Summary Report of Benefit-Risk Assessment

BRAFTOVI HARD CAPSULE 50MG AND 75MG

NEW DRUG APPLICATION

Active Ingredient(s)	Encorafenib
Product Registrant	Zuellig Pharma Pte. Ltd.
Product Registration Number	SIN16824P and SIN16825P
Application Route	Abridged evaluation
Date of Approval	19 July 2023

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A INTRODUCTION

Braftovi is indicated in combination with binimetinib for the treatment of adult patients who have unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by a validated test. It is also indicated in combination with cetuximab for the treatment of adult patients who have metastatic colorectal cancer (mCRC) with a BRAF V600E mutation as detected by a validated test, and who have received prior systemic therapy.

The active substance, encorafenib, is an ATP-competitive small molecule RAF kinase inhibitor that inhibits the RAF/MEK/ERK pathway in tumour cells which expresses mutated forms of BRAF kinase such as V600E, V600D and V600K.

Braftovi is available as capsules containing 50 mg or 75 mg of encorafenib. Other ingredients in the capsule are copovidone, poloxamer 188, microcrystalline cellulose, succinic acid, crospovidone, colloidal anhydrous silica and magnesium stearate. Ingredients in the capsule shell include gelatin, titanium dioxide, iron oxide red, iron oxide yellow and iron oxide black, while ingredients in the printing ink include iron oxide black, pharmaceutical glaze (shellac glaze-45% in ethanol, 20% esterified) and propylene glycol.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, encorafenib, is manufactured by Finorga (Dynamic Synthesis Finorga) / Finorga SAS, Chasse Sur Rhone, France and milled at Jetpharma SA, Balerna, Switzerland. The drug product, Braftovi Hard Capsule 75mg and 50mg, are manufactured at Catalent Pharma Solutions LLC, New Jersey, United States.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The packaging is double polyethylene bags placed into metallic drums. The stability data presented was adequate to support the storage of the drug substance at 30°C with a re-test period of 60 months.

Drug product:

The drug product is manufactured using a hot melt extrusion manufacturing process, which includes blending, screening, melt extrusion, milling, encapsulation and polishing.

The manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The container closure system is a polyamide/aluminium/PVC-aluminium blister containing 6 capsules per blister (for 75 mg strength) and 4 capsules per blister (for 50 mg strength). The stability data submitted was adequate to support the shelf-life of 36 months when stored at or below 30ºC.

C ASSESSMENT OF CLINICAL EFFICACY

Melanoma

The clinical efficacy of encorafenib in combination with binimetinib for the treatment of adult patients who have unresectable or metastatic melanoma with a BRAF V600E or V600K mutation was based primarily on one pivotal Phase III study COLUMBUS. This was a randomised, open-label, multicentre study of encorafenib + binimetinib versus vemurafenib or encorafenib monotherapy in patients with locally advanced, unresectable or metastatic (Stage IIIB, IIIC, or IV) BRAF V600E or V600K mutant melanoma.

The study had two parts. In Part 1, the patients were randomised equally to receive encorafenib 450 mg once daily + binimetinib 45 mg twice daily (Combo 450), encorafenib monotherapy 300 mg once daily or vemurafenib monotherapy 960 mg twice daily. Vemurafenib was the standard of care at the time of the study conduct for the treatment of patients with locally advanced unresectable or metastatic melanoma with BRAF V600 mutation. Hence, the use of vemurafenib as an active comparator was considered acceptable. In Part 2, designed to assess the contribution of binimetinib when combined to encorafenib, the patients were randomised in a 3:1 ratio to receive encorafenib 300 mg once daily + binimetinib 45 mg twice daily (Combo 300) or encorafenib 300 mg monotherapy once daily. Patients were treated until progressive disease, unacceptable toxicity, withdrawal of consent, death, physician decision or early termination of the study.

The primary endpoint was progression-free survival (PFS), defined as the time from the date of randomisation to the date of the first documented progression based on tumour assessment read centrally by a blinded independent review committee (BIRC) according to RECIST v1.1 criteria, or death due to any cause, whichever occurred first. The secondary endpoints included overall survival (OS), objective response rate (ORR), time to response (TTR) and duration of response (DOR). Tumour assessments were performed every 8 weeks during the first 24 months and every 12 weeks thereafter until progression or end of treatment. The statistical methods employed were appropriate for the endpoints studied. To control for Type I error, a hierarchical testing procedure was applied for the PFS comparisons of Combo 450 vs vemurafenib, Combo 450 vs encorafenib, and Combo 300 vs encorafenib. The secondary

endpoint of OS for Combo 450 vs vemurafenib was to be tested only if the former comparisons were statistically significant.

In Part 1, a total of 577 patients were randomised equally: 192 patients in the Combo 450 group, 194 patients in the encorafenib group and 191 patients in the vemurafenib group. The median age of patients was 56.0 years (range 20 to 89) and 26.2% were aged ≥65 years. Slightly more than half (57.9%) of the patients were males. The majority of the patients (90.3%) were Caucasian and 3.3% were Asian; 72.1% of patients had baseline ECOG performance status of 0, 95.5% patients had metastatic (Stage IV) disease and 63.8% were Stage IV M1C. Most patients had BRAF V600E mutation (88.6%) and 10.9% were V600K mutant. A total of 31.9% of patients had received prior systemic antineoplastic regimens and 29.8% had received prior immunotherapy in any disease setting (metastatic and adjuvant), including interferons/interleukins in 26.7% of patients, ipilimumab in 4.2% of patients, and anti-PD1/PDL1 in 0.5%.

In Part 2, a total of 344 patients were randomised in a 3:1 ratio: 258 patients in the Combo 300 group and 86 patients in the encorafenib group. Encorafenib patients from Part 1 (N=194) and Part 2 (N=86) were combined and analysed together in the encorafenib (Parts 1 + 2) group (N=280). In the overall population (N=538), the median age was 56.0 years (range 19 to 94), 56.3% of patients were males, 90.7% were Caucasian, and 5.2% were Asian. The majority of the patients had metastatic disease (96.5%); 17.8% had Stage IV M1B and 65.1% had Stage IV M1C. Most patients had BRAF V600E mutation (88.7%) and 11.0% had V600K mutation; 27.7% of patients had received prior immunotherapy.

Summary of key efficacy results

Part 1	Combo 450 (N=192)	Encorafenib (N=194)	Vemurafenib (N=191)
Primary endpoint			
PFS per BIRC			
PFS events, n (%)	98 (51.0)	96 (49.5)	106 (55.5)
Median PFS (months) (95% CI)	14.9 (11.0, 18.5)	9.6 (7.5, 14.8)	7.3 (5.6, 8.2)
Stratified HR (95% CI) (vs vemurafenib)[a] Stratified p-value[b]	0.54 (0.41, 0.71) <0.001		
Stratified HR (95% CI) (vs vemurafenib)[a] Nominal p-value[b]		0.68 (0.52, 0.90) 0.004[c]	
Stratified HR (95% CI) (vs encorafenib)[a] Stratified p-value[b]	0.75 (0.56, 1.00) 0.026		
Secondary endpoints			
OS			
OS events, n (%)	105 (54.7)	106 (54.6)	127 (66.5)
Median OS (months) (95% CI)	33.6 (24.4, 39.2)	23.5 (19.6, 33.6)	16.9 (14.0, 24.5)
Stratified HR (95% CI) (vs vemurafenib)[a] Nominal p-value[b]	0.61 (0.47, 0.79) <0.0001[c]		
Stratified HR (95% CI) (vs encorafenib)[a] Nominal p-value[b]	0.81 (0.61,1.06) 0.061[c]		
ORR per BIRC			
Confirmed ORR, % (95% CI)	63.0 (55.8, 69.9)	50.5 (43.3, 57.8)	40.3 (33.3, 47.6)
DOR			
Median (months) (95% CI)	16.6 (12.2, 20.4)	14.9 (11.1, NE)	12.3 (6.9, 16.9)

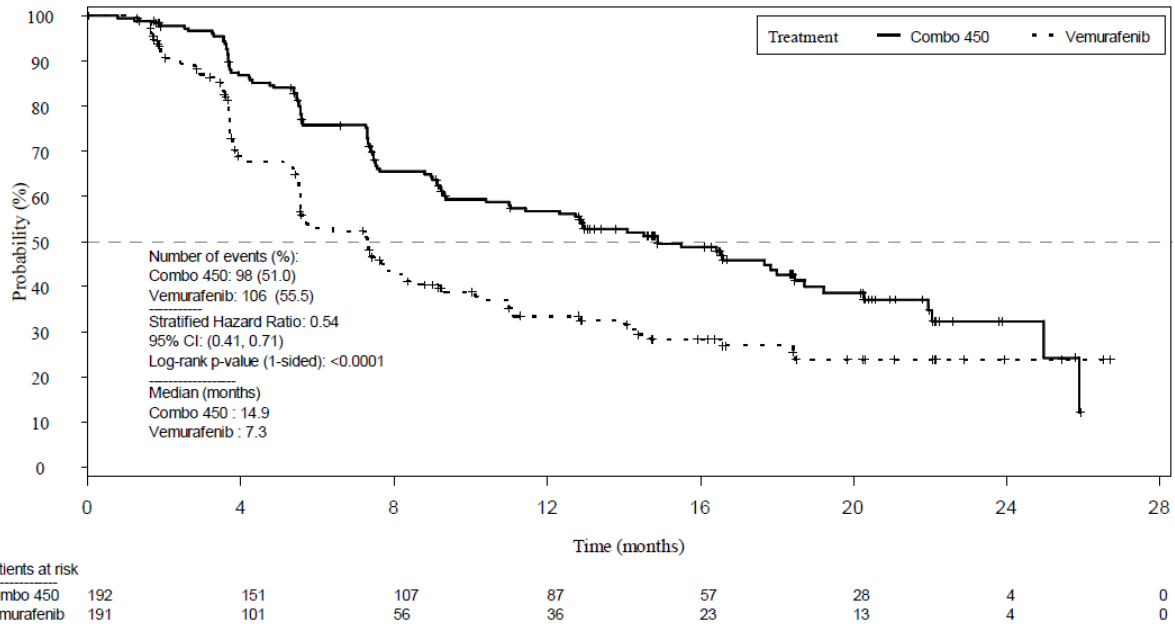
Data cut-off date for PFS, ORR and DOR was 19 May 2016; data cut-off date for OS was 07 Nov 2017.

[a] Hazard ratio based on a stratified Cox proportional hazard model, stratified by AJCC stage and ECOG performance status.
[b] One-sided p-value based on log-rank test, stratified by AJCC stage and ECOG performance status.
[c] As the comparison of PFS between Combo 450 and encorafenib was not statistically significant, as per the hierarchical testing procedure, statistical testing stopped and nominal p-values are presented for descriptive purpose only.

Part 2	Combo 300 (N=258)	Encorafenib (N=280; 194 from Part 1 and 86 from Part 2)
Primary endpoint		
PFS per BIRC		
Median PFS (months) (95% CI)	12.9 (10.1, 14.0)	9.2 (7.4, 11.0)
Stratified HR (95% CI)[a] Nominal p-value[b]	0.77 (0.61, 0.97) 0.015	
Secondary endpoints		
ORR per BIRC		
Confirmed ORR, % (95% CI)	65.9 (59.8, 71.7)	50.4 (44.3, 56.4)
DOR		
Median (months) (95% CI)	12.7 (9.3, 15.1)	12.9 (8.9, 15.5)

Data cut-off date was 9 Nov 2016.
[a] Hazard ratio based on a stratified Cox proportional hazard model, stratified by AJCC stage and ECOG performance status.
[b] One-sided p-value based on log-rank test, stratified by AJCC stage and ECOG performance status.
[c] As the comparison of PFS between Combo 450 and encorafenib in Part 1 was not statistically significant, as per the hierarchical testing procedure, formal statistical testing stopped and nominal p-values are presented for descriptive purpose only.

In Part 1, the primary analysis of PFS demonstrated a statistically significant improvement for subjects in the Combo 450 group compared to the vemurafenib group (HR 0.54; 95% CI: 0.41, 0.71; p<0.001). The median duration of PFS was 14.9 months in the Combo 450 group compared to 7.3 months in the vemurafenib group, which was a 7.6-month difference. Pre-specified sensitivity analyses of PFS yielded similar results to that of the primary analysis, reflecting the robustness of the PFS benefit.



For the comparison of the Combo 450 group versus the encorafenib group, the difference in PFS was not statistically significant (median 14.9 months versus 9.6 months; HR 0.75; 95% CI: 0.56, 1.00; p=0.026).

As the analysis of PFS for Combo 450 versus encorafenib was not statistically significant, per protocol-specified testing hierarchy, the data in the OS analysis are summarised descriptively without formal testing. The median OS was 33.6 months in the Combo 450 group and 16.9 months in the vemurafenib group (HR 0.61; 95% CI: 0.47, 0.79; nominal p<0.0001). The median OS was 33.6 months in the Combo 450 group and 23.5 months in the encorafenib group (HR 0.81; 95% CI: 0.61, 1.06; nominal p=0.061). The median DOR was numerically longer in the Combo 450 group (16.6 months) compared to the encorafenib (14.9 months) or vemurafenib group (12.3 months). The median TTR was similar in the Combo 450 group (1.9 months) compared to encorafenib (2.0 months) or vemurafenib group (2.1 months). The ORR (63.0%) and CR rates (7.8%) were numerically higher in the Combo 450 group compared to either monotherapy group (ORR range: 40% to 51%; CR range: 5.2% to 5.8%).

In Part 2, the median PFS was 12.9 months in the Combo 300 group and 9.2 months in the encorafenib group (HR 0.77; 95% CI: 0.61, 0.97; nominal p=0.015). The ORR was numerically higher in the Combo 300 group compared to the encorafenib group (65.9% versus 50.4%). However, the median DOR was similar between the Combo 300 and encorafenib groups (12.7 months versus 12.9 months).

Overall, efficacy of the combination of encorafenib and binimetinib in the treatment of unresectable or metastatic melanoma patients with a BRAF V600E or V600K mutation was adequately demonstrated in terms of clinically relevant improvements in PFS, OS, ORR and DOR compared to vemurafenib. The results of Part 1 and Part 2 of the study demonstrated the incremental benefit of adding binimetinib to encorafenib as Combo 300 performed numerically better in terms of PFS and ORR compared to encorafenib monotherapy. In addition, although the ORR were similar between Combo 450 and Combo 300, the Combo 450 group resulted in numerically longer PFS and DOR compared to Combo 300 indicating that better responses were obtained with the higher dose of encorafenib.

Colorectal cancer

The clinical efficacy of encorafenib in combination with cetuximab in the treatment of adult patients who had metastatic colorectal cancer (mCRC) with a BRAF V600E mutation was based on one pivotal Phase III study BEACON. This was a multicentre, randomised, open-label, 3-arm study of encorafenib + cetuximab ± binimetinib versus investigator's choice of irinotecan + cetuximab or 5-fluorouracil/folinic acid/irinotecan (FOLFIRI) + cetuximab in patients with BRAF V600E-mutant mCRC whose disease had progressed after 1 or 2 prior regimens in the metastatic setting.

The patients were randomised equally into the triplet arm (encorafenib 300 mg QD + binimetinib 45 mg BID + cetuximab [400 mg/m^2 followed by 250 mg/m^2 IV QW]), doublet arm (encorafenib 300 mg QD + cetuximab [400 mg/m^2 followed by 250 mg/m^2 IV QW]) or the control arm (irinotecan + cetuximab or FOLFIRI + cetuximab). Although the study investigated the triplet therapy of encorafenib + binimetinib + cetuximab, the requested dosing regimen is for the doublet therapy of encorafenib + binimetinib only. Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy, death or discontinuation from study treatment for any other reason.

The primary endpoints were overall survival (OS) of the triplet arm versus the control arm and objective response rate (ORR) by blinded independent central review (BICR) per RECIST v1.1 of the triplet versus the control arm. The key secondary endpoint was OS of the doublet arm versus the control arm. The other secondary endpoints included OS (triplet vs doublet arm), ORR per BICR (doublet arm versus control arm and triplet arm versus doublet arm), as well

as ORR per investigator, progression-free survival (PFS), duration of response (DOR) and time to response (TTR). Tumour assessments were performed every 6 weeks during the first 24 weeks and every 12 weeks thereafter until progression or end of treatment. The overall type I error rate was controlled using a gatekeeping procedure with hierarchical testing.

A total of 665 patients with BRAF V600E-mutant mCRC who had progressed on 1 or 2 prior metastatic regimens were randomised equally into one of the three treatment arms: 224 patients in the triplet arm, 220 patients in the doublet arm and 221 patients in the control arm. The demographics and baseline characteristics were balanced across the arms. There were slightly more females (52.8%) than males. The majority of the patients were White (82.7%) and 12.6% were Asian. The median age of the patients was 61 years (range 26 to 91) and 35.8% were aged ≥65 years. The majority of the patients (92.5%) had BRAF V600E mutation. A total of 65.7% of the patients had one, 34.0% of the patients had two, and a limited number of patients (0.3%) had more than two prior lines of therapy for metastatic disease. Approximately half of the patients (52.2%) had prior treatment with irinotecan and 91.7% had prior treatment with oxaliplatin.

Summary of key efficacy results (data cut-off date 11 Feb 2019)

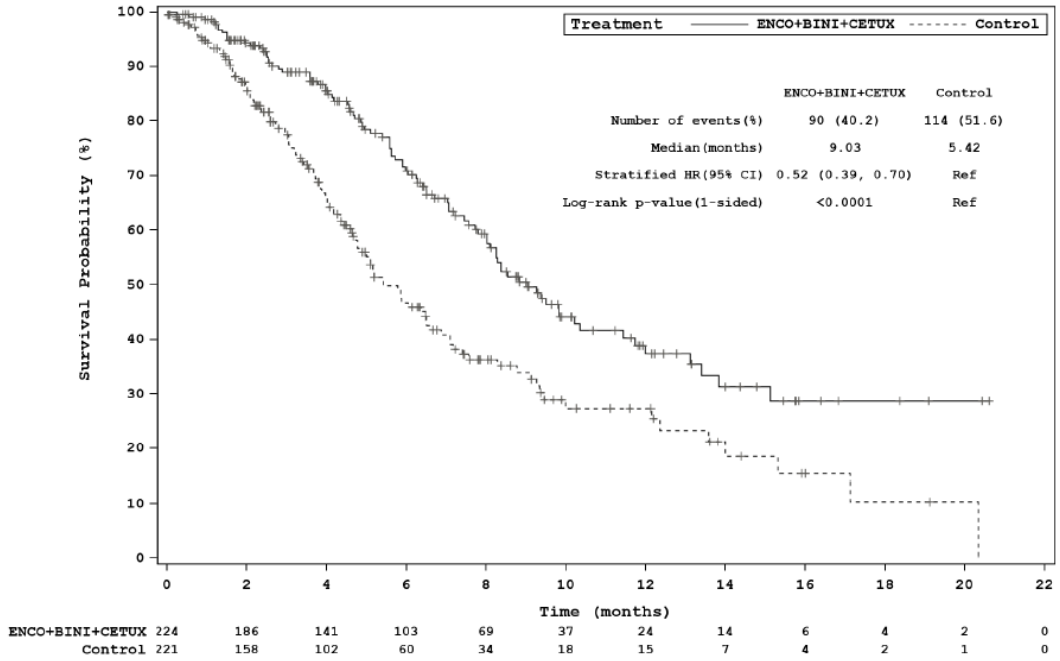
	Control (N=221)	Doublet therapy (N=220)	Triplet therapy (N=224)
Primary endpoint			
OS			
OS events, n (%)	114 (51.6)	93 (42.1)	90 (40.2)
Median OS (months) (95% CI)	5.4 (4.8, 6.6)	8.4 (7.5, 11.0)	9.0 (8.0, 11.4)
Stratified HR (95% CI) (vs control)[a] Stratified log-rank (one-sided) p-value[a]		0.60 (0.45, 0.79) 0.0002	0.52 (0.39, 0.70) <0.0001
Stratified log-rank (one-sided) p-value (vs doublet therapy)			0.0582
ORR per BICR			
Confirmed ORR, % (95% CI)	1.9 (0.2, 6.6)	20.4 (13.4, 29.0)	26.1 (18.2, 35.3)
Stratified (one-sided) p-value[a]		<0.0001	<0.0001
Secondary endpoints			
PFS			
PFS events, n (%)	128 (57.9)	133 (60.5)	118 (52.7)
Median PFS (months) (95% CI)	1.5 (1.5, 1.7)	4.2 (3.7, 5.4)	4.3 (4.1, 5.2)
Stratified HR (95% CI) (vs control)[a] Stratified log-rank (one-sided) p-value[a]		0.40 (0.31, 0.52) <0.0001	0.38 (0.29, 0.49) <0.0001
DOR			
Median DOR (months) (95% CI)	NR (2.6, NR)[b]	6.1 (4.1, 8.3)	4.8 (3.0, 9.7)

[a] Stratified by ECOG performance status, source of cetuximab, and prior irinotecan use at randomisation.
[b] Of the 2 patients in the control arm with confirmed responses, 1 patient had a DOR of 2.6 months; the other patient's DOR was 6.9 months.

The primary analyses showed that the doublet (HR 0.60; 95% CI: 0.45, 0.79; p=0.0002) and triplet therapies (HR 0.52; 95% CI: 0.39, 0.70; p<0.0001) resulted in a statistically significantly longer median OS compared to the control arm. However, there was no significant difference between the doublet and triplet therapies (p=0.0582). Both doublet and triplet therapies also

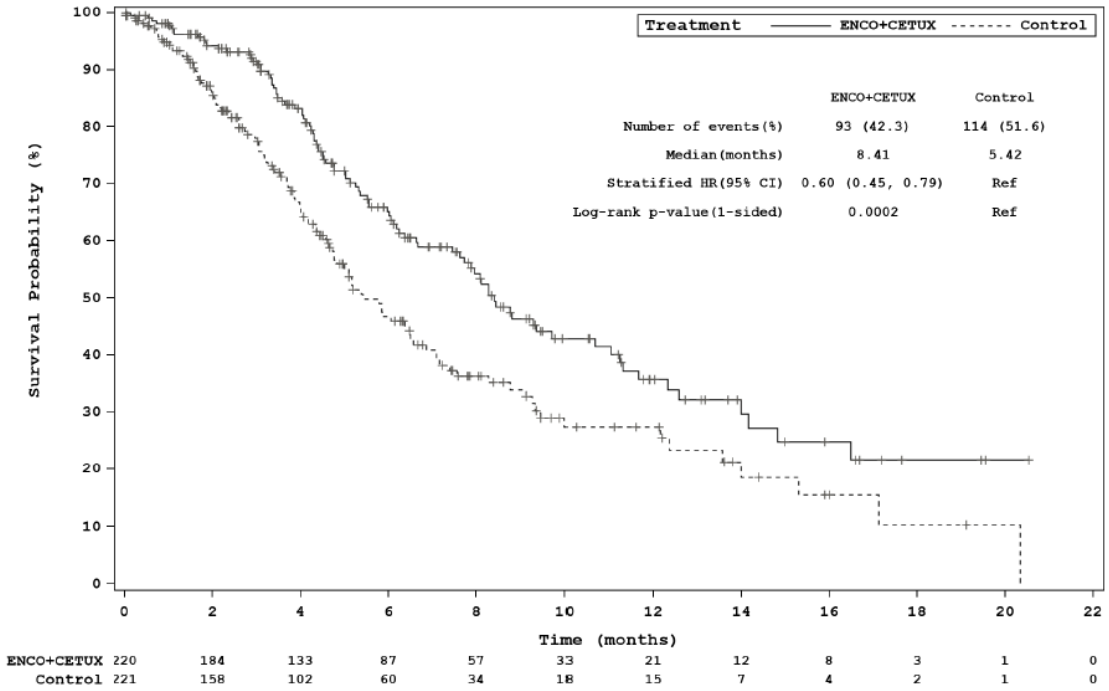
resulted in higher ORR compared to the control arm (20.4% and 26.1% versus 1.9%, respectively).

Kaplan-Meier Plot of OS, Triplet Arm vs. Control Arm



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO= encorafenib; HR= hazard ratio; OS = overall survival; Ref = reference; vs. = versus + indicates censoring.

Kaplan-Meier Plot of OS, Doublet Arm vs. Control Arm



Abbreviations: CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; HR = hazard ratio; OS = overall survival; Ref = reference; vs. = versus + indicates censoring.

In terms of secondary endpoints, the median DOR was the longest in the doublet arm (5.6 months) while the median DOR was 4.4 months in the triplet arm. Of the 2 patients in the control arm with confirmed responses, 1 patient had a DOR of 2.6 months and other patient had a DOR of 6.9 months. The TTR was similar across arms. The median PFS was also statistically significantly longer in the doublet (HR 0.40; 95% CI: 0.31, 0.52; p<0.0001) and triplet (HR 0.28; 95% CI: 0.29, 0.49; p<0.0001) arms compared to the control arm. However, the median PFS was similar between the doublet and triplet arms (4.2 months and 4.3 months, respectively).

An updated efficacy analysis (based on a data cut-off date of 15 Aug 2019) was conducted approximately 6 months after the first data cut-off. The updated efficacy results (summarised in the table below) were consistent with the primary analyses.

Summary of updated efficacy results (data cut-off date 15 Aug 2019)

	Control (N=221)	**Doublet therapy (N=220)**	**Triplet therapy (N=224)**
Primary endpoint			
OS			
OS events, n (%)	157 (71.0)	128 (58.2)	137 (61.2)
Median OS (months) (95% CI)	5.9 (5.1, 7.1)	9.3 (8.1, 11.3)	9.3 (8.3, 10.8)
Stratified HR (95% CI) (vs control)[a] Stratified log-rank (one-sided) p-value[a]		0.61 (0.48, 0.77) <0.0001	0.60 (0.47, 0.75) <0.0001
Stratified log-rank (one-sided) p-value (vs doublet therapy)			0.3288
ORR per BICR			
Confirmed ORR, % (95% CI)	1.8 (0.5, 4.6)	19.5 (14.5, 25.4)	26.8 (21.1, 33.1)
Stratified (one-sided) p-value[a]		<0.0001	<0.0001
Secondary endpoints			
PFS			
PFS events, n (%)	147 (66.5)	167 (75.9)	157 (70.1)
Median PFS (months) (95% CI)	1.5 (1.5, 1.9)	4.3 (4.1, 5.5)	4.5 (4.2, 5.5)
Stratified HR (95% CI) (vs control)[a] Stratified log-rank (one-sided) p-value[a]		0.44 (0.35, 0.55) <0.0001	0.42 (0.33, 0.53) <0.0001
DOR			
Median DOR (months) (95% CI)	5.6 (2.6, NR)	5.6 (4.1, 8.3)	4.4 (3.8, 7.3)

[a] Stratified by ECOG performance status, source of cetuximab, and prior irinotecan use at randomisation.

Overall, the efficacy of the combination of encorafenib and cetuximab in the treatment of adult patients with mCRC with a BRAF V600E mutation, and who have received prior systemic therapy was adequately demonstrated in terms of clinically relevant improvements in OS, ORR, PFS and DOR compared to the control group (irinotecan/cetuximab or FOLFIRI/cetuximab). The results indicated that there was no incremental benefit with the use of the triplet therapy compared to the doublet therapy, suggesting that binimetinib does not contribute to the effect of the triplet therapy.

D ASSESSMENT OF CLINICAL SAFETY

Melanoma

The safety data of the combination of encorafenib and binimetinib was derived primarily from the pivotal Phase III study COLUMBUS, in which a total of 570 patients with unresectable or metastatic BRAF V600 mutant melanoma were treated: 192 patients in the Combo 450 group (encorafenib 450 mg once daily + binimetinib 45 mg twice daily), 192 patients in the encorafenib 300 mg once daily group, and 186 patients in the vemurafenib 960 mg twice daily group.

In addition, the proposed combination of encorafenib + binimetinib was evaluated in a total of 274 patients with unresectable or metastatic BRAF V600 mutant melanoma pooled across three clinical studies (Pooled Combo 450). These included 192 patients from Study COLUMBUS (Part 1), 75 patients from Study CLGX818X2109 (Group A) and 7 patients from Study CMEK162X2110. The median duration of exposure was 50.6 weeks in the pooled Combo 450 group.

In COLUMBUS Part 1, the median duration of encorafenib + binimetinib exposure was longer in the Combo 450 arm compared to the vemurafenib arm (51.2 weeks vs 26.3 weeks) and a higher proportion of patients in the Combo 450 arm were exposed to treatment for ≥48 weeks (52.6% vs 25.3%). Approximately half of the patients (49.3%) received study treatment during at least 12 months in the Combo 450 arm, versus 38.5% in the encorafenib arm and 22.6% in the vemurafenib arm.

Duration of exposure to study treatment

	Pooled Combo 450 (N=274)	**Study COLUMBUS Part 1**		
		Combo 450 (N=192)	**Encorafenib (N=192)**	**Vemurafenib (N=186)**
Median (weeks)	50.64	51.21	31.36	26.29
Exposure ≥48 weeks (n, %)	142 (51.8)	101 (52.6)	75 (39.1)	47 (25.3)

Overview of safety profile

AE	**Pooled Combo 450 (N=274)**	**Study COLUMBUS Part 1**		
		Combo 450 (N=192)	**Encorafenib (N=192)**	**Vemurafenib (N=186)**
Any AE	271 (98.9%)	189 (98.4%)	191 (99.5%)	186 (100.0%)
Treatment-related AE	249 (90.9%)	171 (89.1%)	191 (99.5%)	181 (97.3%)
Grade 3/4 AE	168 (61.3%)	115 (59.9%)	128 (66.7%)	118 (63.4%)
Treatment-related Grade 3/4 AE	95 (34.7%)	70 (36.5%)	96 (50.0%)	85 (45.7%)
SAE	110 (40.1%)	69 (35.9%)	67 (34.9%)	71 (38.2%)
Treatment-related SAE	31 (11.3%)	22 (11.5%)	33 (17.2%)	25 (13.4%)
AE leading to treatment discontinuation	32 (11.7%)	28 (14.6%)	29 (15.1%)	30 (16.1%)
On-treatment deaths	28 (10.2%)	19 (9.9%)	15 (7.8%)	19 (10.2%)

In COLUMBUS Part 1, the most frequently reported AEs (≥20% of patients) in the Combo 450 group were nausea (43.2%), diarrhoea (37.0%), vomiting (30.2%), fatigue (29.2%), arthralgia (26.6%), blood creatine phosphokinase (CK) increased (22.9%), headache (22.9%), constipation (22.4%), and asthenia (20.3%). In the encorafenib group, the most frequently reported AEs included alopecia (56.3%), palmar-plantar erythrodysesthesia (PPE) syndrome (51.0%), arthralgia (43.8%), hyperkeratosis (38.5%), nausea (38.5%), dry skin (30.2%), myalgia (28.6%), vomiting (28.1%), headache (27.6%), palmoplantar keratoderma (26.0%),

fatigue (25.0%), pain in extremity (22.4%), pruritus (21.9%), asthenia (20.8%), decreased appetite (20.8%), and rash (20.8%). In the vemurafenib group, the most frequent AEs included arthralgia (44.6%), alopecia (36.6%), nausea (34.9%), diarrhoea (34.4%), fatigue (30.6%), rash (29.0%), hyperkeratosis (29.0%), pyrexia (28.0%), photosensitivity reaction (24.7%), keratosis pilaris (23.1%), and dry skin (22.6%).

The AEs reported at a higher incidence in the Combo 450 group than in the encorafenib group (≥10% difference) included blood CK increased (22.9% vs 1.0%), diarrhoea (37.0% vs 13.5%), and vision blurred (16.1% vs 2.1%). The AEs reported at a higher incidence in the Combo 450 group than in the vemurafenib group were vomiting (30.2% vs 15.6%), blood CK increased (22.9% vs 2.2%), constipation (22.4% vs 6.5%), abdominal pain (17.2% vs 7.0%), vision blurred (16.1% vs 2.2%), and dizziness (14.1% vs 2.7%).

The incidence of serious AEs (SAEs) was similar in the different groups: 35.9%, 34.9% and 38.2% of patients in the Combo 450, encorafenib and vemurafenib groups, respectively. The most frequently reported SAEs (≥2%) in the Combo 450 arm included nausea (1.0% in Combo 450 group, 3.1% in encorafenib group and none in vemurafenib group), pneumonia (1.6% in Combo 450 group and none in encorafenib and vemurafenib groups), and pyrexia (3.1% in Combo 450 group, 1.6% in encorafenib group and 1.1% in vemurafenib group). SAEs with a suspected relationship to study drug as assessed by the investigator were reported at a lower incidence in the Combo 450 group (11.5%) than the encorafenib (17.2%) or vemurafenib groups (13.4%).

The incidence of AEs leading to treatment discontinuation was 14.6% in the Combo 450 group, 15.1% in the encorafenib group and 16.1% in the vemurafenib group. The AEs leading to study drug discontinuation in the Combo 450 arm included increased ALT and AST (2.6% in Combo 450 group, none in encorafenib group and 1.1% in vemurafenib group).

The incidence of on-treatment deaths was 9.9% in the Combo 450 group, 7.8% in the encorafenib group and 10.2% in the vemurafenib group. The causes of death in the Combo 450 arm included malignant melanoma (6.3%), cerebral haemorrhage, completed suicide, euthanasia, metastases to central nervous system, and multiple organ dysfunction syndrome (0.5% each). However, none of the deaths were considered to be related to the study drugs by the investigator.

The most frequently reported AEs of special interest (AESI, >20%) in the Combo 450 arm were retinopathy excluding retinal vein occlusion (48.4%), rash (26.0%), liver function test (LFT) abnormalities (25.0%) and muscle enzyme/ protein changes (22.9%). The AEs of special interest have been adequately described as warnings and precautions in the proposed package insert.

Most frequently reported AESIs (>20%)

AESI	Pooled Combo 450 (N=274)	Study COLUMBUS Part 1		
		Combo 450 (N=192)	Encorafenib (N=192)	Vemurafenib (N=186)
LFT abnormalities	69 (25.2%)	48 (25.0%)	28 (14.6%)	39 (21.0%)
Rash	65 (23.7%)	50 (26.0%)	95 (49.5%)	111 (59.7)
Retinopathy excluding retinal vein occlusion	144 (52.6%)	93 (48.4%)	26 (13.5%)	23 (12.4%)
Muscle enzyme/protein changes	74 (27.0%)	44 (22.9%)	3 (1.6%)	4 (2.2%)

Overall, the safety profile of binimetinib in combination with encorafenib was considered acceptable and manageable, and was consistent with that documented for MEK and BRAF inhibitors.

Colorectal cancer

The safety profile of the proposed doublet therapy of encorafenib in combination with cetuximab was evaluated in the Phase III study BEACON, in which a total of 631 patients with BRAF V600E mutant mCRC were treated with the triplet therapy of encorafenib + binimetinib + cetuximab (N=222), doublet therapy of encorafenib + cetuximab (N=216) or the control comprising irinotecan + cetuximab or FOLFIRI + cetuximab (N=193).

The median duration of exposure to study treatment was 19.3 weeks in the doublet arm, 21.0 weeks in the triplet arm and 7.0 weeks in the control arm. Within the doublet arm, the median duration of exposure to each component was similar (encorafenib [19.1 weeks], cetuximab [19.0 weeks]). Within the triplet arm, the median duration of exposure to each component was also similar (encorafenib [20.7 weeks], binimetinib [20.4 weeks], cetuximab [20.8 weeks]). Almost half of the patients in the doublet and triplet arms (43.5% and 43.1%, respectively) received ≥24 weeks of study treatment, while a small percentage of patients in the control arm (12.5%) received ≥24 weeks of study treatment.

Overview of safety profile

AE	Triplet (N=222)	Doublet (N=216)	Control (N=193)
Any AE	220 (99.1%)	212 (98.1%)	190 (98.4%)
Grade ≥3 AE	146 (65.8%)	124 (57.4%)	124 (64.2%)
Treatment-related AE	214 (96.4%)	196 (90.7%)	178 (92.2%)
SAE	110 (49.5%)	86 (39.8%)	77 (39.9%)
Grade ≥3 SAE	97 (43.7%)	74 (34.3%)	67 (34.7%)
Treatment-related SAE	40 (18.0%)	21 (9.7%)	25 (13.0%)
AE leading to treatment discontinuation	21 (9.5%)	20 (9.3%)	21 (10.9%)
On-treatment deaths	30 (13.5%)	38 (17.6%)	29 (15.0%)

The most common AEs (≥25%) occurring in patients treated with the doublet therapy (incidences vs control) were diarrhoea (38.4% vs 48.7%), nausea (38.0% vs 43.5%), fatigue (33.3% vs 28.0%), decreased appetite (31.0% vs 29.0%), dermatitis acneiform (30.1% vs 39.9%), abdominal pain (27.8% vs 28.0%), and vomiting (27.3% vs 31.6%). The AEs reported at a higher incidence in the doublet therapy arm than in the control arm (≥10% difference) included arthralgia (22.7% vs 1.6%), headache (19.9% vs 2.6%), melanocytic naevus (15.7% vs 0.0%), myalgia (15.3% vs 2.1%), musculoskeletal pain (13.4% vs 2.6%), and pain in extremity (11.6% vs 1.0%). The most common treatment-related AEs (≥20%) occurring in patients treated with the doublet therapy were diarrhoea (20.8% vs 44.6%), dermatitis acneiform (28.2% vs 39.4%), nausea (22.2% vs 37.3%), and fatigue (24.1% vs 22.3%).

The overall incidence of SAEs was higher in the triplet arm (49.5%) than in the doublet (39.8%) and control arms (39.9%). The most frequently reported SAEs (≥2%) in patients treated with the doublet therapy (incidences vs control) were intestinal obstruction (5.1% vs 3.6%), abdominal pain (2.3% vs 2.1%), urinary tract infection (2.3% vs 0.5%), and cancer pain (2.3% vs 0.5%). SAEs with a suspected relationship to study drug as assessed by the investigator were reported at a lower incidence in the doublet (9.7%) than the triplet (18.0%) or control arm (13.0%).

The percentage of patients who discontinued all study treatments due to an AE was 9.5% in the triplet arm, 9.3% in the doublet arm and 10.9% in the control arm. The AEs leading to study drug discontinuation in the doublet arm (incidences vs control) included infusion-related reaction (0.9% vs 1.0%) and intestinal obstruction (0.9% vs 0.5%).

The incidence of on-treatment death was 17.6% in the doublet arm, 13.5% in the triplet arm and 15.0% in the control arm. The exposure-adjusted incidence rates of on-treatment deaths were similar across arms (0.64 vs 0.79 vs 1.71, respectively), with most deaths due to progression of malignant disease (62.5%, 43.5% and 57.7%, respectively). The causes of death in the doublet arm (incidences vs control) included aspiration (0.9% vs 0%), large intestine perforation (0.5% vs 0%), gastrointestinal haemorrhage (0.5% vs 0%), cardio-respiratory arrest (0.5% vs 0.5%) and sepsis (0.5% vs 0%). None of the deaths were considered to be related to the study drugs by the investigator.

The most frequently reported AESIs (>10%) in the doublet arm were rash (32.9%), haemorrhage (22.2%), myopathy (16.7%), and LFT abnormalities (13.0%). These AEs have been adequately described in the warnings and precautions section in the proposed package insert.

Most frequently reported AESIs (>10%)

AESI	Triplet (N=222)	Doublet (N=216)	Control (N=193)
Rash	84 (37.8%)	71 (32.9%)	57 (29.5%)
Haemorrhage	58 (26.1%)	48 (22.2%)	19 (9.8%)
Myopathy	25 (11.3%)	36 (16.7%)	5 (2.6%)
LFT abnormalities	30 (13.5%)	28 (13.0%)	23 (11.9%)

Overall, the safety profile of encorafenib in combination with cetuximab in mCRC was comparable to the control armand considered acceptable for highly targeted therapy in the second setting. The tolerability profile of the doublet regimen was shown to be more favourable compared to the triplet regimen in terms of lower incidences of treatment-related AEs, SAEs and Grade ≥3 AEs.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Melanoma

The current treatment options for metastatic melanoma include immune checkpoint inhibitors, kinase inhibitors and BRAF inhibitors. However, about 10–20% of cases remain fatal. Therefore, there is a need for therapies with improved survival.

Part 1 of study COLUMBUS demonstrated a clinically meaningful and statistically significantly longer median PFS in the Combo 450 group compared to the vemurafenib group (14.9 months versus 7.3 months; HR 0.54; 95% CI: 0.41, 0.71; p<0.001).

The primary endpoint results were supported by the secondary endpoints, whereby the median PFS was numerically longer in the Combo 450 group compared to the encorafenib group (14.9 months versus 9.6 months; HR 0.75; 95% CI: 0.56, 1.00; p=0.026). In addition, the median OS was numerically longer in the Combo 450 group compared to the monotherapy groups (33.6 months in the Combo 450 group versus 23.5 months in the encorafenib group and 16.9 months in the vemurafenib group). The median TTR was similar between groups at about 2 months.

The ORR was numerically higher in the Combo 450 group compared to the vemurafenib and encorafenib groups (63% versus 40% to 51%). The median DOR was also numerically longer in the Combo 450 group compared to the monotherapy groups (16.6 months versus 12.3 to 14.9 months).

Part 2 of the study demonstrated a numerically longer median PFS in the Combo 300 group compared to the encorafenib group (12.9 months versus 9.2 months; HR 0.77; 95% CI: 0.61, 0.97; nominal p=0.015). With regard to the secondary endpoints, the ORR was numerically higher in the Combo 300 group compared to the encorafenib group (65.9% versus 50.4%). The median DOR was similar between the Combo 300 and encorafenib groups (12.7 months versus 12.9 months).

Overall, the results of the study demonstrated the incremental benefit of adding binimetinib to encorafenib based on the observation of improved efficacy for Combo 300 compared to encorafenib monotherapy. In addition, Combo 450 performed numerically better compared to Combo 300 supporting the use of the higher dose of encorafenib.

The combination treatment was associated with more AEs than monotherapy, however, this was not unexpected due to the presence of more drugs. The most common AEs with Combo 450 were nausea, diarrhoea, vomiting, fatigue, arthralgia, blood CK increased, constipation, headache and asthenia. The incidences of SAEs, discontinuation due to AEs and deaths were comparable between the Combo 450 and monotherapy groups. In addition, none of the deaths were considered to be related to the study drugs by the investigators.

Overall, the benefit-risk profile of encorafenib in combination with binimetinib for the treatment of adult patients who have unresectable or metastatic melanoma with a BRAF V600E or V600K mutation was considered to be favourable as efficacy was demonstrated and the safety profile was manageable and consistent with what is known for the MEK and BRAF inhibitor classes of drugs.

Colorectal cancer

BRAF V600 mutant CRC is a distinct subtype of CRC that has unique clinical characteristics and is associated with a poor prognosis and a negative impact on both OS and PFS. The current available therapies for patients with BRAF V600E mutant mCRC who have failed one prior line of treatment are minimally active with dismal OS, hence there is a need for treatment choices with improved efficacy.

The pivotal Phase III study (BEACON) showed that the doublet therapy with encorafenib + cetuximab (HR 0.60; 95% CI: 0.45, 0.79; p=0.0002) and triplet therapy with encorafenib + binimetinib + cetuximab (HR 0.52; 95% CI: 0.39, 0.70; p<0.0001) resulted in statistically significantly longer median OS compared to the control arm (irinotecan + cetuximab or FOLFIRI + cetuximab) (median 8.4 and 9.0 months versus 5.4 months, respectively).

The ORR was also higher in the doublet (20.4%; 95% CI: 13.4, 29.0) and triplet therapy (26.1%; 95% CI: 18.2, 35.3) arms compared to the control arm (1.9%; 95% CI: 0.2, 6.6) (p<0.0001 for both comparisons). The median DOR was 6.1 months in the doublet arm and 4.8 months in the triplet arm. Of the 2 patients in the control arm with confirmed responses, 1 patient had a DOR of 2.6 months and other patient had a DOR of 6.9 months. The median PFS was statistically significantly longer in the doublet (HR 0.40; 95% CI: 0.31, 0.52; p<0.0001) and triplet arms (HR 0.38; 95% CI: 0.29, 0.49; p<0.0001) compared to the control arm (median 4.2 and 4.3 months versus 1.5 months, respectively).

There was no significant difference in OS between the doublet and triplet therapies (p=0.0582). Although the triplet therapy resulted in a numerically higher ORR compared to the doublet therapy arm (26.1% versus 20.4%), it did not translate into better median OS. The median PFS was also similar between the doublet and triplet therapy arms (4.2 months and 4.3 months, respectively). Taken together, the results indicated that there was no incremental benefit with the use of the triplet compared to doublet therapy.

The most common AEs reported with the doublet therapy included diarrhoea, nausea, fatigue, decreased appetite, dermatitis acneiform, abdominal pain, and vomiting. The doublet and triplet combinations were associated with more AEs than the control arm, however, this was not unexpected due to the presence of more drugs. The incidences of treatment-related AEs, SAEs and Grade ≥3 AEs were also higher in the triplet arm compared to the doublet arm.

Given that the triplet therapy did not demonstrate incremental benefit compared to the doublet therapy and resulted in more AEs, the use of the triplet therapy was not warranted. Only the doublet therapy dosing regimen was requested in this application, which was considered appropriate. Overall, the benefit-risk profile of encorafenib, in combination with cetuximab, for the treatment of adult patients who have mCRC with a BRAF V600E mutation, and who have received prior systemic therapy, was considered to be favourable as efficacy and safety had been adequately demonstrated.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Braftovi in combination with binimetinib for the treatment of adult patients who have unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, or in combination with cetuximab for the treatment of adult patients who have mCRC with a BRAF V600E mutation who have received prior systemic therapy, was deemed favourable and approval of product registration was granted on 19 July 2023.

APPROVED PACKAGE INSERT AT REGISTRATION

▼ This therapeutic product is subject to additional monitoring in Singapore. This will allow quick identification of new safety information.
Healthcare professionals are asked to report any suspected adverse events at HSA: Healthcare professionals' guide to adverse events reporting.

PRODUCT INFORMATION

BRAFTOVI®

(encorafenib)
capsules

1. NAME OF THE MEDICINE

Encorafenib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BRAFTOVI 50 mg hard capsule contains encorafenib 50 mg.
Each BRAFTOVI 75 mg hard capsule contains encorafenib 75 mg.
For the list of excipients, see section 6.1 *List of excipients*.

3. PHARMACEUTICAL FORM

BRAFTOVI 50 mg hard capsules
Swedish orange opaque cap and flesh-coloured opaque body, printed with a stylised "A" on the cap and "LGX 50 mg" 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 75 mg" 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 who have unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation, as detected by a validated test.

Colorectal Cancer
Encorafenib, in combination with cetuximab, is indicated for the treatment of adult patients who have metastatic colorectal cancer (mCRC) with a *BRAF* V600E mutation as detected by a validated test, and who have received prior systemic therapy.

4.2. DOSE AND METHOD OF ADMINISTRATION

Treatment with encorafenib should only be initiated and supervised by a physician experienced in the use of anti-cancer medicines.

Patient selection
Prior to treatment with encorafenib, the *BRAF* V600 mutation status of a patient's melanoma or colorectal cancer must be confirmed by a validated test, conducted by an experienced laboratory (see section 5.1 *Pharmacodynamic properties, Clinical trials*).
The efficacy and safety of encorafenib have only been established in patients who have melanoma with a *BRAF* V600E or V600K mutation or colorectal cancer with a *BRAF* V600E mutation.
Encorafenib should not be used in patients who have wild-type BRAF malignant melanoma or wild type *BRAF* colorectal cancer.

Dosage
Melanoma
The recommended dose of encorafenib is 450 mg (six 75 mg capsules) once daily when used in combination with binimetinib.
For information on binimetinib dosage, refer to section 4.2 *Dose and method of administration* of the binimetinib Product Information (PI).

Colorectal cancer
The recommended dose of encorafenib is 300 mg (four 75 mg capsules) once daily, when used in combination with cetuximab.
For information on cetuximab dosage, refer to section 4.2 *Dose and method of administration* of the cetuximab PI.

Administration
Encorafenib capsules should be swallowed whole with water, with or without food. The concomitant administration of encorafenib with grapefruit juice should be avoided (see section 4.5 *Interactions with other medicines and other forms of interactions*).

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

Missed dose
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 after administration
If a patient vomits after taking encorafenib, the patient should not take an additional dose. The patient should take the next scheduled dose.

Dose modification
The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation. Recommended encorafenib dose levels for dose reduction are different in melanoma (Table 1) compared to mCRC (Table 2). Dose modification recommendations in case of adverse reactions (regardless of treatment indication) are presented in Table 3.

Melanoma
If treatment-related toxicities occur when encorafenib is used in combination with binimetinib, dose modification should generally be undertaken for both drugs.
The following adverse reactions are more likely to be related to binimetinib than encorafenib: retinal pigment epithelial detachment (RPED), retinal vein occlusion (RVO), interstitial lung disease/pneumonitis, cardiac dysfunction, creatine phosphokinase (CK) elevation, rhabdomyolysis and venous thromboembolism. If one of these toxicities occurs, consider dose modification of binimetinib alone.
For information on dosage and recommended dose modifications for binimetinib, refer to section 4.2 *Dose and method of administration* of the binimetinib PI.

Recommended dose levels for encorafenib dose reduction (when used in combination with binimetinib for the treatment of melanoma) are presented in Table 1.

Table 1: Melanoma indication - recommended dose levels for encorafenib dose reduction

Dose level	Encorafenib dose (when used in combination with binimetinib)
Starting dose	450 mg once daily
1st dose reduction	300 mg once daily
2nd dose reduction	200 mg once daily
Subsequent modification	Permanently discontinue encorafenib (and binimetinib) if unable to tolerate encorafenib 200 mg once daily

If encorafenib is temporarily interrupted, interrupt binimetinib.
If binimetinib is temporarily interrupted, reduce encorafenib to 300 mg once daily during the time of binimetinib dose interruption. Administration of encorafenib at a dose of 450 mg once daily as a single agent is not well tolerated, and not recommended.
If encorafenib is permanently discontinued, then discontinue binimetinib.
If binimetinib is permanently discontinued, encorafenib may be continued at a reduced dose of 300 mg, depending on the individual clinical benefit.

Colorectal cancer
For information on dosage and recommended dose modifications for cetuximab, refer to section 4.2 *Dose and method of administration* of the cetuximab PI.

Recommended dose levels for encorafenib dose reduction (when used in combination with cetuximab for the treatment of mCRC) are presented in Table 2.

Table 2: mCRC indication - recommended dose levels for encorafenib dose reduction

Dose level	Encorafenib dose (when used in combination with cetuximab)
Starting dose	300 mg once daily
1st dose reduction	225 mg once daily
2nd dose reduction	150 mg once daily

If encorafenib is permanently discontinued, cetuximab should be discontinued.
If cetuximab is permanently discontinued, encorafenib should be discontinued.

All indications
Dose modification recommendations in case of adverse reactions (regardless of treatment indication) are presented in Table 3.

Table 3: Recommended dose modification for encorafenib for adverse reactions (all indications)

Special populations

Hepatic impairment
Patients with mild to severe hepatic impairment may have increased encorafenib exposure (see section 5.2 *Pharmacokinetic properties*).
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 requirement for dose adjustment cannot be determined for patients with severe renal impairment (see section 4.4 *Special warnings and special precautions for use and section 5.2 Pharmacokinetic properties*).

Elderly patients (65 years and older)
No dose adjustment is required for elderly patients (see section 5.2 *Pharmacokinetic properties*).

Children and adolescents (< 18 years)
The safety and efficacy of encorafenib have not been established in patients below the age of 18 years. There are no data available.

4.3. CONTRAINDICATIONS

Hypersensitivity to the active substance encorafenib or to any of the excipients (see section 6.1 *List of excipients*).

4.4. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Before initiating treatment with encorafenib in combination with binimetinib, or encorafenib in combination with cetuximab, the PI for the relevant combination partner drug must be reviewed. Information on warnings and precautions specific to binimetinib or cetuximab treatment are described in those documents.

Assessment of *BRAF* mutation status
When assessing the *BRAF* mutation status of the tumour, it is important that a well-validated and robust test is used to minimise false-positive and false-negative determinations. *In vitro* experiments have demonstrated paradoxical activation of MAP-kinase signalling and increased cell proliferation in melanoma *BRAF* wild-type cell lines when they are exposed to *BRAF* inhibitors. Giving *BRAF* inhibitors to patients who have *BRAF* wild-type tumours may lead to accelerated tumour growth.

Melanoma that has progressed on a *BRAF* inhibitor
There are limited data on the use of the combination of encorafenib with binimetinib in patients who previously progressed on a prior *BRAF* inhibitor treatment for unresectable or metastatic melanoma with a *BRAF* V600 mutation. These data show that the efficacy of the combination would be lower in these patients.

Patients with melanoma who have brain metastases
There are limited efficacy data on the use of the combination of encorafenib and binimetinib in patients with a *BRAF* V600 mutant melanoma with brain metastases (see section 5.1 *Pharmacodynamic properties*).

New primary malignancies
New primary malignancies (cutaneous and non-cutaneous) have been observed in patients treated with *BRAF* inhibitors, whether administered as a single agent or used in combination.

Cutaneous malignancies
Cutaneous malignancies such as cutaneous squamous cell carcinoma 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 *Adverse effects (undesirable effects)*).
Dermatological 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 by excision and dermatopathological 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 full blood counts prior to initiation, during and at the end of treatment as clinically appropriate. Consider permanently discontinuing 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.

Haemorrhage
Haemorrhages, including major haemorrhagic events, can occur with encorafenib (see section 4.8 *Adverse effects (undesirable effects)*). The risk of haemorrhage may be increased with concomitant use of anticoagulant and antiplatelet therapy. The occurrence of Grade ≥ 3 haemorrhagic events can be managed with dose interruption, or treatment discontinuation and as clinically indicated (see section 4.2 *Dose and method of administration*).

Ocular toxicities
Ocular toxicities including uveitis, iritis and iridocyclitis can occur when encorafenib is administered (see section 4.8 *Adverse effects (undesirable effects)*. Some ocular toxicities (RPED and RVO) are more likely to be related to coadministered binimetinib (see section 4.2 *Dose and method of administration*). Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, a prompt ophthalmological examination is recommended.
Dose modification advice for ocular toxicities is described in section 4.2 *Dose and method of administration*.

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.
Encorafenib may cause mild increases in heart rate and small increases in QTc interval (see section 5.1 *Pharmacodynamic properties*).
There are insufficient data to exclude a clinically significant, exposure-dependent QT prolongation.
Due to the potential risk for QT prolongation, correct serum electrolyte abnormalities (including magnesium, potassium and calcium) and review other risk factors for QT prolongation (e.g. control of congestive heart failure and bradyarrhythmias, and concurrent administration of other medicinal products associated with QT prolongation) before treatment initiation and during treatment.
Perform an electrocardiogram (ECG) 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, treatment interruption or treatment discontinuation with correction of abnormal electrolytes and control of risk factors (see section 4.2 *Dose and method of administration*).

Left ventricular dysfunction
Left ventricular dysfunction (LVD), defined as symptomatic or asymptomatic decreases in ejection fraction, has been reported when encorafenib is used in combination with binimetinib.
Assess LVEF (left ventricular ejection fraction) by echocardiogram or multi-gated acquisition (MUGA) scan before initiating encorafenib in combination with binimetinib, one month after initiation and then at approximately 3-month intervals or more frequently as clinically indicated while on treatment. If LVD occurs during treatment, see section 4.2 *Dose and method of administration of binimetinib* PI.
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 limit of normal. In these patients, binimetinib should be used with caution. For any symptomatic LVD, Grade 3 or 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.

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 *Pharmacokinetic properties*).
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 *Dose and method of administration*).
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 section 4.2 *Dose and method of administration* and section 5.2 *Pharmacokinetic properties*). 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 3 in section 4.2 *Dose and method of administration*). Patients should ensure adequate fluid intake during treatment.

Use in the elderly
Please refer to sections 5.2 *Pharmacokinetic properties* and 4.8 *Adverse effects* (undesirable effects).

Paediatric use
The safety and efficacy of encorafenib in children and adolescents aged < 18 years have not been established. There are no data available.

Effects on laboratory tests
Liver function abnormalities (AST, ALT elevations) have been observed with encorafenib (see section 4.8 *Adverse effects (undesirable effects)*). Liver laboratory values should be monitored before initiation of encorafenib and at least monthly during the first 6 months of treatment, and then as clinically indicated. Liver function abnormalities should be managed with dose reduction, treatment interruption, or treatment discontinuation (see section 4.2 *Dose and method of administration*).

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 *Interactions with other medicines and other forms of interactions*).
Caution should be exercised if a moderate CYP3A inhibitor is co-administered with encorafenib.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug-drug interaction was identified between encorafenib and cetuximab, or between encorafenib and binimetinib.

Effects of other medicinal products 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).

CYP3A4 inhibitors
Co-administration of strong (posaconazole) and moderate (diltiazem) CYP3A4 inhibitors with single doses of encorafenib in healthy volunteers resulted in an increase in overall (AUC, 3- and 2-fold higher, respectively) and peak (C_{max}, 68.3% and 44.6% higher, respectively) encorafenib exposure.
Concomitant administration of encorafenib with strong CYP3A4 inhibitors should be avoided (due to increased encorafenib exposure and potential increase in toxicity). Examples of strong CYP3A4 inhibitors include, but are not limited to, ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole and grapefruit juice. 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.
The safety and tolerability of encorafenib should be carefully monitored for patients in whom concomitant use of a strong or moderate CYP3A4 inhibitor is deemed necessary.

CYP3A4 inducers
The effect of co-administering a CYP3A4 inducer on encorafenib exposure has not been studied in a dedicated trial however, a reduction in encorafenib exposure is likely and may result in compromised efficacy. Examples of moderate or strong CYP3A4 inducers include, but are not limited to carbamazepine, rifampicin, phenytoin and St. John's Wort. Alternative agents with no or minimal CYP3A induction should be considered.

P-gp inhibitors and inducers
Encorafenib is a substrate of P-glycoprotein (P-gp). While oral bioavailability might not be significantly affected by P-gp inhibitors or inducers because of the predicted high intestinal permeability, distribution into the central nervous system may be increased by P-gp inhibitors.

Effects of encorafenib on other medicinal products
CYP and UGT substrates
Encorafenib is both an inhibitor and inducer of CYP3A4. *In vitro*,encorafenib is a relatively potent reversible inhibitor of UGT1A1, CYP2B6, CYP2C9 and CYP3A4/5, a relatively less potent inhibitor of CYP1A2, CYP2C8, CYP2C19 and CYP2D6, and a time-dependent inhibitor of CYP3A4. Encorafenib induced CYP1A2, CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes. Simulations of 450 mg encorafenib co-administered with probe substrates for CYP2B6, CYP1A2, CYP2C9,CYP2C19 and CYP2D6 on Day 1 and Day 15 all indicated no clinically relevant interactions are expected. For CYP3A4 and UGT1A1 substrates that undergo gut extraction, a minor to moderate interaction with encorafenib is expected.
Use caution when co-administering encorafenib with agents that are substrates of CYP3A4 (e.g. hormonal contraceptives) as it may result in increased toxicity or loss of efficacy of those agents.Use caution when co-administering encorafenib with agents that are substrates of UGT1A1 as it may result in increased toxicity of those agents. While binimetinib is a UGT1A1 substrate, it does not undergo gut extraction. Co-administration of encorafenib with binimetinib does not affect binimetinib exposure.

Transporter substrates
Encorafenib potentially inhibits a number of transporters. Based on *in vitro* studies, there is potential for encorafenib to inhibit renal transporters OCT2, OAT1, OAT3 and hepatic transporters OCT1, OATP1B1 and OATP1B3 at clinical concentrations. In addition, encorafenib may inhibit breast cancer resistance protein (BCRP) at the expected clinical concentrations.
Agents that are transporter substrates (OCT2, OAT1, OAT3, OATP1B1, OATP1B3 and BCRP) should be co-administered with caution.
Encorafenib is a weak inhibitor of P-gp, but at high concentrations in the intestine, it may increase oral absorption of drugs that are P-gp substrates.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no data on the effect of encorafenib on fertility in humans. Fertility studies were not conducted with encorafenib. In the sub-acute 28-day and subchronic 13- week rat toxicology studies, encorafenib treatment at 20 mg/kg/day (similar to the human exposure at 450 mg daily based on unbound AUC) 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/day).
Based on findings in male rats, the use of encorafenib may affect fertility in males of reproductive potential. As the clinical relevance of this is unknown, male patients should be informed of the potential risk for impaired spermatogenesis.

Women of childbearing potential
Women of childbearing potential should be advised to use effective contraception during treatment with encorafenib and for at least 1 month after the last dose. Encorafenib may decrease the efficacy of hormonal contraceptives (see section 4.5 *Interactions with other medicines and other forms of interactions*). 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.

Use in pregnancy
Category D.
There are no data on the use of encorafenib in pregnant women. However, studies in animals have demonstrated reproductive toxicity. The embryo-foetal development study in rats indicated that encorafenib induced foetal toxicity with lower foetal weights and delays in skeletal development (incomplete ossification of the bones of the skull and thoracic vertebra) at 20 mg/kg/day (2 times the human exposure at 450 mg daily based on unbound AUC).
The embryo-foetal development study in rabbits indicated that encorafenib induced maternal toxicity and foetal toxicity with lower foetal weights, delays in skeletal development (incomplete ossification of the bones of the skull and thoracic vertebra) and visceral malformations (dilation of the aortic arch and ascending aorta, misshapen globular hearts, cardiac interventricular septal defects, small lung lobes and asplenia) at 75 mg/kg/day (14 times the human exposure at 450 mg daily based on total AUC) and delayed ossification (thoracic vertebra) at 25 mg/kg/day (7 times the human exposure).
Encorafenib should not be administered during pregnancy unless the benefits for the mother outweigh the risks for the foetus.
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.

Use in lactation
It is not known if encorafenib or its metabolites are excreted in human milk. Because many drugs are excreted in breast milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue encorafenib taking into account the benefit of breastfeeding for the child and the benefit of the drug to the mother.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Visual disturbances have been reported in some patients treated with encorafenib during clinical trials. Patients should be advised not to drive or operate machinery if they experience visual disturbances or any other adverse effects that may affect their ability to drive or operate machinery (see section 4.8 *Adverse effects (undesirable effects)*).

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of safety profile
Melanoma studies
Encorafenib 450 mg once daily with binimetinib 45 mg twice daily
The safety of encorafenib (450 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) was evaluated in 274 patients with BRAF V600 mutant unresectable or metastatic melanoma (hereafter referred to as the pooled Combo 450 population), who received this regimen across two Phase II studies (CMEK162X2110 and CLGX818X2109) and one Phase III study (CMEK162B2301, the "COLUMBUS" study; see section 5.1 *Pharmacodynamic properties, Clinical trials*). In the pooled Combo 450 population (n=274), the most common adverse reactions (≥ 25%) occurring in patients treated with encorafenib administered with binimetinib were fatigue, nausea, diarrhoea, vomiting, retinal detachment, abdominal pain, arthralgia, blood CK increase and myalgia.
Encorafenib 300 mg once daily with binimetinib 45 mg twice daily
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) who received this regimen in Part 2 of the COLUMBUS study. The most common adverse reactions (≥ 25%) occurring in patients treated with encorafenib 300 mg administered with binimetinib were fatigue, nausea and diarrhoea.
Encorafenib 300 mg once daily as a single agent
The safety profile of encorafenib as a single agent (at a dose of 300 mg once daily) is based on data from three clinical studies (Columbus Part 1, CLGX818X2102 and CLGX818X2101) that included 217 patients with unresectable or metastatic BRAF V600-mutant melanoma (hereafter referred to as the pooled encorafenib 300 mg population). The most common adverse drug reactions (ADRs) (≥ 25%) reported with encorafenib monotherapy at this dose were hyperkeratosis, alopecia, PPES fatigue, rash, arthralgia, dry skin, nausea, myalgia, headache, vomiting and pruritus.

Colorectal cancer studies
Encorafenib 300 mg once daily with cetuximab
The safety of encorafenib (300 mg orally once daily) in combination with cetuximab (dosed as per its PI) was evaluated in 216 patients with BRAF V600E-mutant metastatic colorectal cancer who received this regimen in the phase III study ARRAY-818-302 "BEACON CRC" (see section 5.1 *Pharmacodynamic properties, Clinical trials*). 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.

Tabulated summary of adverse reactions
Melanoma studies
Adverse reactions that occurred in patients with melanoma in the Combo 450 population (n=274) and in the pooled encorafenib 300 mg population (n=217) are listed in Table 4, by MedDRA body system organ class (SOC).

Table 4: Adverse reactions occurring in patients with melanoma who received encorafenib 300 mg as monotherapy, or encorafenib 450 mg in combination with binimetinib

Colorectal cancer studies
Adverse reactions in patients who received encorafenib 300 mg in combination with cetuximab in the BEACON CRC study (n=216) are listed in Table 5, by MedDRA body system organ class (SOC).
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.

Table 5: Adverse reactions occurring in patients with colorectal cancer receiving encorafenib in combination with cetuximab at the recommended doses

Adverse events
Adverse events in the COLUMBUS study (melanoma)
Table 6 summarises the most common treatment-emergent adverse events (AEs) (≥ 10% any grade or ≥ 2% grade 3 or 4) occurring in patients in Part I of the phase III randomised, active- controlled, open-label, multicentre trial (COLUMBUS) in patients with unresectable or metastatic BRAF V600 E or K mutant melanoma. The COLUMBUS study 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.
In Part 1 of the COLUMBUS study, serious adverse events (SAEs) regardless of relationship to study therapy were reported in 35.9% of patients with melanoma treated with encorafenib 450 mg in combination with binimetinib (Combo 450), 34.9% of patients treated with encorafenib single agent 300 mg (Enco 300) and in 38.2% of patients treated with vemurafenib. Permanent discontinuations due to AEs were reported in 14.6% of patients treated in the Combo 450 arm, 15.1% of patients treated in the Enco 300 arm and 16.1% of patients treated in the vemurafenib arm.

Table 6: Treatment-emergent adverse events occurring very commonly (≥ 10% any grade or ≥ 2% grades 3 or 4) inpatients receiving Combo 450 mg, Enco 300 mg or vemurafenib in Part 1 of the COLUMBUS study

Adverse events in the BEACON CRC study (colorectal cancer)
Table 7 summarises the most common (incidence of at least 10%) treatment-emergent adverse events (AEs) occurring in patients in the BEACON CRC study. The BEACON CRC study 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.
Serious adverse events (SAEs) regardless of relationship to study therapy were reported in 40% of patients who received encorafenib 300 mg in combination with cetuximab. Adverse events leading to dose interruptions of BRAFTOVI occurred in 39% of patients receiving BRAFTOVI in combination with cetuximab; the most common were vomiting (6%), diarrhoea (4%) nausea (4%), pyrexia (3%), and fatigue (2%), Adverse events leading to dose reductions of BRAFTOVI occurred in 10% of patients receiving BRAFTOVI in combination with cetuximab; the most common were fatigue (1.4%), musculoskeletal pain (1.4%), and peripheral neuropathy (1.4%). Permanent discontinuations due to AEs were reported in 11% of patients who received encorafenib 300 mg in combination with cetuximab. None of the adverse events leading to permanent discontinuation of BRAFTOVI occurred in more than 2 patients (0.9%).

Table 7: Treatment- emergent adverse events occurring very commonly (≥ 10%) in patients receiving encorafenib 300 mg in combination with cetuximab in the BEACON CRC study

Description of selected adverse reactions
Cutaneous malignancies
Cutaneous squamous cell carcinoma
Melanoma studies
In the pooled Combo 450 population, cuSCC including keratoacanthomas was observed in 3.3% (9/274) of patients. The median time to onset of the first event of cuSCC (all grades) was 6.5 months (range 1 to 22.8 months).
In the pooled encorafenib 300 mg population, cuSCC was reported in 7.4% (16/217) patients. For patients in the COLUMBUS studywho 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 studies
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 studies
In the pooled encorafenib 300 population, new primary melanoma events occurred in 4.1% of patients (9 /217) and were 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 studies
In patients treated with encorafenib 300 mg in combination with cetuximab,

Table 4: Adverse reactions occurring in patients with melanoma who received encorafenib 300 mg as monotherapy, or encorafenib 450 mg in combination with binimetinib

	Pooled encorafenib 300 mg population [encorafenib 300 mg monotherapy] (n=217)		Combo 450 population [encorafenib 450 mg in combination with binimetinib] (n=274)	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Neoplasms benign, malignant and unspecified				
Skin papilloma*	25 (11.5)	0	22 (8.0)	0
Melanocytic nevus	23 (10.6)	0	4 (1.5)	0
CuSCC[a]	16 (7.4)	0	9 (3.3)	1 (0.4)
Basal cell carcinoma*	2 (0.9)	1 (0.5)	3 (1.1)	0
New primary melanoma*	9 (4.1)	2 (0.9)	1 (0.4)	1 (0.4)
Blood and lymphatic system disorders				
Anaemia	16 (7.4)	5 (2.3)	54 (19.7)	13 (4.7)
Immune system disorders				
Hypersensitivity [b]	8 (3.7)	1 (0.5)	9 (3.3)	0
Metabolism and nutrition disorders				
Decreased appetite	48 (22.1)	1 (0.5)	21 (7.7)	0
Psychiatric disorders				
Insomnia	48 (22.1)	6 (2.8)	23 (8.4)	0
Nervous system disorders				
Headache*	64 (29.5)	7 (3.2)	59 (21.5)	4 (1.5)
Neuropathy peripheral*	49 (22.6)	4 (1.8)	36 (13.1)	3 (1.1)
Dysgeusia*	30 (13.8)	0	18 (6.6)	0
Dizziness*	15 (6.9)	1 (0.5)	42 (15.3)	7 (2.6)
Facial paresis[c]	16 (7.4)	3 (1.4)	2 (0.7)	1 (0.4)
Eye disorders				
Visual impairment*	12 (5.5)	0	59 (21.5)	1 (0.4)
RPED*	5 (2.3)	0	81 (29.6)	5 (1.8)
Uveitis*	1 (0.5)	0	12 (4.4)	1 (0.4)
Cardiac disorders				
Supraventricular tachycardia[d]	9 (4.1)	2 (0.9)	5 (1.8)	0
LVD[h]	4 (1.8)	2 (0.9)	23 (8.4)	3 (1.1)
Vascular disorders				
Haemorrhage[i]	25 (11.5)	5 (2.3)	49 (17.9)	9 (3.3)
Hypertension*	11 (5.1)	6 (2.8)	32 (11.7)	15 (5.5)
VTE[j]	6 (2.8)	2 (0.9)	13 (4.7)	3 (1.1)
Gastrointestinal disorders				
Nausea	82 (37.8)	8 (3.7)	114 (41.6)	7 (2.6)
Vomiting*	60 (27.6)	9 (4.1)	77 (28.1)	6 (2.2)
Constipation	37 (17.1)	0	66 (24.1)	0
Abdominal pain*	34 (15.7)	6 (2.8)	75 (27.4)	7 (2.6)
Diarrhoea*	27 (12.4)	3 (1.4)	104 (38.0)	9 (3.3)
Colitis[k]	2 (0.9)	0	6 (2.2)	2 (0.7)
Pancreatitis*	1 (0.5)	1 (0.5)	2 (0.7)	2 (0.7)
Skin and subcutaneous tissue disorders				
PPES	112 (51.6)	27 (12.4)	17 (6.2)	0
Hyperkeratosis*	127 (58.5)	13 (6.0)	57 (20.8)	1 (0.4)
Rash*	94 (43.3)	10 (4.6)	54 (19.7)	2 (0.7)
Dry skin*	82 (37.8)	0	40 (14.6)	0
Pruritus*	64 (29.5)	1 (0.5)	32 (11.7)	1 (0.4)
Alopecia*	124 (57.1)	0	40 (14.6)	0
Erythema[e]	37 (17.1)	3 (1.4)	22 (8.0)	0
Skin hyperpigmentation*	22 (10.1)	0	5 (1.8)	0
Dermatitis acneiform*	17 (7.8)	0	12 (4.4)	0
Skin exfoliation[f]	14 (6.5)	1 (0.5)	3 (1.1)	0
Photosensitivity*	9 (4.1)	0	11 (4.0)	1 (0.4)
Panniculitis*	1 (0.5)	0	4 (1.5)	0
Musculoskeletal and connective tissue disorders				
Arthralgia*	94 (43.3)	20 (9.2)	74 (27.0)	2 (0.7)
Myalgia[g]	78 (35.9)	20 (9.2)		
Muscular disorders/Myalgia[l]			71 (25.9)	2 (0.7)
Pain in extremity	46 (21.2)	2 (0.9)	29 (10.6)	4 (1.5)
Back pain	33 (15.2)	5 (2.3)	30 (10.9)	2 (0.7)
Arthritis*	11 (5.1)	3 (1.4)	4 (1.5)	0
Rhabdomyolysis	0	0	1 (0.4)	1 (0.4)
Renal and urinary disorders				
Renal failure *	6 (2.8)	3 (1.4)	9 (3.3)	6 (2.2)
General disorders and administration site conditions				
Fatigue*	95 (43.8)	10 (4.6)	120 (43.8)	8 (2.9)
Pyrexia*	33 (15.2)	2 (0.9)	47 (17.2)	8 (2.9)
Peripheral oedema[m]	22 (10.1)	0	42 (15.3)	3 (1.1)
Investigations				
Blood CK increased	2 (0.9)	0	74 (27.0)	16 (5.8)
Gamma-glutamyl transferase (GGT) increased*	25 (11.5)	11 (5.1)	40 (14.6)	23 (8.4)
Transaminase increased*	14 (6.5)	3 (1.4)	43 (15.7)	15 (5.5)
Blood alkaline phosphatase increased	6 (2.8)	0	20 (7.3)	2 (0.7)
Blood creatinine increased*	5 (2.3)	0	17 (6.2)	2 (0.7)
Amylase increased	1(0.5)	0	9 (3.3)	4 (1.5)
Lipase increased	5 (2.3)	3 (1.4)	14 (5.1)	7 (2.6)

* composite terms which included more than one preferred term
[a] includes keratoacanthoma, squamous cell carcinoma, lip squamous cell carcinoma and squamous cell carcinoma of skin
[b] includes angioedema, drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis and urticaria
[c] includes facial nerve disorder, facial paralysis, facial paresis
[d] includes extrasystoles, sinus tachycardia, supraventricular extrasystoles, tachyarrhythmia, 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 cerebral haemorrhage
[j] includes pulmonary embolism, deep vein thrombosis, embolism, thrombophlebitis, thrombophlebitis superficial and thrombosis
[k] includes colitis, colitis ulcerative, enterocolitis and proctitis
[l] includes myalgia, muscular weakness, muscle spasm, muscle injury, myopathy, myositis
[m] includes fluid retention, peripheral oedema, localised oedema

Table 5: Adverse reactions occurring in patients with colorectal cancer receiving encorafenib in combination with cetuximab at the recommended doses

	Encorafenib 300 mg in combination with cetuximab (n=216)	
	All grades n (%)	Grade 3/4 n (%)
Neoplasms benign, malignant and unspecified		
Melanocytic naevus	34 (15.7)	0
cuSCC[a]	3 (1.4)	0
Skin papilloma*	15 (6.9)	0
New primary melanoma*	4 (1.9)	2 (0.9)
Basal cell carcinoma	1 (0.5)	0
Immune system disorders		
Hypersensitivity[b]	4 (1.9)	3 (1.4)
Metabolism and nutrition disorders		
Decreased appetite	67 (31.0)	3 (1.4)
Psychiatric disorders		
Insomnia	29 (13.4)	0
Nervous system disorders		
Neuropathy peripheral*	32 (14.8)	4 (1.9)
Headache*	44 (20.4)	0
Dizziness*	20 (9.3)	0
Dysgeusia	10 (4.6)	0
Cardiac disorders		
Supraventricular tachycardia[c]	10 (4.6)	3 (1.4)
Vascular disorders		
Haemorrhage[d]	46 (21.3)	4 (1.9)
Gastrointestinal disorders		
Nausea	82 (38.0)	1 (0.5)
Vomiting	59 (27.3)	3 (1.4)
Constipation	39 (18.1)	0
Abdominal pain*	79 (36.6)	11 (5.1)
Diarrhoea*	83 (38.4)	6 (2.8)
Pancreatitis*	1 (0.5)	1 (0.5)
Skin and subcutaneous tissue disorders		
Dermatitis acneiform*	72 (33.3)	2 (0.9)
Rash*	66 (30.6)	1 (0.5)
Dry skin*	33 (15.3)	0
Pruritus*	33 (15.3)	0
Skin hyperpigmentation	16 (7.4)	0
PPES	11 (5.1)	1 (0.5)
Hyperkeratosis*	12 (5.6)	0
Alopecia	9 (4.2)	0
Erythema[e]	13 (6.0)	1 (0.5)
Skin exfoliation[f]	1 (0.5)	0
Musculoskeletal and connective tissue disorders		
Arthralgia/Musculoskeletal pain*	68 (31.5)	3 (1.4)
Myopathy/Muscular disorder*	38 (17.6)	1 (0.5)
Back pain	28 (13.0)	3 (1.4)
Pain in extremity	25 (11.6)	0
Renal and urinary disorders		
Renal failure*	5 (2.3)	5 (2.3)
General disorders and administration site conditions		
Fatigue*	123 (56.9)	17 (7.9)
Pyrexia*	41 (19.0)	4 (1.9)
Investigations		
Blood creatinine increased*	6 (2.8)	1 (0.5)
Transaminase increased*	19 (8.8)	3 (1.4)
Amylase increased	1 (0.5)	0
Lipase increased	1 (0.5)	1 (0.5)

*composite terms which included more than one preferred term
[a] includes keratoacanthoma, squamous cell carcinoma, lip squamous cell carcinoma and squamous cell carcinoma of skin
[b] includes angioedema, drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis and urticaria
[c] includes extrasystoles, sinus tachycardia, supraventricular extrasystoles, tachyarrhythmia, tachycardia
[d] includes haemorrhage at various sites including cerebral haemorrhage
[e] includes erythema, generalised erythema, plantar erythema
[f] includes dermatitis exfoliative, skin exfoliation, exfoliative rash

Table 6: Treatment-emergent adverse events occurring very commonly (≥ 10% any grade or ≥ 2 % grades 3 or 4) inpatients receiving Combo 450 mg, Enco 300 mg or vemurafenib in Part 1 of the COLUMBUS study

	Combo 450 N=192 n (%)		Enco 300 N=192 n (%)		Vemurafenib N=186 n (%)	
Grade	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Any event	189 (98.4)	115 (59.9)	191 (99.5)	128 (66.7)	186 (100.0)	118 (63.4)
Nausea	83 (43.2)	3 (1.6)	74 (38.5)	8 (4.2)	65 (34.9)	3 (1.6)
Diarrhoea	71 (37.0)	5 (2.6)	26 (13.5)	3 (1.6)	64 (34.4)	4 (2.2)
Vomiting	58 (30.2)	3 (1.6)	54 (28.1)	9 (4.7)	29 (15.6)	2 (1.1)
Fatigue	56 (29.2)	4 (2.1)	48 (25.0)	1 (0.5)	57 (30.6)	4 (2.2)
Arthralgia	51 (26.6)	1 (0.5)	84 (43.8)	18 (9.4)	83 (44.6)	11 (5.9)
Blood CK increased	44 (22.9)	13 (6.8)	2 (1.0)	0	4 (2.2)	0
Headache	44 (22.9)	3 (1.6)	53 (27.6)	6 (3.1)	36 (19.4)	1 (0.5)
Constipation	43 (22.4)	0	29 (15.1)	0	12 (6.5)	1 (0.5)
Asthenia	39 (20.3)	3 (1.6)	40 (20.8)	5 (2.6)	35 (18.8)	8 (4.3)
Pyrexia	37 (19.3)	7 (3.6)	30 (15.6)	2 (1.0)	52 (28.0)	0
Abdominal pain	33 (17.2)	5 (2.6)	13 (6.8)	4 (2.1)	13 (7.0)	1 (0.5)
Vision blurred	31 (16.1)	0	4 (2.1)	0	4 (2.2)	0
Anaemia	30 (15.6)	9 (4.7)	12 (6.3)	5 (2.6)	15 (8.1)	5 (2.7)
GGT increased	29 (15.1)	18 (9.4)	23 (12.0)	10 (5.2)	21 (11.3)	6 (3.2)
Dry skin	28 (14.6)	0	58 (30.2)	0	42 (22.6)	0
Hyperkeratosis	28 (14.6)	1 (0.5)	74 (38.5)	7 (3.6)	54 (29.0)	0
Myalgia	28 (14.6)	0	55 (28.6)	19 (9.9)	34 (18.3)	1 (0.5)
Rash	28 (14.6)	2 (1.0)	40 (20.8)	4 (2.1)	54 (29.0)	6 (3.2)
Alopecia	27 (14.1)	0	108 (56.3)	0	68 (36.6)	0
Dizziness	27 (14.1)	4 (2.1)	11 (5.7)	0	5 (2.7)	0
Abdominal pain upper	23 (12.0)	2 (1.0)	18 (9.4)	2 (1.0)	17 (9.1)	1 (0.5)
Pruritus	23 (12.0)	1 (0.5)	42 (21.9)	1 (0.5)	20 (10.8)	0
Pain in extremity	22 (11.5)	2 (1.0)	43 (22.4)	2 (1.0)	26 (14.0)	2 (1.1)
ALT increased	21 (10.9)	10 (5.2)	10 (5.2)	2 (1.0)	14 (7.5)	3 (1.6)
Hypertension	21 (10.9)	10 (5.2)	11 (5.7)	6 (3.1)	22 (11.8)	6 (3.2)
Oedema peripheral	21 (10.9)	3 (1.6)	15 (7.8)	0	20 (10.8)	1 (0.5)
Muscle spasms	20 (10.4)	1 (0.5)	6 (3.1)	0	4 (2.2)	0
Nasopharyngitis	20 (10.4)	0	14 (7.3)	0	19 (10.2)	0
Back pain	19 (9.9)	1 (0.5)	29 (15.1)	5 (2.6)	12 (6.5)	3 (1.6)
Insomnia	19 (9.9)	0	35 (18.2)	5 (2.6)	15 (8.1)	0
Palmoplantar keratoderma	18 (9.4)	0	50 (26.0)	3 (1.6)	31 (16.7)	2 (1.1)
AST increased	16 (8.3)	4 (2.1)	8 (4.2)	1 (0.5)	15 (8.1)	3 (1.6)
Decreased appetite	16 (8.3)	0	40 (20.8)	1 (0.5)	36 (19.4)	2 (1.1)
Skin papilloma	15 (7.8)	0	19 (9.9)	0	31 (16.7)	0
Erythema	14 (7.3)	0	25 (13.0)	1 (0.5)	31 (16.7)	1 (0.5)
PPES	14 (7.3)	0	98 (51.0)	26 (13.5)	26 (14.0)	2 (1.1)
Musculoskeletal pain	11 (5.7)	0	31 (16.1)	6 (3.1)	11 (5.9)	2 (1.1)
Dysgeusia	10 (5.2)	0	22 (11.5)	0	17 (9.1)	0
Hyperglycaemia	9 (4.7)	4 (2.1)	6 (3.1)	4 (2.1)	0	0
Keratosis pilaris	9 (4.7)	0	33 (17.2)	0	43 (23.1)	0
Photosensitivity reaction	7 (3.6)	1 (0.5)	7 (3.6)	0	46 (24.7)	2 (1.1)
Weight decreased	6 (3.1)	0	29 (15.1)	2 (1.0)	20 (10.8)	0
General physical health deterioration	5 (2.6)	4 (2.1)	4 (2.1)	3 (1.6)	9 (4.8)	8 (4.3)
Keratoacanthoma	5 (2.6)	1 (0.5)	13 (6.8)	0	21 (11.3)	6 (3.2)
Metastases to central nervous system	5 (2.6)	3 (1.6)	5 (2.6)	4 (2.1)	3 (1.6)	3 (1.6)
Pain	4 (2.1)	2 (1.0)	12 (6.3)	7 (3.6)	3 (1.6)	0
Pleural effusion	4 (2.1)	4 (2.1)	3 (1.6)	2 (1.0)	2 (1.1)	1 (0.5)
Pruritus generalised	4 (2.1)	0	18 (9.4)	0	19 (10.2)	2 (1.1)
Rash generalised	4 (2.1)	0	13 (6.8)	1 (0.5)	17 (9.1)	8 (4.3)
Rash maculo-papular	4 (2.1)	0	18 (9.4)	1 (0.5)	27 (14.5)	8 (4.3)
Squamous cell carcinoma	2 (1.0)	0	3 (1.6)	0	12 (6.5)	8 (4.3)
Sunburn	0	0	1 (0.5)	0	19 (10.2)	1 (0.5)

A patient is counted once within each preferred term.
Preferred terms are sorted in descending frequency in the 'Combo 450' column.
MedDRA Version 19.0 has been used for the reporting of adverse events.

Table 3: Recommended dose modification for encorafenib for adverse reactions (all indications)

Severity of adverse reaction[a]	Recommended encorafenib dose modification
New Primary Malignancies[b]	
New primary non-cutaneous, RAS mutation-positive malignancies	
Any grade	Consider permanently discontinuing encorafenib.
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, withhold encorafenib for up to 6 weeks. Repeat ophthalmic monitoring within 2 weeks: - If uveitis is Grade 1 and it improves to Grade 0, then resume at the same dose. - If uveitis is Grade 2 or Grade 3 and it improves to Grade 0 or 1, then resume at a reduced dose. If not improved within 6 weeks, repeat ophthalmic monitoring and permanently discontinue encorafenib.
Grade 4	Permanently discontinue encorafenib and follow up with ophthalmologic monitoring.
QTc prolongation	
First or second occurrence of QTcF > 500 ms and change ≤ 60 ms from pre- treatment value	Withhold encorafenib and monitor as described in section 4.4 *Special warnings and special precautions for use*. Resume encorafenib at a reduced dose when QTcF ≤ 500 ms.
Third occurrence of QTcF > 500 ms and change ≤ 60 ms from pre-treatment value	Permanently discontinue encorafenib.
QTcF > 500 ms and increased by > 60 ms from pre-treatment value	Permanently discontinue encorafenib (see monitoring in section 4.4 *Special warnings and special precautions for use*).
Cutaneous reactions	
Grade 2	Maintain encorafenib. If rash worsens or does not improve within 2 weeks with treatment, withhold encorafenib until Grade 0 or 1 and then resume at the same dose.
Grade 3	Withhold encorafenib dose until improved to Grade 0 or 1 and resume at the same dose if first occurrence, or resume at a reduced dose if recurrent Grade 3.
Grade 4	Permanently discontinue encorafenib.
Palmar-plantar erythrodysaesthesia syndrome (PPES)	
Grade 2	Maintain encorafenib and institute supportive measures such as topical therapy. If not improved despite supportive therapy within 2 weeks, withhold encorafenib until improved to Grade 0 or 1 and resume treatment at the same dose level or at a reduced dose.
Grade 3	Withhold encorafenib and institute supportive measures such as topical therapy and reassess the patient weekly. Resume at the same dose level or at a reduced dose level when improved to Grade 0 or 1.
Liver laboratory abnormalities	
Grade 2 (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x – ≤ 5x upper limit of normal (ULN))	Maintain encorafenib dose. If no improvement within 4 weeks, withhold encorafenib until improved to Grade 0 or 1 or to pre-treatment/ baseline levels and then resume at the same dose.
First occurrence of Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	Withhold encorafenib for up to 4 weeks: - If improved to Grade 0 or 1 or to baseline levels, encorafenib can be resumed at a reduced dose. - If not improved, permanently discontinue encorafenib.
First occurrence of Grade 4 (AST or ALT > 20 ULN)	Either withhold encorafenib for up to 4 weeks: - If improved to Grade 0 or 1 or to baseline levels, encorafenib can be resumed at a reduced dose. - If not improved, permanently discontinue encorafenib. Or, permanently discontinue encorafenib
Recurrent Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	Consider permanently discontinuing encorafenib.
Recurrent Grade 4 (AST or ALT > 20 ULN)	Permanently discontinue encorafenib.
Other[c]	
Recurrent or intolerable Grade 2 adverse reactions First occurrence of Grade 3 adverse reactions	Withhold encorafenib for up to 4 weeks - If improved to Grade 0 or 1 or baseline levels, then resume at a reduced dose. - If not improved, permanently discontinue encorafenib.
First occurrence of any Grade 4 adverse reaction	Either withhold encorafenib for up to 4 weeks: - If improved to Grade 0 or 1 or baseline levels, then resume at a reduced dose. - If not improved, permanently discontinue encorafenib. Or, permanently discontinue encorafenib.
Recurrent Grade 3 adverse reactions	Consider permanently discontinuing encorafenib.
Recurrent Grade 4 adverse reactions	Permanently discontinue encorafenib.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
[b] Dose modification of encorafenib is not required for new primary cutaneous malignancies.
[c] Dose modification of encorafenib is not required for events attributable to binimetinib (see above Table 1).

XXXXXX

XXXXXX

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information.
You can help by reporting any side effects you may get. You can report side effects to your doctor, or physicians.

BRAFTOVI®

(encorafenib)
capsules

Active ingredient(s): *encorafenib*

This leaflet provides important information about using BRAFTOVI. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using BRAFTOVI.**

Where to find information in this leaflet:

1. Why am I taking BRAFTOVI?

BRAFTOVI contains the active ingredient encorafenib.
BRAFTOVI is an anti-cancer medicine, which belongs to a group of medicines called 'BRAF inhibitors'.
BRAFTOVI can be used in combination with binimetinib (called MEKTOVI) to treat adult patients who have a type of skin cancer called melanoma, which has spread to other parts of the body, or cannot be removed by surgery, and which has a particular change (mutation) in the gene that produces a protein called BRAF.
BRAFTOVI can also be used in combination with cetuximab to treat adult patients who have previously been treated with other anticancer medicines, and who have a type of large intestine cancer (colorectal cancer), which has spread to other parts of the body, and which has a particular change (mutation) in the gene that produces a protein called BRAF.
BRAFTOVI can only be used to treat patients whose cancer has one of these particular mutations in the BRAF gene.
Before you start treatment, your doctor will have tested your tumour to confirm that it has one of these BRAF mutations.
When BRAFTOVI is used in combination with MEKTOVI or cetuximab, it can slow down or stop the growth of your cancer.
Ask your doctor if you have any questions about why this medicine has been prescribed for you.
BRAFTOVI is not recommended for children and adolescents aged under 18 years. The safety and efficacy of this medicine has not been established in this age group.

2. What should I know before I take BRAFTOVI?

BRAFTOVI is to be used in combination with either MEKTOVI or cetuximab, therefore you should also read the CMI for the other medicine you are planning to take.

Warnings
Do not take BRAFTOVI if:
- You are allergic to encorafenib, or any of the ingredients listed at the end of this leaflet. Some of the symptoms of an allergic reaction may include:
  - shortness of breath
  - wheezing or difficulty breathing
  - swelling of the face, lips, tongue or other parts of the body
  - rash, itching or hives on the skin
- Always check the ingredients to make sure you can use this medicine.

Check with your doctor if you:
- Have any other medical conditions such as:
  - heart problems, including alteration of the electrical activity of your heart (QT prolongation)
  - liver problems
  - kidney problems
  - bleeding problems, or if you are taking medicines that may increase your risk of bleeding
  - eye problems
- Have had a different type of cancer from melanoma or colorectal cancer as BRAFTOVI may cause progression of certain other types of cancers.
- Take any medicines for any other condition.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section 6. *Are there any side effects?*

Pregnancy and breastfeeding
Check with your doctor if you are pregnant or intend to become pregnant. Taking BRAFTOVI during pregnancy is not recommended. BRAFTOVI may cause permanent harm or birth defects to an unborn baby.
Talk to your doctor if you are breastfeeding or intend to breastfeed. BRAFTOVI is not recommended while breast-feeding. It is not known if BRAFTOVI passes into breastmilk.

3. What if I am taking other medicines?

Tell your doctor or pharmacist if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with BRAFTOVI and affect how it works. These include:
- some medicines to treat fungal infections (such as itraconazole, posaconazole, fluconazole)
- some medicines to treat bacterial infections (such as rifampicin, clarithromycin, telithromycin, erythromycin)
- medicines typically used to treat epilepsy (seizures) (such as phenytoin, carbamazepine)
- imatinib (a medicine used to treat cancer)
- a herbal treatment for depression called St. John's wort
- some medicines for HIV treatment such as ritonavir or amprenavir
- birth control medicines containing hormones
- medicines typically used to treat high blood pressure (such as diltiazem)
- medicines used to treat an uneven heartbeat such as amiodarone.

These medicines may be affected by BRAFTOVI or these medicines may affect how well BRAFTOVI works. You may need different amounts of your medicines, or you may need to take different medicines.
Keep a list of the medicines you take so you can show it to your doctor, nurse or pharmacist when you get a new medicine.
Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect BRAFTOVI.

4. How do I take BRAFTOVI?

How much to take
- Always take BRAFTOVI exactly as your doctor has prescribed.
- The recommended dose of BRAFTOVI to treat melanoma, when taken in combination with MEKTOVI, is six 75 mg capsules once daily (corresponding to a daily dose of 450 mg).
- The recommended dose of BRAFTOVI to treat colorectal cancer, when taken in combination with cetuximab, is four 75 mg capsules once daily (corresponding to a daily dose of 300 mg).
- Be aware that your dose of BRAFTOVI may change during treatment, depending on your response to treatment.
- If you have liver or kidney problems, your doctor may start you on a lower dose of BRAFTOVI. If you experience serious side effects (such as skin, heart, liver, eye or bleeding problems), your doctor may lower the dose of BRAFTOVI, or stop treatment temporarily or permanently.
- Follow the instructions provided and use BRAFTOVI until your doctor tells you to stop.

When to take
- Swallow the capsules whole with a full glass of water.
- BRAFTOVI can be taken with or without food. Avoid grapefruit juice.
- If vomiting occurs at any time after taking the capsules, do not take an additional dose. Take the next dose as scheduled.

Continue taking BRAFTOVI for as long as your doctor tells you to.
Do not stop unless your doctor advises you to.

If you forget to take BRAFTOVI
If the missed dose is less than 12 hours late, take it as soon as you remember.
If the missed dose is more than 12 hours late, skip that dose and take your next dose at the usual time. Then go back to taking your capsules as you would normally.
If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.
Do not take a double dose to make up for the dose you missed.
If you are not sure what to do, ask your doctor or pharmacist.
If you have trouble remembering to take your medicine, ask your doctor, nurse or pharmacist for some hints.

If you take too much BRAFTOVI
If you think that you have taken too much BRAFTOVI, you may need urgent medical attention.
You should immediately:
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while taking BRAFTOVI?

Things you should do
If you are about to be started on any new medicine, remind your doctor and pharmacist that you are taking BRAFTOVI.
Tell any other doctors, dentists, and pharmacists who treat you that you are taking BRAFTOVI.
If you are going to have surgery, tell the surgeon or that you are taking BRAFTOVI.
If you become pregnant while taking BRAFTOVI, tell your doctor immediately.
If you are a woman who could become pregnant, you must use effective birth control (contraception) while you are taking BRAFTOVI, and you must continue to use effective 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) which release hormones) may not work as well as expected while you are taking BRAFTOVI. You will need to use another reliable method of birth control such as a barrier method (e.g. condom) to prevent falling pregnant while you are taking BRAFTOVI. Ask your doctor, pharmacist or nurse for advice.
Tell your doctor if you are breastfeeding while being treated with BRAFTOVI.

Call your doctor straight away if you experience the following while you are taking BRAFTOVI:
- **Skin changes**
  Tell your doctor immediately if you detect any skin changes including new warts, skin soreness, reddish bumps which bleed or don't heal, or any changes in the size or colour of a mole.
  BRAFTOVI may cause other types of skin cancer such as cutaneous squamous cell carcinoma. New melanoma lesions may also occur while taking BRAFTOVI.
  Your doctor will periodically check for new cancers on your skin and inside your body before, during and after your treatment with BRAFTOVI.
- **Heart problems**
  BRAFTOVI may lower the amount of blood pumped by your heart, alter the electrical activity of your heart, or make existing heart problems worse. Your doctor will run tests to check that your heart is working properly before and during your treatment with these medicines.
- **Bleeding problems**
  BRAFTOVI may cause serious bleeding problems. Tell your doctor immediately if you have any signs of bleeding.
- **Eye problems**
  BRAFTOVI may cause serious eye problems. Your doctor will examine your eyes for any new or worsening problems with your sight while you are taking these medicines.
- **Liver problems**
  BRAFTOVI may increase the amounts of liver enzymes in your blood. Your doctor will run blood tests to monitor your liver function before and during treatment.
- **Kidney problems**
  BRAFTOVI may alter your kidney activity (often it may cause abnormal blood tests, but more rarely it can cause dehydration and vomiting, or kidney failure). 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.

Remind any doctor, dentist or pharmacist you visit that you are using BRAFTOVI. Keep all of your doctor's appointments so that your progress can be checked.

Things you should not do
Do not take BRAFTOVI to treat any other complaints unless your doctor tells you to.
Do not give your medicine to anyone else, even if their symptoms seem similar to yours or they have the same condition as you.
Do not stop taking your medicine or lower the dosage without checking with your doctor.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how BRAFTOVI affects you.
BRAFTOVI can affect your ability to drive or use machines.
If you experience any problems with your vision, or any other side-effects that may affect your ability, avoid driving or using machines. Talk to your doctor if you are not sure if you should drive.

Looking after your medicine
- Keep your BRAFTOVI capsules in their original pack until it is time to take them.
- Keep your BRAFTOVI capsules in a place where the temperature stays below 25°C.

Follow the instructions in the carton on how to take care of your medicine properly.
Store it in a cool dry place away from moisture, heat or sunlight; for example, do not store it:
- in the bathroom or near a sink, or
- in the car or on windowsills.

Keep it where young children cannot reach it.

Getting rid of any unwanted medicine
If you no longer need to use this medicine or it is out of date, take it to any pharmacy for safe disposal.
Do not use this medicine after the expiry date.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.
See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.
When BRAFTOVI was taken with MEKTOVI by patients with melanoma, the following side effects were reported.

Less serious side effects
Head and neurology related: • problems with nerves that can cause pain, loss of sensation or tingling in hands and feet • headache • dizziness • fever • fatigue • changes in the way things taste • weakness and paralysis of the face muscles (facial paresis) **Bleeding related:** • reduced red blood cell count (anaemia) • bleeding at various sites in the body • blood clots **Heart related:** • high blood pressure • abnormal blood test results related to blood creatine kinase, indicating damage to the heart and muscle **Eyes related:** • problems with your vision (visual impairment) • inflammation of the eye (uveitis) **Gastrointestinal related:** • stomach pain • diarrhoea • being sick (vomiting) • feeling sick (nausea) • constipation • abnormal blood test results for liver function • inflammation of the colon (colitis) • 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) • inflammation of the pancreas (pancreatitis) causing severe abdominal pain **Muscle related:** • joint pain (arthralgia) • muscle pain (myalgia), weakness or spasm • back pain • pain in the hands and feet **Skin and hair related:** • itching • dry skin • abnormal hair loss or thinning (alopecia) • thickening of the outer layers of the skin • some types of benign (non-cancerous) skin tumours such as skin papilloma • type of skin cancer such as basal cell carcinoma • redness, chapping or cracking of the skin • inflammation of the fatty layer under the skin, symptoms include tender skin nodules • skin rash with flat discoloured area or raised bumps like acne (dermatitis acneiform) • redness, skin peeling or blisters on hands and feet (called palmar-plantar erythrodysaesthesia or hand and foot syndrome) • increased skin sensitivity to sunlight
What to do
Speak to your doctor if you have any of these less serious side effects and they worry you.

Serious side effects

Serious side effects
Heart related: BRAFTOVI can affect the strength with which your heart pumps blood into your arteries or makes existing heart problems worse. 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 **Bleeding related:** • 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 **Eye related:** Fluid leakage under the retina in the eye can be induced that results in detachment of different layers in the eye (retinal pigment epithelial detachment). Signs and symptoms can include: • blurred vision, loss of vision or other vision changes (e.g. coloured dots in your vision) • halo (seeing blurred outline around objects) • eye pain, swelling or redness **Muscle related:** Breakdown of muscles (rhabdomyolysis) may occur 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 related:** • BRAFTOVI may cause other types of skin cancer such as cutaneous squamous cell carcinoma. Usually these skin cancers can be removed with surgery and treatment with BRAFTOVI and MEKTOVI can be continued without interruption. • new melanoma lesions may also appear while taking BRAFTOVI. These melanomas are usually removed by surgery and treatment with BRAFTOVI and MEKTOVI can be continued without interruption. **Allergy related:** • swelling of the hands or feet (peripheral oedema), localised swelling • allergic reaction that may include swelling of the face and difficulty breathing
What to do
Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.

If you continue BRAFTOVI on its own while MEKTOVI has been temporarily stopped based on your doctor's decision, you may notice new side effects, or changes in the side effects you experience.

When BRAFTOVI was taken with cetuximab by patients with colorectal cancer, the following side effects were reported:

Less serious side effects
Head and neurology related: • problems with nerves that can cause pain, loss of sensation or tingling in hands and feet • headache • dizziness • fever • fatigue • difficulty sleeping • changes in the way things taste **Bleeding related:** • reduced red blood cell count (anaemia) • bleeding at various sites in the body **Heart related:** • abnormal blood test results related to blood creatine kinase, indicating damage to the heart and muscle • fast heart beat **Gastrointestinal related:** • stomach pain • diarrhoea • being sick (vomiting) • feeling sick (nausea) • constipation • 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) • loss of appetite • inflammation of the pancreas (pancreatitis) causing severe abdominal pain **Muscle related:** • joint pain (arthralgia) • muscle pain (myalgia), weakness or spasm • bone pain • back pain • pain in the hands and feet **Skin and hair related:** • new moles **called "melanocytic naevus"** • itching • dry skin • abnormal hair loss or thinning (alopecia) • thickening of the outer layers of the skin • some types of benign (non-cancerous) skin tumours such as skin papilloma • type of skin cancer such as basal cell carcinoma • redness, chapping or cracking of the skin • skin darkening • inflammation of the fatty layer under the skin, symptoms include tender skin nodules • skin rash with flat discoloured area or raised bumps like acne (dermatitis acneiform) • redness, skin peeling or blisters on hands and feet (called palmar-plantar erythrodysaesthesia or hand and foot syndrome)
What to do
Speak to your doctor if you have any of these less serious side effects and they worry you.

Serious side effects

Serious side effects
Heart related: BRAFTOVI can affect the strength with which your heart pumps blood into your arteries or makes existing heart problems worse. 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 **Bleeding related:** • 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 • blood clots **Allergy related:** • swelling of the hands or feet (peripheral oedema), localised swelling • allergic reaction that may include swelling of the face and difficulty breathing **Other skin cancers related:** • BRAFTOVI may cause other types of skin cancer such as cutaneous squamous cell carcinoma or new melanomas. Usually these skin cancers can be removed with surgery.
What to do
Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

Reporting side effects
Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details
This medicine is only available with a doctor's prescription.

What BRAFTOVI contains

Active ingredient (main ingredient)	50 or 75 mg of encorafenib
Other ingredients (inactive ingredients)	**Capsule fill:** • copovidone • poloxamer • microcrystalline cellulose • succinic acid • crospovidone • colloidal anhydrous silica • magnesium stearate **Capsule shell:** • gelatin • titanium dioxide • iron oxide red • iron oxide yellow • iron oxide black **Printing ink:** • shellac • iron oxide black • propylene glycol
Potential allergens	No

Do not take this medicine if you are allergic to any of these ingredients.

What BRAFTOVI looks like
BRAFTOVI 50 mg hard capsules are supplied in blister packs of 28 capsules (7 strips of 4 capsules).

The 50 mg capsules have an orange opaque cap and a flesh-coloured opaque body, with a stylised "A" printed on the cap and "LGX 50 mg" printed on the body.

50 mg: SINxxxxxP

BRAFTOVI 75 mg hard capsules are supplied in blister packs of 42 capsules (7 strips of 6 capsules).

The 75 mg capsules have a flesh-coloured opaque cap and a white opaque body, with a stylised "A" printed on the cap and "LGX 75 mg" printed on the body.

75 mg: SINxxxxxP

Who distributes BRAFTOVI
Zuellig Pharma Pte Ltd
15 Changi North Way #01-01
Singapore 498770

® = Registered Trademark

Pierre Fabre Médicament

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 studies
In the pooled Combo 450 population, RPED was reported in 29.6% (81/274) of patients. RPED was Grade 1 (asymptomatic) in 21.2% (58/274) of patients, Grade 2 in 5.8% (16/274) and Grade 3 in 1.8% (5/274). Most of these events were reported as retinopathy (9.5%, 26/274), retinal detachment (6.6%, 18/274), subretinal fluid (6.2%, 17/274), macular oedema (5.1%, 14/274) and chorioretinopathy (3.3%, 9/274); and led to dose interruptions or dose modifications in 4.7% (13/274) of patients. RPED was generally reversible. The median time to onset of the first event of RPED (all grades) was 1.5 months (0.03 to 17.5 months).
Uveitis was reported in 4.4% (12/274) of patients and was Grade 1 in 0.4% (1/274), Grade 2 in 3.6% (10/274) and Grade 3 in 0.4% (1/274). Visual impairment, including blurred vision and reduced visual acuity, occurred in 21.5% (59/274) of patients. Uveitis and visual impairment were generally reversible.

Left ventricular dysfunction
Melanoma studies
LVD was reported when encorafenib is used in combination with binimetinib in patients with melanoma (see section 4.8 *Adverse effects (undesirable effects)* of binimetinib PI).

Haemorrhage
Melanoma studies
Haemorrhagic events have been observed in 17.9% (49/274) of patients in the pooled Combo 450 population. Most of these events were Grade 1 or 2 (14.6%) and 3.3% were Grade 3 or 4 events. Few patients required dose interruptions or dose reductions (0.7% or 2/274).
Haemorrhagic events led to discontinuation of treatment in 1.1% (3/274) of patients. The most frequent haemorrhagic events were haematuria in 3.3% (9/274) of patients, rectal haemorrhage in 2.9% (8/274) and haematochezia in 2.9% (8/274) of patients. Fatal gastric ulcer haemorrhage, with multiple organ failure as a concurrent cause of death, occurred in one patient. Cerebral haemorrhage occurred in 1.5% (4/274) of patients; with fatal outcome in 3 patients. All events occurred in the setting of new or progressive brain metastases.
In the Combo 300 population of the COLUMBUS study, haemorrhagic events were observed in 6.6% (17/257) of patients and were Grade 3 or 4 in 1.6% (4/257) of patients.
Colorectal cancer studies
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
Melanoma studies
Hypertension was reported when encorafenib was used in combination with binimetinib in melanoma patients (see section 4.8 *Adverse effects (undesirable effects)* of binimetinib PI).

Venous thromboembolism
Melanoma studies
VTE was reported when encorafenib was used in combination with binimetinib in melanoma patients (see section 4.8 *Adverse effects (undesirable effects)* of binimetinib PI).

Pancreatitis
Melanoma studies
In the pooled Combo 450 population, pancreatic enzyme elevation, mostly asymptomatic, was reported. Amylase and lipase elevations have been reported in 3.3% (9/274) and 51% (14/274) of patients, respectively. Pancreatitis adverse reactions were reported in 0.7% (2/274) of patients. Both patients experienced Grade 3 events. Pancreatitis led to dose interruption in 0.4% (1/274) of patients.
Colorectal cancer studies
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%). Pancreatitis recurred on re-challenge twice, despite dose reductions each time, and led to permanent discontinuation.

Dermatological reactions

Rash
Melanoma studies
In the pooled Combo 450 population, rash occurred in 19.7% (54/274) of patients. Most of the events were mild, with Grade 3 or 4 events reported in 0.7% (2/274) of patients. Rash led to discontinuation in 0.4% (1/274) of patients and to dose interruption or dose modification in 1.1% (3/274) of patients.
In the pooled encorafenib 300 mg population, rash was reported in 43.3% (94/217) of patients. Most of the events were mild, with Grade 3 or 4 events reported in 4.6% (10/217) of patients who received encorafenib as a single agent. 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 studies
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
Melanoma studies
PPES was reported in 6.2% (17/274) of patients in the pooled Combo 450 population. All the PPES adverse reactions were either Grade 1 (3.3%) or Grade 2 (2.9%). Dose interruption or dose modification occurred in 1.1% (3/274) of patients.
In the pooled encorafenib 300 mg population, PPES was reported in 51.6% (112/217) of patients. Most of the events were mild to 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 studies
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 either 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 studies
Dermatitis acneiform was reported when encorafenib was used in combination with binimetinib (see section 4.8 *Adverse effects (undesirable effects)* of the binimetinib PI).
Colorectal cancer studies
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 studies
In the pooled Combo 450 population, photosensitivity was observed in 4.0% (11/274) of patients. Most events were Grade 1 or 2, with Grade 3 reported in 0.4% (1/274) of patients and no event led to discontinuation. Dose interruption or dose modification was reported in 0.4% (1/274) of patients.
In the pooled encorafenib 300 mg 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 studies
In the pooled Combo 450 population, facial paresis occurred in 0.7% (2/274) of patients including Grade 3 in 0.4% (1/274) of patients. The events were reversible, and no event led to treatment discontinuation. Dose interruption or modification was reported in 0.4% (1/274) of patients.
In the pooled encorafenib 300 mg population, facial paresis was observed in 7.4% (16/217) of patients. Most events were mild to 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 / rhabdomyolysis
Melanoma studies
CK elevation and rhabdomyolysis occurred when encorafenib was used in combination with binimetinib in melanoma patients (see section 4.8 *Adverse Effects (undesirable effects)* of binimetinib PI).

Renal dysfunction
Melanoma studies
In the pooled Combo 450 population, mildly mostly Grade 1 asymptomatic blood serum creatinine elevation was reported in 6.2% (17/274) of patients. The incidence of Grade 3 or 4 elevation was 0.7% (2/274). Renal failure events including acute kidney injury and renal impairment were reported in 3.3% (9/274) of patients with Grade 3 or 4 events in 2.2% (6/274) of patients. Renal failure was generally reversible with dose interruption, rehydration and other general supportive measures.
Colorectal cancer studies
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 abnormalities
Melanoma studies
The incidences of liver laboratory abnormalities reported in the pooled Combo 450 population are listed below:
• Increased transaminases: 15.7% (43/274) overall – Grade 3-4: 5.5% (15/274)
• Increased GGT: 14.6% (40/274) overall – Grade 3-4: 8.4% (23/274)
In the Combo 300 arm of the COLUMBUS study, the incidence of liver laboratory abnormalities was:
• Increased transaminases: 13.2% (34/257) overall – Grade 3-4: 5.4% (14/257)
• Increased GGT: 14.0% (36/257) overall – Grade 3-4: 4.7% (12/257)
Colorectal cancer studies
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 studies
In the pooled Combo 450 population, diarrhoea was observed in 38% (104/274) of patients and was Grade 3 or 4 in 3.3% (9/274) of patients. Diarrhoea led to dose discontinuation in 0.4% of patients and to dose interruption or dose modification in 4.4% of patients.
Constipation occurred in 24.1% (66/274) of patients and was Grade 1 or 2. Abdominal pain was reported in 27.4% (75/274) of patients and was Grade 3 in 2.6% (7/274) patients. Nausea occurred in 41.6% (114/274) with Grade 3 or 4 observed in 2.6% (7/274) of patients.
Vomiting occurred in 28.1% (77/274) of patients with Grade 3 or 4 reported in 2.2% (6/274) of patients.
Colorectal cancer studies
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.

Anaemia
Melanoma studies
In the pooled Combo 450 population, anaemia was reported in 19.7% (54/274) of patients; 4.7% (13/274) patients had a Grade 3 or 4. No patients discontinued treatment due to anaemia, 1.5% (4/274) required dose interruption or dose modification. In the Combo 300 population of the COLUMBUS study, anaemia was observed in 9.7% (25/257) of patients with Grade 3 or 4 reported in 2.7% (7/257) of patients.

Headache
Melanoma studies
In the pooled Combo 450 population, headache occurred in 21.5% (59/274) of patients, including Grade 3 in 1.5% (4/274) of patients. In the Combo 300 population of the COLUMBUS study, headache was reported in 12.1% (31/257) of patients and was Grade 3 in 0.4% (1/257) of patients.
Colorectal cancer studies
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 studies
In the pooled Combo 450 population, fatigue occurred in 43.8% (120/274) of patients including Grade 3 in 2.9% (8/274) of patients. In the Combo 300 population of the COLUMBUS study, fatigue was observed in 33.5% (86/257) of patients with 1.6% (4/257) Grade 3 or 4 events.
Colorectal cancer studies
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 patients
The number of patients aged 75 years or older enrolled in clinical studies was not sufficient to enable meaningful assessment of differential safety in this population compared to younger patients, in any tumour type.
Melanoma studies
In patients treated with Combo 450 (n=274), 194 patients (70.8%) were < 65 years, 65 patients (23.7%) were 65 to 74 years and 15 patients (5.5%) were aged > 75. No overall differences in safety or efficacy were observed between elderly patients (≥ 65) and younger patients. The proportions of patients experiencing AEs and SAEs were similar in patients aged < 65 years and those aged ≥ 65 years. The most common AEs reported with a higher incidence in patients aged ≥ 65 years compared to patients aged < 65 years included diarrhoea, pruritus, GGT and blood phosphatase alkaline elevation.
Colorectal cancer studies
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 AEs reported with a higher incidence in patients aged ≥ 65 years compared to patients aged < 65 years included, anaemia, asthenia, decreased appetite and dyspnoea.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at HSA: Healthcare professionals' guide to adverse events reporting.

4.9. OVERDOSE

At doses of encorafenib between 600 to 800 mg once daily, renal dysfunction (grade 3 hypercreatinemia) 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). AEs reported by this patient were Grade 1 events of nausea, vomiting and blurred vision; all were subsequently resolved.

Management of overdose
There is no specific treatment for overdose with encorafenib. If overdose occurs, 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. Since encorafenib is moderately bound to plasma proteins, haemodialysis is likely to be ineffective in the treatment of overdose with encorafenib.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action
Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitor.
ATC code: L01EC03
Encorafenib is an ATP-competitive small molecule RAF kinase inhibitor. The 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, V600D and V600K). However, it does not inhibit RAF/MEK/ERK signalling in cells expressing wild- type BRAF. Encorafenib also binds to other kinases *in vitro* including STK36, JNK1/2/3, LIMK1/2 and MEK4/5, at clinically achievable concentrations. Specifically, encorafenib inhibits *in vitro* and *in vivo* BRAF V600E, V600D and V600K mutation-positive melanoma cell growth and BRAF V600E mutant colorectal cancer cell growth. *In vivo*, encorafenib has been evaluated for its ability to inhibit pERK and pMEK, and tumour growth in xenograft models in nude mice. Overall, encorafenib has demonstrated potent activity against RAF enzymes and possesses anti-proliferative activity *in vitro* and *in vivo* in BRAF mutant tumour xenograft models.

Combination with binimetinib
In non-clinical studies, the combination of encorafenib and binimetinib demonstrated additive or synergistic anti-proliferative activity *in vitro* in numerous BRAF-mutant cell lines. *In vivo*, treatment with the combination resulted in greater anti-tumour activity with respect to tumour growth inhibition and better tumour responses (PR and SD) in BRAF V600E mutant human melanoma xenograft studies in mice than that which was achieved with either agent alone.
Additionally, the combination of encorafenib and binimetinib prevented the emergence of treatment resistance in BRAF V600E mutant human melanoma xenografts in mice.

Combination with cetuximab
One of the main mechanisms of resistance of BRAF-mutant mCRC 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) with agents targeting EGFR (e.g. cetuximab) have been shown to improve anti-tumour efficacy in non-clinical models.

Cardiac electrophysiology
Melanoma studies
In a pooled safety analysis across melanoma studies, the incidence of new QTcF prolongation > 500 ms was 0.7% (2/268) in the Combo 450 population, and 2.5% (5/203) in the pooled encorafenib 300 mg population. QTcF prolongation of > 60 ms compared to pre-treatment values was observed in 4.9% (13/268) patients in the Combo 450 population, and in 3.4% (7/204) in the pooled encorafenib 300 mg population (see Sections 4.2 *Dose and method of administration* and 4.4 *Special warnings and special precautions for use*).
Colorectal cancer studies
In the encorafenib plus cetuximab arm of BEACON CRC, 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 (see section 4.2 *Dose and method of administration* and section 4.4 *Special warnings and special precautions for use*).

Clinical trials
COLUMBUS - BRAF V600 mutant unresectable or metastatic melanoma
The safety and efficacy of encorafenib in combination with binimetinib were evaluated in the COLUMBUS study: a Phase III, randomised (1:1:1) active-controlled, open-label, multicentre trial in patients with unresectable or metastatic BRAF V600 E or K mutant melanoma (also known as CMEK162B2301). 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 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. In Part 1 of the study, patients were randomised to receive encorafenib 450 mg orally once daily and binimetinib 45 mg orally twice daily (Combo 450, N=192), encorafenib 300 mg orally once daily (Enco 300, N=194), or vemurafenib 960 mg orally twice daily (Vem, N=191). In Part 2, patients were randomised to receive encorafenib 300 mg orally once daily and binimetinib 45 mg orally twice daily (Combo 300, N=258) or encorafenib 300 mg orally once daily (n=86). Safety data from Part 2 are reflected in section 4.8 *Adverse effects (undesirable effects)*. Treatment continued until disease progression or unacceptable toxicity. Randomisation was stratified by 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) and prior immunotherapy for unresectable or metastatic disease (yes versus 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. The key 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 for patients was 56 years (range 20 to 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 LDH, and 45% of patients had ≥ 3 organs with tumour involvement at baseline and 3.5% had brain metastases. A total of 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). Most patients were BRAF V600E mutant (88.6%), while the remainder were V600K mutant (10.9%).
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 99.6 % for binimetinib and 100% for encorafenib; the median RDI was 86.2% for Enco 300 and 94.5% for vemurafenib.
The COLUMBUS study demonstrated a statistically significant improvement in PFS in patients treated with Combo 450 compared with patients treated with vemurafenib. Patients treated with Combo 450 also had improved ORR, DCR, and DoR compared with patients treated with vemurafenib. Table 9 and Figure 1 summarise the PFS and other efficacy results based on central review of the data by the BIRC.

Table 9: Progression-free survival and confirmed overall response results (cut-off date: 19 May 2016, independent central review)

Figure 1: Kaplan-Meier plot of progression-free survival by independent central review (cut-off date: 19 May 2016)

The efficacy results based on investigator assessment were consistent with the independent central assessment The PFS analysis per investigator assessment showed an improvement of PFS in patients treated with Combo 450 compared with patients treated with vemurafenib (14.8 vs 7.3 months, respectively), HR 0.49 (95 % CI 0.37, 0.64) (p < 0.001 one sided).
The ORR analysis per investigator assessment showed an improvement of ORR in patients treated with Combo 450 compared with patients treated with vemurafenib: (75% (95 % CI 68.3, 81.0) vs 49.2 % (95% CI 41.9 56.5), respectively (p < 0.001 one sided). In the Combo 450 arm, CR was 16.1%, PR 58.9 % and SD 18.2%.
At a cut-off date of 7 November 2017, an update of the PFS analyses was performed. The PFS analysis per independent central review showed an improvement of PFS in patients treated with Combo 450 compared with patients treated with vemurafenib (14.9 vs 7.3 months, respectively), HR 0.51 (95 % CI 0.39, 0.67) (p < 0.001 one sided) and also compared with patients treated with encorafenib (14.9 vs 9.6 months, respectively), HR 0.77 (95 % CI 0.59, 1.0) (p = 0.0249 one sided). The analysis per central review showed that encorafenib improved PFS vs. vemurafenib (9.6 vs 7.3 months, respectively), HR 0.68 (95 % CI 0.52, 0.88) (p = 0.0019 one sided). The PFS results per investigator review showed consistent results.
An interim OS analysis of Part 1 of the COLUMBUS study, performed at the cut-off date of 7 November 2017, demonstrated a statistically significant improvement in OS for Combo 450 compared with vemurafenib (HR 0.61, 95% CI 0.47, 0.79). See Table 100 and Figure 2.
A similar proportion of patients in each treatment arm received subsequent treatment with checkpoint inhibitors, mainly pembrolizumab, nivolumab and ipilimumab (34.4% Combo 450 arm, 36.1% Enco 300 arm, 39.8% vemurafenib arm).

Table 10: Overall survival interim results (cut-off date: 7 November 2017)

Figure 2: Kaplan-Meier plot of interim overall survival (cut-off date: 7 November 2017)

Subgroup analyses of PFS
All subgroup analyses of PFS per BIRC including gender, age (< 65/≥ 65), region (North America, Europe, Australia, other), number of organs involved at baseline (1, 2, 3, > 3), LDH at baseline (< ULN/≥ ULN), ECOG performance status (0/1), AJCC Stage (IIIB, IIIC, IVM1a, IVM1b/IVM1c), and prior adjuvant therapy (Yes/No) demonstrated point estimates in favour of the Combo 450 arm, except for the presence of brain metastases at baseline, a subgroup that only included 12 patients. Most of the HRs in the Combo 450 arm relative to the vemurafenib arm were within the range of the HR observed in the overall population.

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 side effects. The data showed favourable outcomes for the Combo 450 arm over the vemurafenib arm. 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). The median time to definitive 10% deterioration in the EORTC QLQ-C30 global health status score was delayed by more than 7 months in the Combo 450 arm compared to the vemurafenib arm: 23.9 months (95% CI 20.4, NE) vs. 16.6 months (95% CI 11.9, NE) with a HR for the difference of 0.55 (95% CI 0.37, 0.80). As these were exploratory endpoints, they must be interpreted with caution in the context of an open-label study design.
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 (p-values < 0.001).

BEACON CRC - BRAF V600E mutant metastatic colorectal cancer (mCRC)
Encorafenib in combination with cetuximab was evaluated in BEACON CRC: a randomised, active-controlled, open-label, multicentre trial (also known as ARRAY 818-302). Eligible patients were required to have metastatic colorectal cancer harbouring a BRAF V600E mutation (as detected using the Qiagen therascreen BRAF V600E RGQ polymerase chain reaction (PCR) Kit) that had progressed 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 labelling with respect to tumour RAS status, and ECOG performance status (PS) 0-1. Randomisation 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).
A total of 665 patients were randomised (1:1:1) to one of the following treatment arms:
• Encorafenib 300 mg orally once daily in combination with cetuximab (encorafenib plus cetuximab arm) [n=220]
• Encorafenib 300 mg orally once daily in combination with binimetinib and cetuximab [n=224]
• Irinotecan with cetuximab or irinotecan/5-fluorouracil/folinic acid (FOLFIRI) with cetuximab (control arm) [n=221]
Cetuximab was dosed as per its approved European label (SmPC). 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.
The primary efficacy outcomes were overall survival (OS) and Overall Response Rate (ORR). Additional efficacy outcome measures included progression-free survival (PFS), , and duration of response (DoR) as assessed by blinded independent central review (BICR). OS and PFS were assessed in all randomised patients. ORR and DoR were assessed in the first 330 patients randomised (plus any additional patients randomised on the same day as the 330th randomised patient.).
A total of 220 patients were randomized to the BRAFTOVI/cetuximab arm and 221 to the control arm.
The median age of patients randomised to the encorafenib plus cetuximab or the control arm was 61 years (range 27-91), 47% were male, 80% were white and 15% were asian. Half had a baseline ECOG performance status of 0, 66% had received one prior line of systemic therapy and 34% had received two; 93% had previously received oxaliplatin and 52% had previously received irinotecan. Half of patients had at least 3 organs with tumour involvement at baseline.
The median duration of exposure was 3.2 months in the encorafenib plus cetuximab arm, and 1.4 months in the control arm. In the encorafenib plus cetuximab arm, the median relative dose intensity (RDI) was 98% for encorafenib and 94% for cetuximab. In the control arm, the median RDI was 85% for cetuximab, 76% for irinotecan and (in the subset of patients who received them) 75% for Folinic acid and 74% for 5-FU.
Encorafenib 300 mg in combination with cetuximab demonstrated a statistically significant improvement in OS, ORR and PFS compared to the control arm. Efficacy results are summarised in Table 11 and Figure 3.
The efficacy results based on investigator assessment were consistent with the independent central assessment.

Table 11: Efficacy results from the BEACON CRC study (ARRAY-818-302), data cut-off date 11 February 2019

Figure 3: Kaplan-Meier plot of OS in BEACON CRC (cut-off date: 11 February 2019)

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

5.2. PHARMACOKINETIC PROPERTIES

The pharmacokinetics of encorafenib were studied in adult healthy subjects and patients with solid tumours, including advanced and unresectable or metastatic cutaneous melanoma harbouring a BRAF-V600E or BRAF-V600K mutation, and in patients with metastatic colorectal cancer with a BRAF V600E mutation. The pharmacokinetics of encorafenib have been shown to be approximately 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 intersubject variability (CV %) of AUC 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 maximum encorafenib concentration (C_{max}) by 36%, while the area under the concentration-time curve (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%).

Metabolism
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.

Excretion
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).

Special populations
Hepatic impairment
Results from a dedicated clinical trial indicate a 25% higher encorafenib exposure 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 section 4.2 *Dose and method of administration* and section 4.4 *Special warnings and special precautions for use*).
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 PK 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.
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.
The elderly
Based on results from a population PK analysis of encorafenib in combination with binimetinib, the pharmacokinetics of encorafenib are similar in elderly patients as compared to younger patients.
Children and adolescents (< 18 years)
The pharmacokinetics of encorafenib have not been established in patients below the age of 18 years.
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.
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.
Race
There have been no clinically relevant differences in encorafenib PK observed specifically in the Asian population. There are insufficient data to evaluate potential differences in the exposure of encorafenib on the basis of race or ethnicity.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity
Based on the results of *in vitro* bacterial reverse mutation assays, an *in vitro* human peripheral blood lymphocyte chromosomal aberration assay and an *in vivo* rat bone marrow micronucleus test, encorafenib is not genotoxic.

Carcinogenicity
The carcinogenic potential of encorafenib was not evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS
BRAFTOVI capsules are capsules for oral administration.
Each capsule contains 50 or 75 mg encorafenib.
The capsules also contain the excipients: copovidone, poloxamer, microcrystalline cellulose, succinic acid, crospovidone, colloidal anhydrous silica and magnesium stearate; the capsule shell contains the excipients: gelatin, titanium dioxide, iron oxide red, iron oxide yellow and iron oxide black; and the printing ink contains the excipients: shellac, iron oxide black, propylene glycol.

6.2. INCOMPATIBILITIES
Not applicable.

6.3. SHELF LIFE
The expiry date can be found on the packaging.

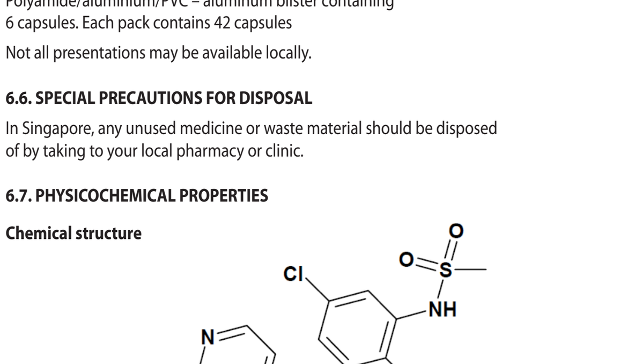
6.4. SPECIAL PRECAUTIONS FOR STORAGE
Store at or below 30°C.
Store in original container.

6.5. NATURE AND CONTENTS OF CONTAINER
Braftovi 50 mg capsules
Polyamide/aluminium/PVC – aluminum blister containing 4 capsules. Each pack contains 28 capsules
Braftovi 75 mg capsules
Polyamide/aluminium/PVC – aluminum blister containing 6 capsules. Each pack contains 42 capsules
Not all presentations may be available locally.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL
In Singapore, any unused medicine or waste material should be disposed of by taking to your local pharmacy or clinic.

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical Abstracts Service (CAS) registry number
1269440-17-6

Chemical name
Methyl *N*-{(1*S*)-2-[(4-{3-[5-chloro-2-fluoro-3-(methylsulfonyl)amino)phenyl]-1-(1-methylethyl)-1*H*-pyrazol-4-yl}-2-pyrimidinyl)amino]-1-methylethyl} carbamate

Encorafenib is a white to almost white powder with the molecular formula $C_{22}H_{27}ClFN_7O_4S$ and a molecular weight of 540.0.
It is slightly soluble in aqueous media at pH 1, very slightly soluble at pH 2 (0.01 to 0.1%), and insoluble at pH 3 and above.
Its dissociation constants (pKa) are 4.49 and 7.21.
Encorafenib is not hygroscopic.

7. FORENSIC CLASSIFICATION
Prescription only medicine.

8. NAME AND ADDRESS OF MANUFACTURER
Drug Product Manufacturer
Catalent Pharma Solutions LLC
14 Schoolhouse Road
Somerset
NEW JERSEY 08873
United States

9. PRODUCT OWNER
PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

10. DATE OF REVISION
February 2022

Pierre Fabre Médicament

Table 7: Treatment- emergent adverse events occurring very commonly (≥ 10%) in patients receiving encorafenib 300 mg in combination with cetuximab in the BEACON CRC study

	Encorafenib plus cetuximab N=216 (%)		Irinotecan plus cetuximab or FOLFIRI plus cetuximab N=193 (%)	
Grade	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Any event	212 (98.1)	124 (57.4)	190 (98.4)	124 (64.2)
Diarrhoea	83 (38.4)	6 (2.8)	94 (48.7)	20 (10.4)
Nausea	82 (38.0)	1 (0.5)	84 (43.5)	3 (1.6)
Fatigue	72 (33.3)	9 (4.2)	54 (28.0)	9 (4.7)
Decreased appetite	67 (31.0)	3 (1.4)	56 (29.0)	6 (3.1)
Dermatitis acneiform	65 (30.1)	1 (0.5)	77 (39.9)	5 (2.6)
Abdominal pain	60 (27.8)	7 (3.2)	54 (28.0)	10 (5.2)
Vomiting	59 (27.3)	3 (1.4)	61 (31.6)	6 (3.1)
Asthenia	52 (24.1)	8 (3.7)	53 (27.5)	10 (5.2)
Arthralgia	49 (22.7)	3 (1.4)	3 (1.6)	0 (0.0)
Headache	43 (19.9)	0 (0.0)	5 (2.6)	0 (0.0)
Anaemia	42 (19.4)	12 (5.6)	36 (18.7)	13 (6.7)
Pyrexia	40 (18.5)	3 (1.4)	28 (14.5)	1 (0.5)
Constipation	39 (18.1)	0 (0.0)	39 (20.2)	2 (1.0)
Melanocytic naevus	34 (15.7)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	33 (15.3)	1 (0.5)	4 (2.1)	0 (0.0)
Rash	32 (14.8)	0 (0.0)	28 (14.5)	3 (1.6)
Musculoskeletal pain	29 (13.4)	0 (0.0)	5 (2.6)	0 (0.0)
Back pain	28 (13.0)	3 (1.4)	27 (14.0)	2 (1.0)
Dyspnoea	28 (13.0)	2 (0.9)	20 (10.4)	6 (3.1)
Dry skin	28 (13.0)	0 (0.0)	16 (8.3)	1 (0.5)
Hypomagnesaemia	25 (11.6)	1 (0.5)	19 (9.8)	3 (1.6)
Pain in extremity	25 (11.6)	0 (0.0)	2 (1.0)	0 (0.0)
Weight decreased	24 (11.1)	1 (0.5)	12 (6.2)	0 (0.0)
Insomnia	24 (11.1)	0 (0.0)	13 (6.7)	0 (0.0)
Pruritus	24 (11.1)	0 (0.0)	10 (5.2)	0 (0.0)
Oedema peripheral	23 (10.6)	0 (0.0)	14 (7.3)	1 (0.5)
Abdominal pain upper	22 (10.2)	2 (0.9)	15 (7.8)	1 (0.5)
Alopecia	22 (10.2)	2 (0.9)	15 (7.8)	1 (0.5)

A patient is counted once within each preferred term.
Preferred terms are sorted in descending frequency in the 'Encorafenib+cetuximab' column.
MedDRA Version 21.0 has been used for the reporting of adverse events.

Table 9: Progression-free survival and confirmed overall response results (cut-off date: 19 May 2016, independent central review)

	Combo 450 Encorafenib and binimetinib N = 192	Enco 300 Encorafenib N = 194	Vem N = 191
Progression Free Survival			
Number of progressive disease (PD) 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) <0.001		
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 (ORR), 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; HR = hazard ratio; 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 without a target lesion who do not achieve CR or have PD).
[a] Hazard ratio based on a stratified Cox proportional hazard model
[b] Log-rank p-value (2 sided)

Figure 1: Kaplan-Meier plot of progression-free survival by independent central review (cut-off date: 19 May 2016)

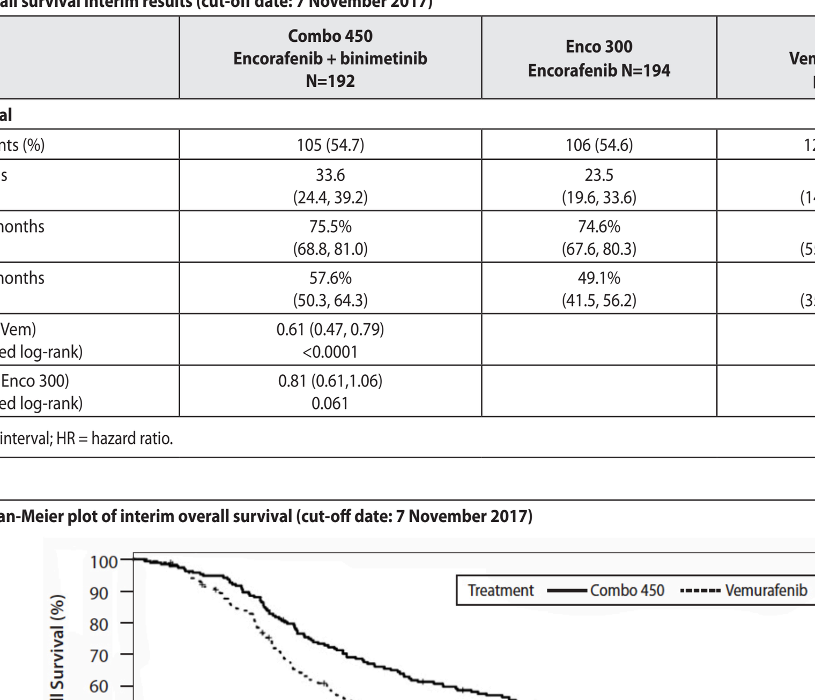


Table 10: Overall survival interim results (cut-off date: 7 November 2017)

	Combo 450 Encorafenib + binimetinib N=192	Enco 300 Encorafenib N=194	Vem Vemurafenib N=191
Overall Survival			
Number of events (%)	105 (54.7)	106 (54.6)	127 (66.5)
Median, months (95% CI)	33.6 (24.4, 39.2)	23.5 (19.6, 33.6)	16.9 (14.0, 24.5)
Survival at 12 months (95% CI)	75.5% (68.8, 81.0)	74.6% (67.6, 80.3)	63.1% (55.7, 69.6)
Survival at 24 months (95% CI)	57.6% (50.3, 64.3)	49.1% (41.5, 56.2)	43.2% (35.9, 50.2)
HR (95% CI) (vs Vem) p-value (stratified log-rank)	0.61 (0.47, 0.79) <0.0001		
HR (95% CI) (vs Enco 300) p-value (stratified log-rank)	0.81 (0.61,1.06) 0.061		

CI = confidence interval; HR = hazard ratio.

Figure 2: Kaplan-Meier plot of interim overall survival (cut-off date: 7 November 2017)

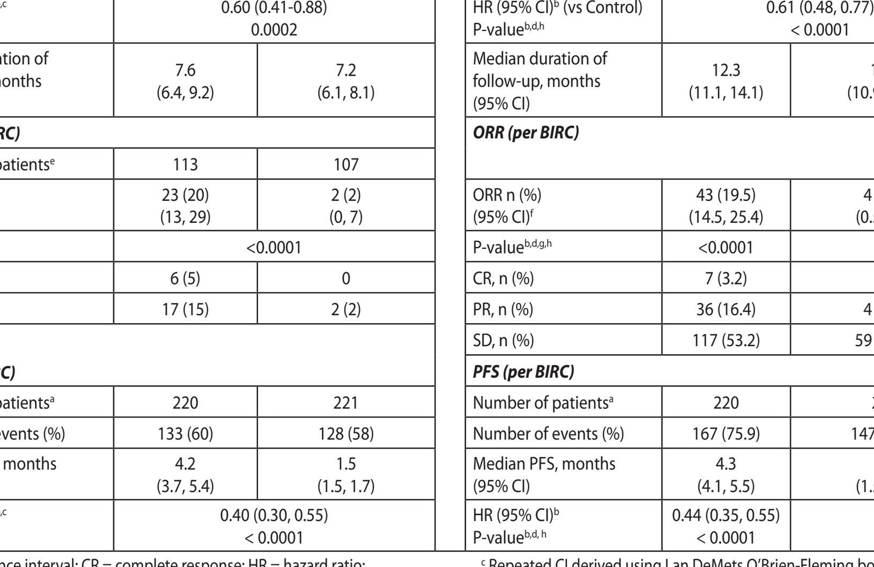


Table 11: Efficacy results from the BEACON CRC study (ARRAY-818-302), data cut- off date 11 February 2019

	Encorafenib plus cetuximab	Control (irinotecan or FOLFIRI plus cetuximab)
Overall Survival		
Number of patients[a]	220	221
Number of events (%)	93 (42)	114 (52)
Median, months (95% CI)	8.4 (7.5, 11.0)	5.4 (4.8, 6.6)
HR (95% CI)[b,c] p-value[b,c]	0.60 (0.41-0.88) 0.0002	
Median duration of follow-up, months (95% CI)	7.6 (6.4, 9.2)	7.2 (6.1, 8.1)
ORR (per BIRC)		
Number of patients[e]	113	107
ORR n (%) (95% CI)[f]	23 (20) (13, 29)	2 (2) (0, 7)
P-value[b,d,g]	<0.0001	
CR, n (%)	6 (5)	0
PR, n (%)	17 (15)	2 (2)
PFS (per BIRC)		
Number of patients[a]	220	221
Number of events (%)	133 (60)	128 (58)
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	Encorafenib plus cetuximab	Control (irinotecan or FOLFIRI plus cetuximab)
Overall Survival		
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)		
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)
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 = objective response rate; OS = overall survival; PR = partial response;
SD = Stable disease; BIRC = blinded independent central review
[a] Randomised phase 3 Full Analysis Set
[b] Hazard ratio of encorafenib plus cetuximab versus control arm, stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomisation
[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

Figure 3: Kaplan-Meier plot of OS in BEACON CRC (cut-off date: 11 February 2019)

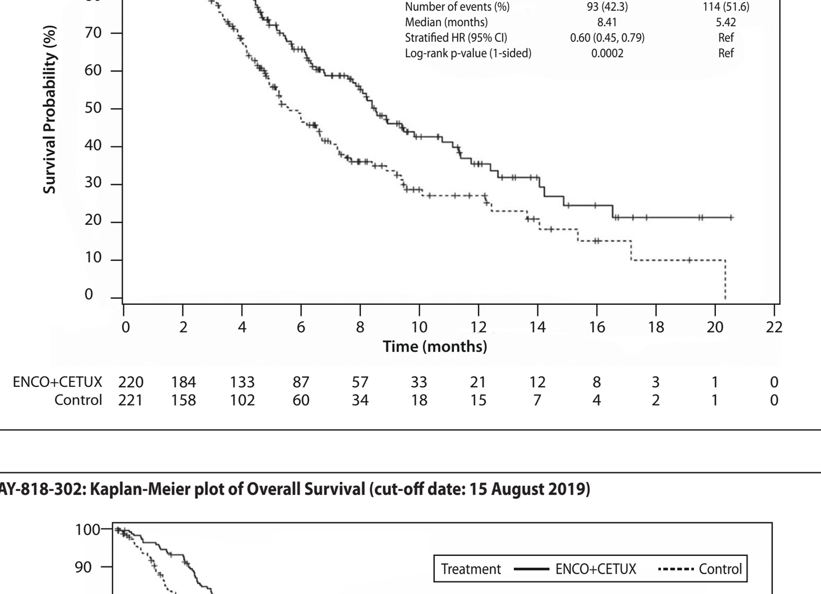


Figure 4: Study ARRAY-818-302: Kaplan-Meier plot of Overall Survival (cut-off date: 15 August 2019)