptoms of heart problems such as feeling dizzy, tired, lightheaded, if you have shortness of breath, if you feel like your heart is pounding, racing, beating irregularly, or if you have swelling in the legs.

- Bleeding problems: Braftovi may cause serious bleeding problems. Talk to your doctor immediately if you have any symptoms of bleeding problems such as coughing up of blood, blood clots, vomit containing blood or that looks like "coffee grounds", red or black stools that look like tar, passing blood in the urine, stomach (abdominal) pain, unusual vaginal bleeding. Also tell your doctor if you have headache, dizziness or weakness.

- Eye problems: Braftovi, when taken with binimetinib, can cause serious eye problems. Talk to your doctor immediately if you get blurred vision, loss of vision, or other vision changes (*e.g.* coloured dots in your vision), halo (seeing blurred outline around objects). Your doctor will examine your eyes for any problems with your sight while you are taking Braftovi.

- Skin changes: Braftovi may cause other types of skin cancer such as cutaneous squamous cell carcinoma. New melanomas may also occur while taking Braftovi. Your doctor will check your skin for any new skin cancers before treatment, every 2 months during treatment, and for up to 6 months after you stop taking Braftovi. Tell your doctor immediately if you detect skin changes during and after treatment including: new wart, skin sore or reddish bump that bleeds or does not heal, or a change in size or colour of a mole. Additionally, your doctor needs to check for squamous cell carcinoma on your head, neck, mouth and lymph glands, and you will have CT scans regularly. This is a precaution in case a squamous cell carcinoma develops inside your body. Genital examinations (for women) and anal examinations are also recommended before and at the end of your treatment.

- Liver problems: Braftovi can cause abnormal blood tests related to how your liver works (raised levels of liver enzymes). Your doctor will run blood tests to check your liver before and during treatment.

- Kidney problems: Braftovi can alter your kidney activity (often abnormal blood tests, more rarely dehydration and vomiting). Your doctor will run blood tests to monitor your kidneys

before and during treatment. Drink plenty of fluids during treatment. Tell your doctor immediately if you vomit and become dehydrated.

If you experience the following symptoms, contact your doctor immediately as this can be a life-threatening condition: nausea, shortness of breath, irregular heartbeat, muscular cramps, seizures, clouding of urine, decrease in urine output and tiredness. These may be caused by a group of metabolic complications that can occur during treatment of cancer that are caused by the breakdown products of dying cancer cells (Tumour lysis syndrome (TLS)) and can lead to changes in kidney function (see also section 4. Possible side effects).

Children and adolescents
Braftovi is not recommended for children and adolescents under 18 years of age. This medicine has not been studied in this age group.

Other medicines and Braftovi
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.
Some medicines may affect how Braftovi works or make it more likely that you will have side effects. In particular, tell your doctor if you are taking anything in this list or any other medicines:
- some medicines to treat fungal infections (such as itraconazole, posaconazole, fluconazole)
- some medicines to treat bacterial infections (such as rifampicin, clarithromycin, telithromycin, erythromycin, penicillin)
- medicines typically used to treat epilepsy (seizures) (such as phenytoin, carbamazepine)
- medicines typically used to treat cancer (such as methotrexate, imatinib)
- medicines typically used to treat high cholesterol (such as rosuvastatin, atorvastatin)
- an herbal treatment for depression: St. John's wort
- some medicines for HIV treatment such as ritonavir, amprenavir, raltegravir, dolutegravir
- birth control medicines containing hormones
- medicines typically used to treat high blood pressure (such as diltiazem, bosentan, furosemide)
- a medicine used to treat an uneven heartbeat: amiodarone.

Braftovi with food and drink
Do not have grapefruit juice during your treatment with Braftovi. This is because it could increase Braftovi side effects.

Pregnancy
Braftovi is not recommended during pregnancy. It may cause harm or birth defects to an unborn baby. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
If you are a woman who could become pregnant, you must use reliable contraception while you are taking Braftovi, and you must continue to use reliable contraception for at least 1 month after taking your last dose. Birth control medicines containing hormones (such as pills, injections, patches, implants and certain intrauterine devices (IUDs) that release hormones) may not work as well as expected while you are taking Braftovi. You should use another reliable method of birth control such as a barrier method (*e.g.* condom) so you do not become pregnant while you are taking this medicine. Ask your doctor, pharmacist or nurse for advice.
Contact your doctor straightaway if you become pregnant while taking Braftovi.

Breast-feeding
Braftovi is not recommended while breast-feeding. It is not known if Braftovi passes into breast milk. If you are breast-feeding, or planning to breast-feed, ask your doctor for advice before taking this medicine.

Fertility
Braftovi may reduce sperm count in males. This could affect the ability to father a child. Talk to your doctor if this is a concern for you.

Driving and using machines
Braftovi can affect your ability to drive or use machines. Avoid driving or using machines if you have any problems with your vision, or have any other side effects that can affect your ability to drive or use machines (see section 4), while taking Braftovi. Talk to your doctor if you are not sure you can drive.

3. How to take Braftovi

How much to take
Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

For melanoma and NSCLC treatment
The recommended dose of Braftovi is 6 capsules of 75 mg once daily (corresponding to a daily dose of 450 mg). You will also receive treatment with another medicine, binimetinib.

For large intestine cancer treatment
The recommended dose of Braftovi to treat large intestine cancer is 4 capsules of 75 mg once daily (corresponding to a daily dose of 300 mg). You will also receive treatment with another medicine cetuximab.

If you have liver or kidney problems, your doctor may start you on a lower dose.
If you get serious side effects (such as heart, eye or bleeding problems) your doctor may lower the dose or stop treatment temporarily or permanently.

How to take Braftovi

Instructions to open the blister:
- Do not push the capsule through the blister.
- Separate one blister cell by bending it and gently tearing along the perforations.
- Carefully peel off the blister foil starting at the corner labelled with an arrow.
- Gently remove the capsule.

Swallow the capsules whole with water. Braftovi can be taken with food or between meals.

If you are sick
If you vomit at any time after taking Braftovi, do not take an additional dose. Take the next dose as scheduled.

If you take more Braftovi than you should
If you take more capsules than you should, contact your doctor, pharmacist or nurse straightaway. Side effects of Braftovi such as nausea, vomiting, dehydration and blurred vision may appear or worsen. If possible, show them this leaflet and the medicine package.

If you forget to take Braftovi
If you miss a dose of Braftovi, take it as soon as you remember. However if the missed dose is more than 12 hours late, skip that dose and take your next dose at the usual time. Then continue taking your capsules at regular times as usual.
Do not take a double dose to make up for a forgotten dose.

If you stop taking Braftovi
It is important to take Braftovi for as long as your doctor prescribes it. Do not stop taking this medicine unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Braftovi may cause serious side effects. Tell your doctor immediately if you have any of the following serious side effects, either for the first time or if they get worse (see also section 2):

Heart problems: Braftovi when taken with binimetinib can affect how well your heart works (left ventricular ejection fraction decrease); signs and symptoms can include:
- feeling dizzy, tired or lightheaded
- shortness of breath
- feeling like your heart is pounding, racing or beating irregularly
- swelling in the legs

Eye problems: Braftovi, when taken with binimetinib can cause serious eye problems such as fluid to leak under the retina in the eye, leading to detachment of different layers in the eye (retinal epithelial pigmental detachment). Call your doctor right away if you get these symptoms of eye problems:
- blurred vision, loss of vision, or other vision changes (such as coloured dots in your vision)
- halo (seeing blurred outline around objects)
- eye pain, swellling or redness

Bleeding problems: Braftovi can cause serious bleeding problems. Tell your doctor right away if you have any unusual signs of bleeding, including:
- headaches, dizziness or weakness
- coughing up of blood or blood clots
- vomit containing blood or that looks like “coffee grounds”
- red or black stools that look like tar
- passing blood in the urine
- stomach (abdominal) pain
- unusual vaginal bleeding

Muscle problems: Braftovi, when taken with binimetinib can cause breakdown of muscles (rhabdomyolysis) which can lead to kidney damage and can be fatal; signs and symptoms can include:
- muscle pain, cramps, stiffness or spasm
- dark urine

Other skin cancers: Treatment with Braftovi may result in a type of skin cancer such as cutaneous squamous cell carcinoma. Usually, these skin changes (see also section 2) are confined to a small area and can be removed with surgery and treatment with Braftovi can continue without interruption. Some people taking Braftovi may also notice new melanomas. These melanomas are usually removed by surgery and treatment with Braftovi can continue without interruption.

Tumour lysis syndrome: Braftovi can cause a rapid breakdown of cancer cells which in some people may be fatal. Symptoms may include nausea, shortness of breath, irregular heartbeat, muscular cramps, seizures, clouding of urine, decrease in urine output and tiredness.

Other side effects
Besides the serious side effects mentioned above, people taking Braftovi may also get other side effects.

Side effects when Braftovi and binimetinib are taken together for treatment of melanoma or NSCLC

Very common (may affect more than 1 in 10 people):
- reduced red blood cell count (anaemia)
- problem with the nerves resulting in pain, loss of sensation or tingling in hands and feet
- headache
- dizziness
- bleeding at various sites in the body
- high blood pressure
- problems with your vision (visual impairment)
- stomach pain
- diarrhoea
- being sick (vomiting)
- feeling sick (nausea)
- constipation
- itching
- dry skin
- hair loss or thinning (alopecia)
- skin rash of various types
- thickening of the outer layers of the skin
- joint pain (arthralgia)
- muscle disorders
- back pain
- pain in the extremities
- fever
- swelling of the hands or feet (peripheral oedema), localised swelling
- fatigue
- abnormal blood test results for liver function
- abnormal blood test results related to blood creatine kinase (an enzyme found in the blood that may indicate muscle inflammation or damage)

Common (may affect up to 1 in 10 people)
- some types of skin tumours such as skin papilloma
- allergic reaction that may include swelling of the face and difficulty breathing
- changes in the way things taste
- inflammation of the eye (uveitis)
- blood clots
- inflammation of the colon (colitis)
- redness, chapping or cracking of the skin
- inflammation of the fatty layer under the skin, symptoms include tender skin nodules
- skin rash with a flat discoloured area or raised bumps like acne (dermatitis acneiform)
- redness, skin peeling or blisters on hand and feet (palmar-plantar erythrodysesthesia or hand and foot syndrome)
- kidney failure
- abnormal kidney test results (creatinine elevations)
- abnormal blood test results for liver function (blood alkaline phosphatase)
- abnormal blood test results for pancreas function (amylase, lipase)
- increased skin sensitivity to sunlight

Uncommon (may affect up to 1 in 100 people)
- some types of skin tumours such as basal cell carcinoma
- weakness and paralysis of face muscles
- inflammation of the pancreas (pancreatitis) causing severe abdominal pain

Side effects when Braftovi was used on its own in clinical trials conducted in patients with melanoma

If you continue Braftovi on its own while the other medicine (binimetinib) is temporarily stopped based on your doctor's decision, you may get some of the side effects given in the lists above, although the frequency may change (increase or decrease).

Very common (may affect more than 1 in 10 people)
- fatigue
- feeling sick (nausea)
- being sick (vomiting)
- constipation
- skin rash of various types
- redness, skin peeling or blisters on hand and feet (called palmar-plantar erythrodysesthesia or hand and foot syndrome)
- thickening of the outer layers of the skin (hyperkeratosis)
- dry skin
- itching
- abnormal hair loss or thinning (alopecia)
- redness, chapping or cracking of the skin
- skin darkening
- lost of appetite
- difficulty sleeping (insomnia)
- headache
- problem with the nerves that can produce pain, loss of sensation or tingling in hands and feet
- changes in the way things taste
- joint pain (arthralgia)
- muscle pain, spasm or weakness
- pain in the extremities
- back pain
- fever
- some types of benign skin tumour such as melanocytic naevus and skin papilloma
- abnormal blood tests results related to the liver

Common (may affect up to 1 in 10 people)
- allergic reaction that may include swelling of the face and difficulty in breathing
- weakness and paralysis of face muscles
- fast heart beat
- skin rash with a flat discoloured area or raised bumps like acne (dermatitis acneiform)
- peeling or scaly skin
- inflammation of joints (arthritis)
- kidney failure
- abnormal kidney test results (creatinine elevations)
- increased skin sensitivity to sunlight
- abnormal blood test result for pancreas function (lipase)

Uncommon (may affect up to 1 in 100 people)
- type of skin cancer such as basal cell carcinoma
- inflammation of the eye (uveitis)
- inflammation of the pancreas (pancreatitis) causing severe abdominal pain
- abnormal blood test result for pancreas function (amylase)

Side effects when Braftovi is taken together with cetuximab for treatment of large intestine cancer
Besides the serious side effects mentioned above, people taking Braftovi together with cetuximab may also get the following side effects.

Very common (may affect more than 1 in 10 people)
- new moles called “melanocytic naevus”
- lost of appetite
- difficulty sleeping (insomnia)
- problem with the nerves resulting in pain, loss of sensation or tingling in hands and feet
- headache
- bleeding at various sites in the body
- diarrhoea
- stomach pain
- feeling sick (nausea)
- being sick (vomiting)
- constipation
- skin rash with a flat discoloured area or raised bumps like acne (dermatitis acneiform)
- skin rash of various types
- dry skin
- itching
- joint pain (arthralgia) and muscle and/or bone pain (musculosketal pain)
- muscle pain, weakness or spasm
- pain in the extremities
- back pain
- fatigue
- fever

Common (may affect up to 1 in 10 people)
- some types of skin tumours such as skin papilloma.
- allergic reaction that may include swelling of the face and difficulty breathing
- dizziness
- changes in the way things taste
- fast heart beat
- skin darkening
- redness, skin peeling or blisters on hand and feet (palmar plantar erythrodysesthesia or hand and foot syndrome)
- thickening of the outer layers of the skin (hyperkeratosis)
- redness, chapping or cracking of the skin
- hair loss or thinning (alopecia)
- kidney failure
- abnormal kidney test results (creatinine elevations)
- abnormal blood test results for liver function

Uncommon (may affect up to 1 in 100 people)
- some types of skin tumours such as basal cell carcinoma
- inflammation of the pancreas (pancreatitis) causing severe abdominal pain
- skin peeling
- abnormal blood test results for pancreas function (amylase, lipase)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Braftovi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

Store below 30°C. Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Braftovi contains

- The active substance is encorafenib.
  Braftovi 50 mg hard capsules: Each hard capsule contains 50 mg encorafenib.
  Braftovi 75 mg hard capsules: Each hard capsule contains 75 mg encorafenib.
- The other ingredients are:
  - Capsule contents: copovidone (E1208), poloxamer 188, cellulose microcrystalline (E460i), succinic acid (E363), crospovidone (E1202), silica colloidal anhydrous (E551), magnesium stearate (E470b)
  - Capsule shell: gelatin (E441), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172)
  - Printing ink: shellac (E904), iron oxide black (E172), propylene glycol (E1520)

What Braftovi looks like and contents of the pack

Braftovi 50 mg hard capsules
The hard capsule (capsule) has an orange opaque cap and flesh opaque body, with a stylised "A" printed on the cap and "LGX 50mg" printed on the body.
Braftovi 50 mg is available in packs of 28x1 capsules or 112x1 capsules in perforated unit dose blisters. Not all pack sizes may be marketed.

Braftovi 75 mg hard capsules
The hard capsule (capsule) has a flesh coloured opaque cap and white opaque body, with a stylised "A" printed on the cap and "LGX 75mg" printed on the body.
Braftovi 75 mg is available in packs of 42x1 capsules or 168x1 capsules in perforated unit dose blisters. Not all pack sizes may be marketed.

Marketing Authorisation Holder
PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

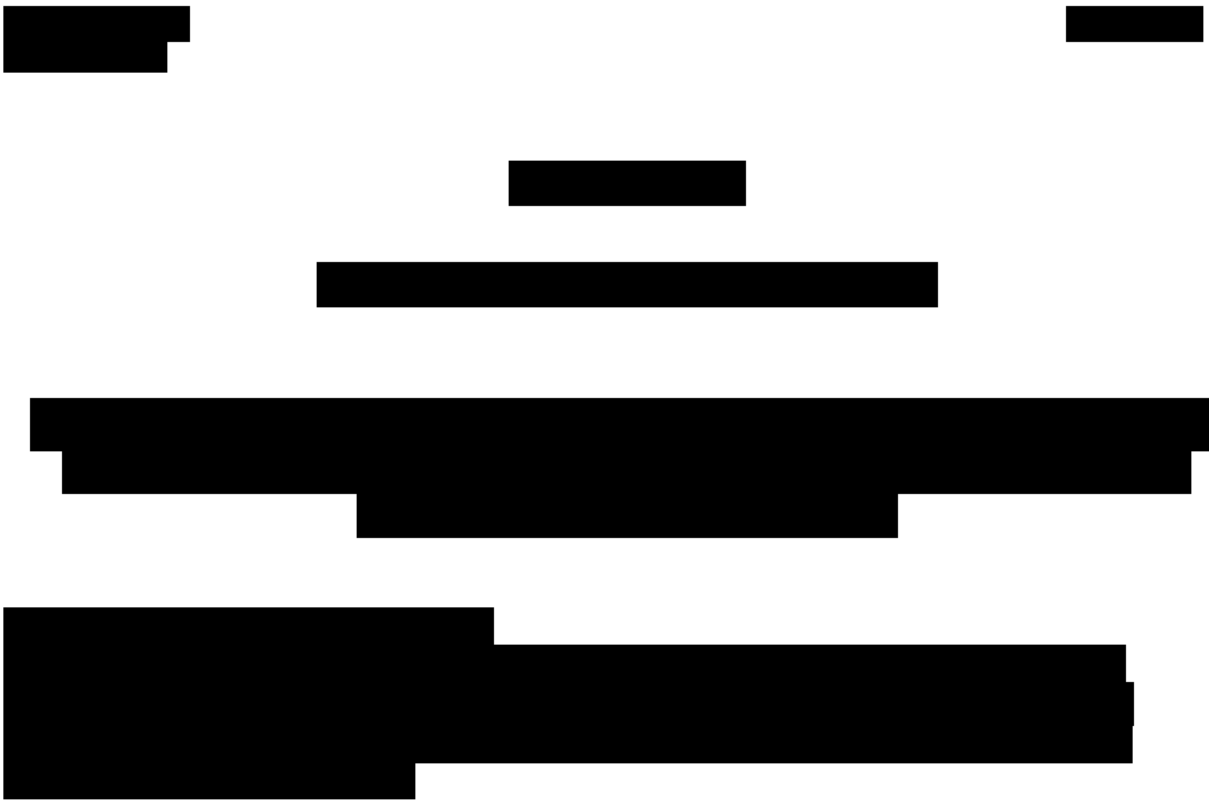
Manufacturer
PIERRE FABRE MEDICAMENT PRODUCTION
Site Progipharm, Rue du Lycée
45500 GIEN
France

This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

1.6.4　企業中核データシート

以下に、企業中核データシート（Company Core Data Sheet：CCDS）を添付する。



PREPARED BY PFIZER INC

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ENCORAFENIB

CORE DATA SHEET

[redacted]

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