30 April 2020
EMA/CHMP/271532/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Braftovi	encorafenib

Procedure No. EMEA/H/C/xxxx/WS/1695

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADME	Absorption/Distribution/Metabolism/Excretion
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALT	Alanine Transaminase
ATP	Adenosine Tri-Phosphate
AUC	Area Under the Concentration Time Curve
BA	Bioavailability
BCRP	Breast Cancer Resistance Protein
BID	Twice Daily
BICR	Blinded Independent Review Committee
BLRM	Bayesian Logistic Regression Model
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase
BRAF	Serine/Threonine-Protein Kinase B-Raf
CA19-9	Carbohydrate Antigen 19-9
CEA	Carcinoembryonic Antigen
CDER	Center for Drug Evaluation and Research
CDK	Cyclin Dependent Kinase
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL/F	Total Clearance
Cmax	Maximum Observed Plasma Concentration
cMET	MET Proto-Oncogene, Receptor Tyrosine Kinase
CNS	Central Nervous System
the Triplet	Encorafenib 300 mg QD in combination with binimetinib 45 mg BID
Combo°450	Encorafenib 450 mg QD in combination with binimetinib 45 mg BID
CR	Complete Response
CSR	Clinical Study Report
CT	Computed Tomography
cuSCC	Cutaneous Squamous Cell Carcinoma
D	Day

DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DLT(s)	Dose Limiting Toxicity(ies)
DMC	Data Monitoring Committee
DOR	Duration of Response
EAIR	Exposure Adjusted Incidence Rate
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group-Performance Status
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
Enco 300	Encorafenib 300 mg
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	End of Treatment
EQ-5D-5L	EuroQoL-5D-5 Level
ERK	Extracellular Signal-Regulated Kinase
ESMO	European Society for Medical Oncology
EU	European Union
EWOC	Escalation With Overdose Control
FACIT	Functional Assessment of Chronic Illness
FACT-C	Functional Assessment of Cancer Therapy-Colorectal Cancer
FAS	Full Analysis Set
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
GCP	Good Clinical Practice
HR	Hazard Ratio
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND(s)	Investigational New Drug(s)
ITT	Intent to Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System (also described as IXRS in data listings)

JSLI	Japanese Safety Lead-in
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
LME	Linear Mixed-Effects
LVEF	Left Ventricular Ejection Fraction
MAA	Marketing Authorisation Application
Max	Maximum
MEB	Medicines Evaluation Board
MEK	Mitogen-Activated Protein Kinase Kinase
Min	Minimum
MPA	Medical Products Agency
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NE	Not Estimable
NGS	Next Generation Sequencing
NRAS	Neuroblastoma RAS Viral Oncogene Homolog
NS	Not Specified
ORR	Objective Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PDL-1	Programmed Death (Receptor) Ligand 1
pERK	Phosphorylated Extracellular Signal-Regulated Kinase
PFS	Progression-Free Survival
PGIC	patient global impression of change
P-gp	P-glycoprotein
PI3K	Phosphoinositide 3-Kinase
PK(s)	Pharmacokinetic(s)
PopPK	Population PK
PPE	Palmar Plantar Erythrodysaesthesia
PPS	Per-Protocol Set

PR	Partial Response
PRO	Patient-Reported Outcome
PS	Performance Status
QD	Once Daily
QoL	Quality of Life
RAF	Serine/Threonine-Protein Kinase
RAS	Rat Sarcoma Viral Oncogene Homologue
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended Phase 2 Dose
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SC	Steering Committee
SCE	Summary of Clinical Efficacy
SD	Standard Deviation
SLI	Safety Lead-in
Tmax	Time to Maximum Observed Plasma Concentration
TSST	Time to Second Subsequent Therapy
TTR	Time to Response
ULN	Upper Limit of Normal
US	United States (of America)
vs.	versus
Vz/F	Volume of Distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pierre Fabre Medicament submitted to the European Medicines Agency on 14 October 2019 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include encorafenib in combination with binimetinib and cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy, as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 1.1 has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.1.

The worksharing procedure requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

The MAH in the course of the assessment withdrew Mektovi (binimetinib) from the applied indication. Therefore, the extension of indication only concerns the product Braftovi (encorafenib).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0049/2019 for encorafenib (Braftovi) and P/0037/2019 for binimetinib (Mektovi) on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the WSA did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

WSA request for additional market protection

The WSA requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The WSA sought Scientific Advice on the clinical development at the CHMP on 22 October 2015, 25 February 2016 and 26 May 2016.

The applicant Emas Pharma Ltd has applied for CHMP scientific advices in relation to the substances binimetinib and encorafenib in the intended indication BRAF mutant CRC as early as 2015. The applicant of this WS (Pierre Fabre Medicament) has also requested follow up scientific advices starting as early as 2018. These advices concerned in principle planning of the pivotal trial of this WS (BEACON) at different stages of the clinical development of the substances/products (namely binimetinib, encorafenib, cetuximab).

1.2. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure:

Janet Koenig

Timetable	Actual dates
Submission date:	14 October 2019
Start of procedure:	2 November 2019
CHMP Rapporteur's preliminary assessment report circulated on:	23 December 2019
PRAC Rapporteur's preliminary assessment report circulated on:	3 January 2020
Updated PRAC Rapporteur Assessment Report	9 January 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	16 January 2020
CHMP members comments	
CHMP Rapporteur's updated assessment report circulated on:	24 January 2020
Request for supplementary information and extension of timetable adopted by the CHMP on:	30 January 2020
WSA's responses submitted to the CHMP on:	26 March 2020
PRAC Rapporteur's preliminary assessment report on the WSA's responses circulated on:	7 April 2020
PRAC Rapporteur's updated assessment report on the WSA's responses circulated on:	9 April 2020
CHMP Rapporteur's preliminary assessment report on the WSA's responses circulated on:	16 April 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	17 April 2020
CHMP Rapporteur's updated assessment report on the WSA's responses circulated on:	24 April 2020
CHMP opinion:	30 April 2020
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Braftovi in comparison with existing therapies	30 April 2020

2. Scientific discussion

2.1.1. Problem statement

Disease or condition

The intended indication is: encorafenib in combination with binimetinib and cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.

Epidemiology

Globally, CRC is the fourth most commonly diagnosed cancer worldwide, with about 1.3 million new cases and over 550,000 deaths (GLOBOCAN, 2018). It is also the second most common type of cancer and the second deadliest cancer in Europe with an estimated 500,000 new cases diagnosed in 2018 and around 242,000 deaths (Ferlay, 2018).

Despite major treatment advances over the past decades, metastatic colorectal cancer (mCRC) remains a serious, life-threatening condition, with significant years of potential life lost and substantial losses

in productivity due to high incidence rates (Bradley, 2011).

Biologic features

At diagnosis, 8 -12% of metastatic colorectal cancers harbour BRAF mutations (Troiani, 2016) with a broad range of estimates ranging from as low as 5% to as high as 21%. These mutations are usually (> 95%) at the V600E codon and essentially mutually exclusive with RAS mutations (Barras, 2017; Bylsma, 2018; Clarke, 2015; Davies, 2002; De Roock, 2010; Sorbye, 2015). BRAF V600 mutations lead to constitutive activation of BRAF kinase and sustained RAS/RAF/MEK/ERK pathway signalling, resulting in increased cell proliferation and survival (Corcoran, 2012).

In a recent metanalysis, BRAF mutant CRC tumours that are microsatellite -instability high (MSI-H) have been shown to have a better prognosis than those with a proficient DNA mismatch repair system in all stages of disease except for mCRC, in which MSI-H showed poor effects on OS in BRAF wildtype patients but not in BRAF-mutant patients (Yang, 2018). The incidence of MSI in CRC varies according to the stage of the disease, with a low incidence in the metastatic setting (4%-5%) (Battaglin, 2018), which suggests that the majority of BRAF mutant- mCRC tumours are microsatellite stable (MSS).

Clinical presentation and diagnosis

Approximately 25% of newly diagnosed CRC patients present with metastases and 50% of patients eventually develop metastatic disease (Van Cutsem, 2014).
Overall survival (OS) for patients with mCRC has now reached durations of 30 months or longer in the most recent generation of randomised clinical trials (Vogel, 2018; Venook, 2014; Loupakis, 2014, Heinemann, 2013); however, the 5-year survival for the 22% of patients who are initially diagnosed with metastatic disease is 14% (SEER, 2018). The key contributors for longer survival are the increase in resection rates of metastases at diagnosis, emerging treatment options in the therapeutic sequence but also improvement of first-line therapies.
BRAF V600-mutant CRC is considered a distinct subtype of CRC that has unique clinical characteristics

and is associated with a worse prognosis, with a negative impact on both overall survival (OS) and progression-free survival (PFS) (Cremolini, 2015; Loupakis, 2014; Ursem, 2018). In a cohort of 524 patients, OS for patients with BRAF-mutant colorectal cancer was 10.4 months compared with 34.7 months for BRAF wild-type patients. In a multivariate analysis, the hazard ratio (HR) for survival was 10.662 ($p < 0.001$) (Tran, 2011); the situation is similar in patients with failure of prior systemic therapy (De Roock, 2010; Peeters, 2014b), emphasizing the need to develop novel therapeutic approaches.

Management

BRAF genetic testing is currently recommended by the European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and Japanese Society for Medical Oncology (JESMO) for all patients with CRC tumours as a prognostic indicator (Van Cutsem, 2016; NCCN V2, 2019; Yamazaki, 2018).The standard first-line therapy for metastatic disease consists of a combination of chemotherapy (based on fluoropyrimidine/leucovorin (5-FU/LV) or capecitabine with irinotecan or oxaliplatin, or in combination with both) with targeted agents (monoclonal antibodies targeting the vascular endothelial growth factor (VEGF) – bevacizumab – and the epidermal growth factor receptor (EGFR) – panitumumab and cetuximab) (Vogel, 2018).

Currently, there are no agents specifically indicated for the treatment of patients with BRAF V600Emutant mCRC and all therapies used in this setting have never been tested in dedicated phase 3 studies.

Since BRAF and KRAS mutations are almost always mutually exclusive (De Roock, 2010; Zheng, 2019), patients with BRAF V600E-mutant mCRC have typically been treated with standard of-care regimens for KRAS wild-type (KRASwt) mCRC in the first line setting i.e. a combination of chemotherapy (based on fluoropyrimidine/leucovorin (5-FU/LV) or capecitabine with or without irinotecan, oxaliplatin, or in combination with both) with targeted agents (monoclonal antibodies targeting the vascular endothelial growth factor (VEGF), mostly bevacizumab or the epidermal growth factor receptor (EGFR), i.e. panitumumab and cetuximab) (Vogel, 2018).

Recommended second-line options depend on the first-line treatment regimen. Common second-line regimens include infusional FOLFIRI or irinotecan with or without cetuximab or panitumumab. The combination of irinotecan/cetuximab is one of the options recommended by the ESMO and NCCN for patients who have previously received irinotecan- or oxaliplatin-based combination regimens, and its use in this setting is consistent with current labelling of cetuximab (Van Cutsem, 2016; NCCN V2, 2019). FOLFIRI has also been used in the control arm of several recent Phase 3 studies in the second-line setting in patients with mCRC unselected for specific mutations (Peeters, 2014b; Tabernero, 2015).

The median OS for patients with BRAF V600E mutant mCRC, who have failed one prior line of treatment is 10 to 14 months and for patients who have failed 2 prior lines of treatment it is 6 to 9 months (Seymour, 2013; Peeters, 2010, Grothey, 2013; Li, 2015; Van Cutsem, 2019; Longo-Muñoz, 2017). A retrospective study reported similar PFS of 5 to 6 months irrespective of whether oxaliplatin- or irinotecan-based chemotherapy was administered in the first-line setting in patients with BRAF-mutant mCRC (Morris, 2014). The more intensive regimen of infusional 5-FU/FA/oxaliplatin/irinotecan (FOLFOXIRI) + bevacizumab has been shown to be both more active and more toxic than typical irinotecan- or oxaliplatin-based regimens (Cremolini, 2015; Loupakis, 2014), which is in line with the results of studies of irinotecan or FOLFIRI, with or without anti-EGFR (Seymour, 2013; Peeters, 2010).

The EMA approved the single -agents regorafenib and trifluridine + tipiracil as oral salvage therapies in patients with chemorefractory disease, who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan- based chemotherapy, and antiVEGF- biological therapy and, if patients are RAS wild type, an antiEGFR- therapy, irrespective of KRAS or BRAF mutational status. Current ESMO and NCCN guidelines include these agents as an additional line of therapy in patients with mCRC who have

progressed through standard therapies (Van Cutsem, 2016; NCCN V2, 2019). However, they are minimally active with OS ranging from 6.4 to 8.8 months, a PFS of 1.9 to 3.2 months and an ORR of 1% to 6 % in BRAF wild type mCRC (Grothey, 2013; Mayer, 2015).

The use of single-agent BRAF inhibitors or of a combination of BRAF and MEK inhibitors without the addition of an EGFR inhibitor has shown minimal clinical activity in BRAF V600E-mutant mCRC (Hyman, 2015; Kopetz, 2015), potentially due to feedback reactivation of EGFR (Corcoran, 2012; Prahallad,2012).

2.1.2. About the product

Binimetinib (ATC code L01XE41; product name Mektovi) and encorafenib (ATC code L01XE46; product name Braftovi) are two protein kinase inhibitors labelled to be specifically a MEK and a BRAF inhibitor. Both products (each containing single active substances) received their first Marketing Authorisation (MA) within the EU in the indication(s) 'for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation' concomitantly on 20/09/2018. The pivotal trial for the melanoma application is known as the COLOMBUS study.

Of note in this overall context of tumours diagnosed specifically for mutations is that prior to the first EU MA for the product Mektovi, the MAH had applied for an (initial) MA for binimetinib as monotherapy in patients with NRAS mutant melanoma. This first application has been withdrawn prior to granting a MA to the product(s) Mektovi and Braftovi (in a, by mutation, different indication). The pivotal trial of this withdrawn application is known as the NEMO study.

The current application, a work sharing procedure initially applied for the 2 products (Mektovi/Braftovi) of the applicant/MAH, concerns 3 substances (binimetinib, cetuximab [monoclonal Ab, ATC L01XC06], encorafenib) to be administered as a free combination, orally and intravenously, in adult patients with mCRC with a BRAF V600E mutation.

The MAH in the course of the assessment withdrew the binimitenib portion (Mektovi) of the indication, therefore the extension of indication only affects encorafenib (Braftovi).

The applicant of this procedure had searched regulatory advice in the past for planning the pivotal trial of this (WSP) application, known now as the BEACON study (ARRAY-818-302) (a multicenter, randomized, open-label, 3-arm phase 3 study of encorafenib + cetuximab plus or minus binimetinib vs. irinotecan/cetuximab or infusional 5-fluorouracil (5-fu)/folinic acid (FA)/irinotecan (FOLFIRI)/cetuximab with a safety lead-in of encorafenib + binimetinib + cetuximab in patients with BRAF V600E-mutant metastatic colorectal cancer.

This is/are, in the terminology of BEACON, the 'Doublet' (and control) arm actually investigated in a randomized way. To develop rather, a clinical trial with three arms, with the primary objective to show that 'Triplet' is superior to Control (standard of care, investigators/centres chosen standard of care), is a more recent development in the clinical development program of the applicant (of this WSP).

On January 21, 2020 the document "StudyARRAY-818-302 (BEACON) Summary of updated results (August 2019 Data Cutoff); Date: January 2020" was received.

Encorafenib is indicated:

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

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

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

Melanoma
The recommended dose of encorafenib is 450 mg (six 75 mg capsules) once daily, when used in combination with binimetinib.

Colorectal cancer
The recommended dose of encorafenib is 300 mg (four 75 mg capsules) once daily, when used in combination with cetuximab.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

In terms of CHMP scientific advice and the development of a combination, therapy in BRAF mutated CRC, the dossier of this procedure contains first CHMP advices as early as of 2015 EMEA/H/SA/3177/1/2015/SME/II, EMEA/H/SA/3177/2/2016/SME/II, EMEA/H/SA/3177/2/FU/1/2016/SME/II and EMEA/H/SA/3177/1/FU/1/2018/II. These advices, over their time course, however, concerned initially the planning of a confirmatory trial concerning the substances (as of different substance classes) encorafenib and cetuximab only.

2.2. Non-clinical aspects

2.2.1. Introduction

In order to support the new indication, previous data from *in vitro* and *in vivo* studies with encorafenib in combination with cetuximab and encorafenib as single agent have been re-analysed with the focus of the doublet combination. However, the initially provided data are still valid. New non-clinical studies have been performed to underline the new indication.

Encorafenib is a potent and highly selective ATP-competitive small molecule RAF kinase inhibitor Encorafenib suppresses the RAF/MEK/ERK pathway in tumour cells expressing several mutated forms of BRAF kinase (V600E, D and K). Specifically, encorafenib inhibits in vitro and in vivo BRAFV600E, D and K mutant melanoma cell growth. Encorafenib does not inhibit RAF/MEK/ERK signalling in cells expressing wild-type BRAF.

Binimetinib is an ATP-uncompetitive, reversible inhibitor of the kinase activity of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. In cell free system, binimetinib inhibits MEK1 and MEK2 with the half maximal inhibitory concentration (IC50)'s in the 12-46 nM. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. In melanoma and other cancers, this pathway is often activated by mutated forms of BRAF which activates MEK. Binimetinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity. Binimetinib inhibits growth of BRAF V600 mutant melanoma cell lines and demonstrates anti-tumour effects in BRAF V600 mutant melanoma animal models.

The combination of binimetinib and encorafenib both inhibit the MAPK pathway resulting in higher anti-tumour activity.

Cetuximab is a chimeric monoclonal Immunoglobulin G1 (IgG1) antibody directed against the Epidermal Growth Factor Receptor (EGFR). EGFR signaling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration and cellular invasion/metastasis. Cetuximab binds to the EGFR with an affinity higher than that of endogenous ligands. Cetuximab blocks binding of endogenous EGFR ligands resulting in inhibition of the function of the receptor and induces the internalization of EGFR,

which can lead to down-regulation of the receptor. Cetuximab also targets cytotoxic immune effector cells towards EGFR-expressing tumour cells (antibody dependent cell-mediated cytotoxicity, ADCC).

Non-clinical documentation submitted with this application concerns studies on primary pharmacology in order to evaluate the magnitude of activity of binimetinib when combined with encorafenib and with or without cetuximab. No PK, ADME or toxicology studies have been performed with the combination.

2.2.2. Pharmacology

Primary pharmacodynamic studies

MEKTOVI (Binimetinib, MEK162)

Effect of ARRY-438162 on the growth of subcutaneous Colo-205 xenografts in female nude mice Study Number 060304-789

The purpose of this non-GLP study was to evaluate the MEK inhibitor ARRY-438162 (binimetinib) for its ability to inhibit the growth of Colo-205 (human colon carcinoma) subcutaneous xenografts in female nude mice. Colo-205 cells harbor the BRAF V600E mutation and the p53 Y103 L111 > L in frame deletion, ARRY-438162 was dosed PO, QD at 3, 10 and 30 mg/kg for 19 days.

Overall, ARRY-438162 was well tolerated at all three doses over the entire course of the experiment, with no significant effect on weight or any other outward signs of morbidity. Treatment with ARRY-438162 resulted in dose dependent inhibition of the growth of subcutaneous Colo-205 tumors. On day 12, the time of maximum tumor growth inhibition in the 30 mg/kg group, 7/7 mice had tumor regressions of greater than 50%. On day 19, the average tumor growth inhibition was 33% at 3 mg/kg, 59% at 10 mg/kg and 85% at 30 mg/kg. There were three partial responses (>50% tumor growth inhibition) and one complete response on day 19 at 30 mg/kg.

Exploratory (non-GLP) study evaluating the effect of the triple combination MEK162/LGX818/cetuximab on growth on CRC563 human CRC (BRAF V600E) patient-derived xenografts in NCr NU/Nu mice (Study 060304-1678)

This study examined the growth characteristics and tolerability following treatment with a MEK inhibitor (MEK162), a RAF inhibitor (LGX818) and an anti-EGFR antibody (cetuximab) as single agents and in combination in immunocompromised mice with CRC562 (BRAF V600E) tumor fragments.

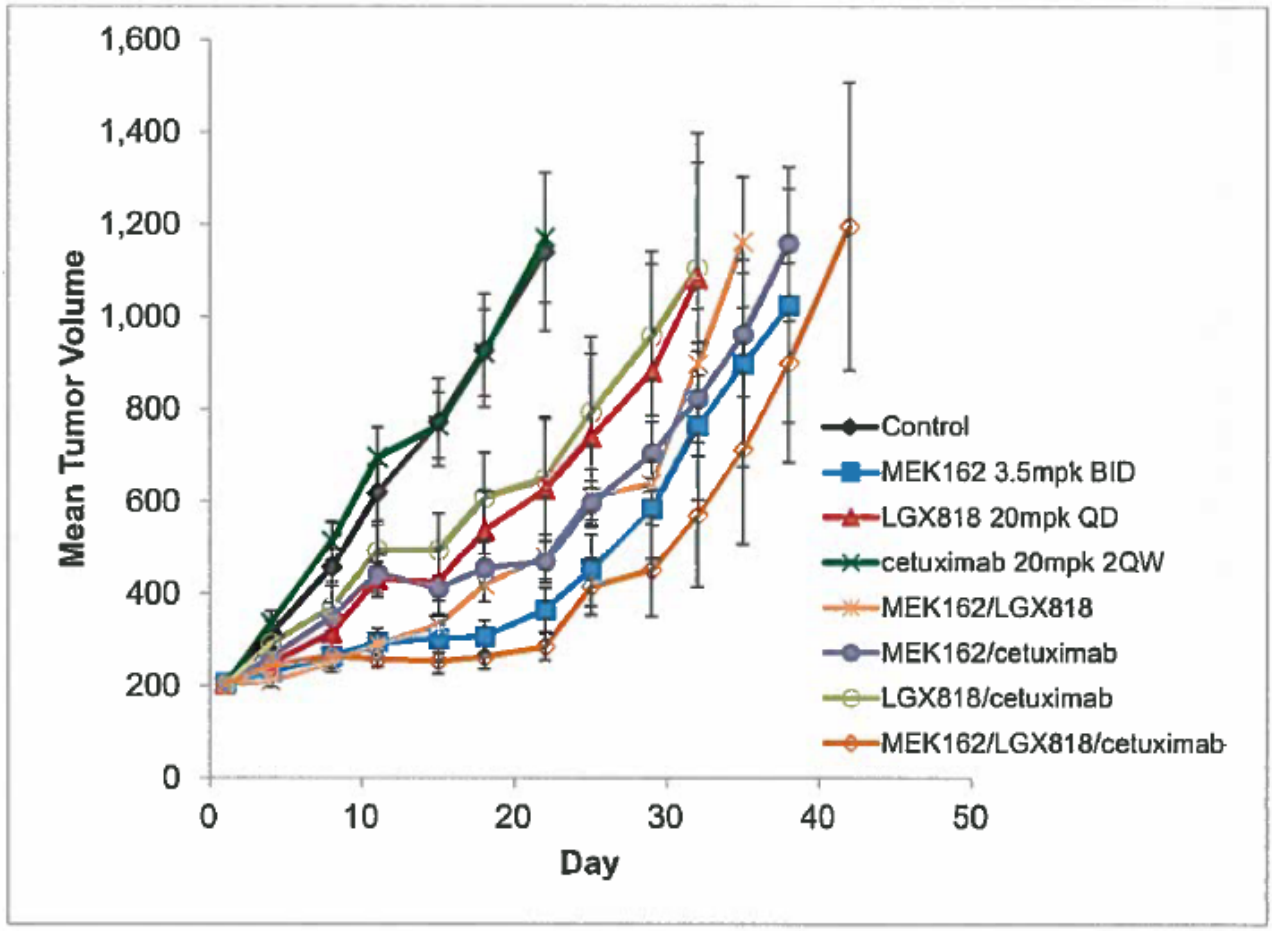
Animals were dosed with vehicle, MEK at 3.5 mg/kg twice daily by oral gavage, 20 mg/kg LGX818 once daily by oral gavage or 20 mg/kg twice weekly by intraperitoneal injection as single agent or in combination for 21 days. Cetuximab was administered intraperitoneal at a dose of 20 mg/kg.

All treatments were tolerated with a maximum body weight loss of about 19% in the vehicle control group. One animal in the LGX818 single agent group was sacrificed after the dosing period due to body weight loss which is thought to be the result of the tumor itself. The cetuximab, LGX818 and LGX818/cetuximab group had less than 50% tumor growth inhibition (%TGI) with 0%, 45% and 43%, respectively. The MEK162, MEK162/cetuximab and the MEK162/LGX818 groups had similar %TGI with 68%, 59% and 58%, respectively. The triple combination of MEK162/LGX818/cetuximab was the most efficacious with 75% tumor growth inhibition.

Table 1: Tumor Growth and Tolerability of encorafenib, binimetinib and cetuximab as single dose and in combination

Group #	Test Article	%R	Growth Delay (days)	%TGI	%netTGI	CR/PR/SD	PD	%Body Weight Loss
1	Vehicle	-	-	-	-	0/0/0	8	19.7%
2	MEK162 3.5 mg/kg	-	18	68%	83%	0/1/2	5	11.3%
3	LGX818 20 mg/kg	-	13	45%	55%	0/1/0	7	5.5%
4	cetuximab 20 mg/kg	-	0	0%	0%	0/0/0	8	9.7%
5	MEK162 3.5 mg/kg/ LGX818 20 mg/kg	-	15	58%	70%	0/0/0	8	10.6%
6	MEK162 3.5 mg/kg/ cetuximab 20 mg/kg	-	18	59%	72%	0/0/1	7	8.9%
7	LGX818 20 mg/kg/ cetuximab 20 mg/kg	-	12	43%	52%	0/0/0	8	2.9%
8	MEK162 3.5 mg/kg/ LGX818 20 mg/kg/ cetuximab 20 mg/kg	-	20	75%	91%	0/0/5	3	3.3%

Fig. 1: Anti-Tumor Activity of MEK162/LGX818/cetuximab in CRC563 BRAFV600E Human Colon Tumor Xenografts



Exploratory (non-GLP) study evaluating the anti-tumor effect of the triple combination MEK162/LGX818/cetuximab on growth of CRC769 human CRC (BRAF600E) patient-derived xenografts in NCr NU/Nu mice (Study 060304-1681)

The purpose of this study was to examine the growth characteristics and tolerability following treatment with a MEK inhibitor (MEK162), a RAF inhibitor (LGX818) and an anti-EGFR antibody (cetuximab) as single agents and in combination in immunocompromised mice with CRC769 (BRAFV600E) tumor fragments, a human colon PDX.

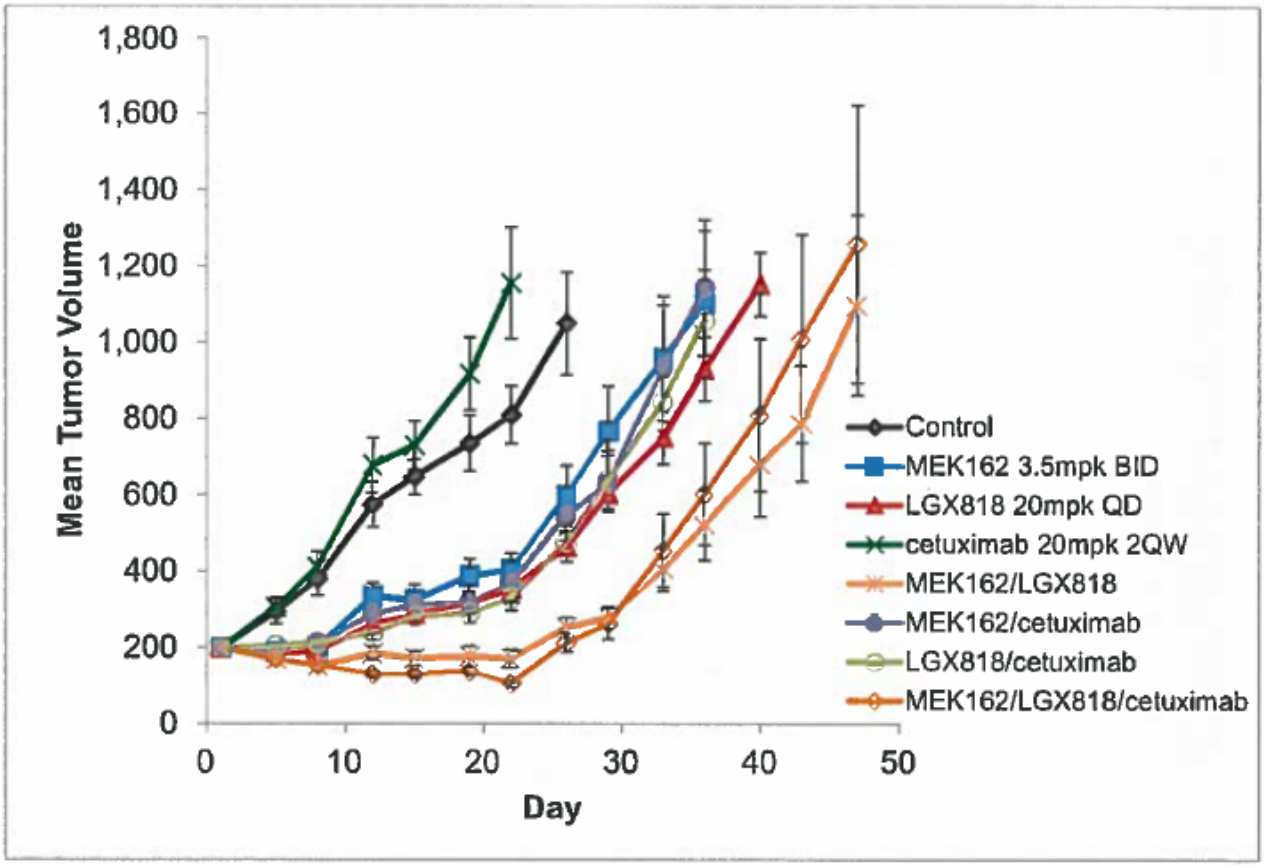
Animals were dosed with vehicle, MEK at 3.5 mg/kg twice daily by oral gavage, 20 mg/kg LGX818 once daily by oral gavage or 20 mg/kg twice weekly by intraperitoneal injection as single agent or in combination for 21 days. Cetuximab was administered twice weekly for 3 weeks intraperitoneal at a dose of 20 mg/kg on days 1, 5, 8, 12, 15 and 18.

All treatments were tolerated with a maximum body weight loss of about 8%. One animal was found dead in the LGX818/cetuximab group; but it is thought not to be treatment related but possibly due to body weight loss as an adverse event of the tumor itself. Cetuximab administered as a single agent was not effective. The cetuximab, MEK162 and MEK162/cetuximab groups had less than 50% tumor growth inhibition (%TGI) with 0%, 43% and 55%, respectively. The LGX818 and LGX818/cetuximab groups had similar %TGI with 56% and 55%, respectively. The most efficacious groups were MEK162/LGX818 (75% TGI, 24% regression) and the triple combination of MEK162/LGX818/cetuximab (80% TGI, 46% regression).

Table 2: Tumor Growth and Tolerability of encorafenib, binimetinib and cetuximab as single dose and in combination

Group #	Test Article	%R	Growth Delay (days)	%TGI	%netTGI	CR/PR/SD	PD	%Body Weight Loss
1	Vehicle	-	-	-	-	0/0/0	8	8.1%
2	MEK162 3.5 mg/kg	4%	8	43%	53%	0/0/1	7	8.1%
3	LGX818 20 mg/kg	6%	11	56%	69%	0/0/2	6	3.8%
4	cetuximab 20 mg/kg	0%	0	0%	0%	0/0/0	8	5.5%
5	MEK162 3.5 mg/kg/ LGX818 20 mg/kg	24%	20	76%	93%	0/1/7	0	9.7%
6	MEK162 3.5 mg/kg/ cetuximab 20 mg/kg	5%	8	48%	59%	0/0/3	5	7.2%
7	LGX818 20 mg/kg/ cetuximab 20 mg/kg	0%	9	56%	67%	0/0/4	4	5.4%
8	MEK162 3.5 mg/kg/ LGX818 20 mg/kg/ cetuximab 20 mg/kg	46%	17	80%	98%	0/3/5	0	6.2%

Fig. 2: Anti-Tumor Activity of MEK162/LGX818/cetuximab in CRC769 BRAFV600E Human Colon Tumor Xenografts



Anti-tumor effects of triple combination of LGX818/MEK162/cetuximab in HT-29 CRC model (Study RD-2013-50350)

This study evaluated the effects of LGX818, MEK162 and Cetuximab as single agents and in combinations in the BRAF V600E mutant HT-29 colorectal cancer (CRC) xenograft tumor model in mice.

Animals were dosed with vehicle, MEK at 3.5 mg/kg twice daily by oral gavage, 20 mg/kg LGX818 once daily by oral gavage or 20 mg/kg twice weekly by intraperitoneal injection as single agent or in combination for 21 days. Cetuximab was administered twice weekly for 3 weeks intraperitoneal at a dose of 20 mg/kg. After the last dose of treatment tumors were monitored for three more weeks.

All treatments were tolerated with maximum body weight loss as -7.7%. Cetuximab administered as a single agent was not effective. LGX818 at 20 mg/kg, MEK162 at 3.5 mg/kg and Cetuximab at 20 mg/kg produced statistically non-significant anti-tumor effects with tumor volume change (T/C) of 42%, 28%, and 95% respectively. LGX818 in combination with MEK162 resulted in T/C 22% ($p>0.05$ vs vehicle treated group); LGX818 in combination with Cetuximab resulted in T/C 6% ($p<0.05$ vs vehicle or Cetuximab treated groups); MEK162 in combination with Cetuximab resulted in T/C 5% ($p<0.05$ vs vehicle or Cetuximab treated groups). The triple combination of LGX818 + MEK162 + Cetuximab led to tumor regression with T/T0 -14%. The triple combination treatment is statistically significant ($p<0.05$), when compared with vehicle, LGX818 or Cetuximab monotherapy. However, it not statistically significant when compared with MEK162 monotherapy, LGX818 + MEK162 or MEK162 + Cetuximab treated groups (see table 3).

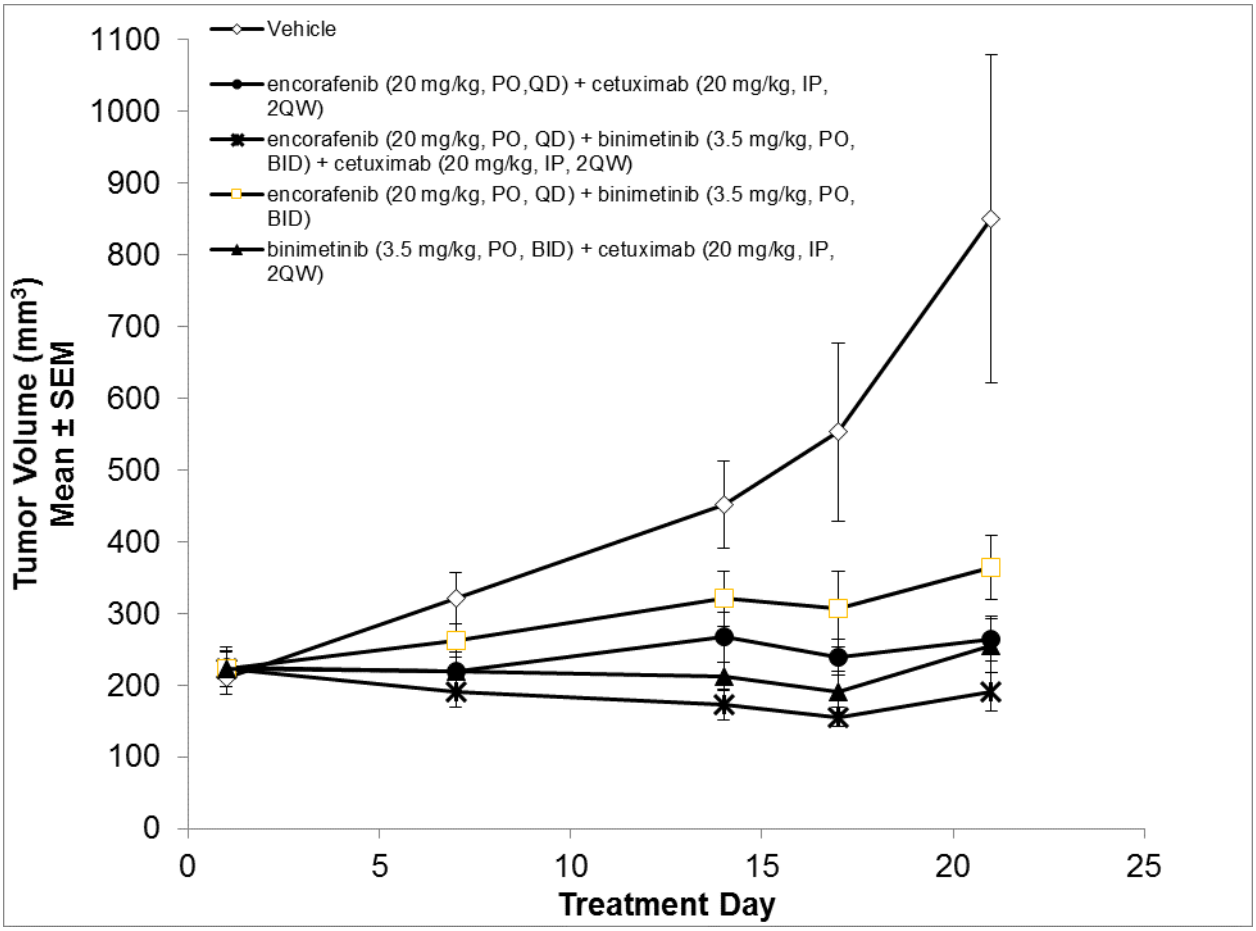
After termination of treatment, tumors resumed growth in all the treatment groups, which suggests that continuous treatment is necessary to achieve sustained antitumor efficacy.

Table 3: Mean anti-tumor effect and body weight change summary on the last day of treatment of encorafenib, binimetinib or cetuximab as single dose and in combination

Groups	Treatment	Dose & Schedule	Tumor Response (day 43)		Host Response (day 43)	
			T/C (%)	Regression (%)	% Change of BW	Survival
1	Vehicle IgG control	10 ml/kg po bid 20 mg/kg ip 2qw	100	-	-0.4 ± 0.8	8/9
2	Cetuximab	20 mg/kg ip 2qw	95	-	2.3 ± 1.5	9/9
3	LGX818	20 mg/kg po qd	42	-	0.6 ± 1.2	9/9
4	MEK162	3.5 mg/kg po bid	28	-	-0.5 ± 1.3	9/9
5	LGX818 MEK162	20 mg/kg po qd 3.5 mg/kg po bid	22	-	0.8 ± 1.2	9/9
6	LGX818 Cetuximab	20 mg/kg po qd 20 mg/kg ip 2qw	6*	-	3.1 ± 1.1	8/9
7	MEK162 Cetuximab	3.5 mg/kg po bid 20 mg/kg ip 2qw	5*	-	-0.2 ± 2.1	9/9
8	LGX818 MEK162 Cetuximab	20 mg/kg po qd 3.5 mg/kg po bid 20 mg/kg ip 2qw	-	-14**	-1.1 ± 1.5	9/9

*$p<0.05$ compared to Vehicle and Cetuxiamb treated groups by One way ANOVA post hoc Dunn's test.
**$p<0.05$ compared to Vehicle, Cetuximab and LGX818 treated groups by One way ANOVA post hoc Dunn's test.

Fig. 3: Tumor growth curve in HT29 xenograft model following 21 days of LGX818, MEK162, and cetuximab as single agents or in combinations



It was clarified that not all animals reached a tumor volume of approx. 220 mm^3 that was considered a requirement for the study. Therefore, only a reduced number of animals were used (9 instead of 10).

BRAFTOVI (Encorafenib)

Dose and Schedule Dependence of LGX818-NX Activity and Response to in the COLO 205 Human Colorectal Adenocarcinoma Nude Mouse Xenograft Model (Study Colo205-e293) (updated)

One purpose of this study was to determine the dose and schedule dependence of LGX818-NX activity in the subcutaneous COLO 205 human colorectal adenocarcinoma nude mouse xenograft model.

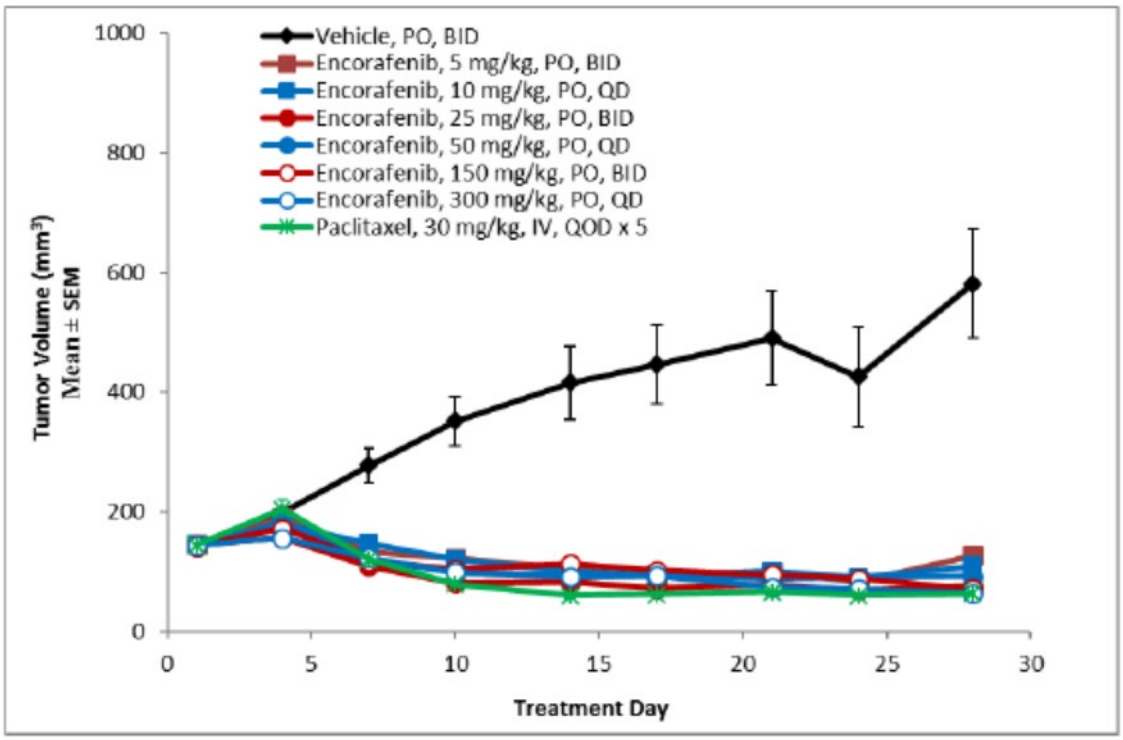
LGX818-NX was administered orally for four weeks at three dose intensities: 5, 25, and 150 mg/kg twice daily (bid x 28) and 10, 50, and 300 mg/kg once daily (qd x28). Control mice received the LGX818-NX vehicle, and a reference group received a standard preclinical paclitaxel regimen (30 mg/kg, i.v. once daily on alternate days for five days (pod x 5)).

Table 4: Efficacy of Single Agent Encorafenib in Colo205 Human BRAF-mutant CRC Xenograft Model in Nude Mice

Treatment	Dose (mg/kg)	Regimen	Tumour Responses				
			Mean T/C or T/T_0 (%)	Regression			Mean Δ tumour volume (mm^3)
				PR	CR	TFS	
Vehicle	0	PO, BID x 28d	100	0	0	0	438
Encorafenib	5	PO, BID x 28d	-12	2	0	0	-18
Encorafenib	10	PO, QD x 28d	-25	1	0	0	-36
Encorafenib	25	PO, BID x 28d	-48	3	0	0	-69
Encorafenib	50	PO, QD x 28d	-35	3	2	2	-50
Encorafenib	150	PO, BID x 28d	-50	1	0	0	-71
Encorafenib	300	PO, QD x 28d	-56	3	1	1	-80
Paclitaxel	30	IV, QOD x 5	-56	8	0	0	-81

T/C = Mean tumour volume in treated group /mean tumour volume in control group
T/T_0 = Mean tumour volume in treated group at Day 28/ Mean tumour volume in treated group at Day 1; negative values

Figure 4: Effects of Single Agent Encorafenib on Tumour Growth in Colo205 Human BRAF-mutant CRC Xenograft Model in Nude Mice



Twice daily LGX818-NX at 5, 25, and 150 mg/kg produced –12%, –48%, and –50% T/T0 and extended median survival by 51%, 118% and 76%, respectively. Once daily 10, 50, and 300 mg/kg doses produced –25%, –35%, and –56% T/T0 and extended median survival by 58%, 80%, and 121%, respectively. At each dose intensity, there were no significant advantages to BID versus QD dosing (Kruskal- Wallis analysis and post hoc Dunn's multiple comparison test). Enhanced anti-tumour activity

was seen at the 50 mg/kg/day dose level compared to the 10 mg/kg/day dose level, but there was no consistent improvement at 300 mg/kg/day. Encorafenib was well tolerated at all dose levels and schedules with no significant body weight loss noted; a transient, 4.3%, decrease in body weight was seen at the 300 mg/kg/day dose level on Day 7. No other signs of toxicity or mortality were observed.

Interactions of and with LGX818-NX in the HT-29 Human Colorectal Adenocarcinoma Nude Mouse Xenograft Model (Study HT29-e375) (Updated)

The study assessed the interactions of LGX818-NX with the HCl salt of a pan-PI3K inhibitor AA (LR27-AA) in the HT-29 human colorectal adenocarcinoma nude mouse xenograft model.

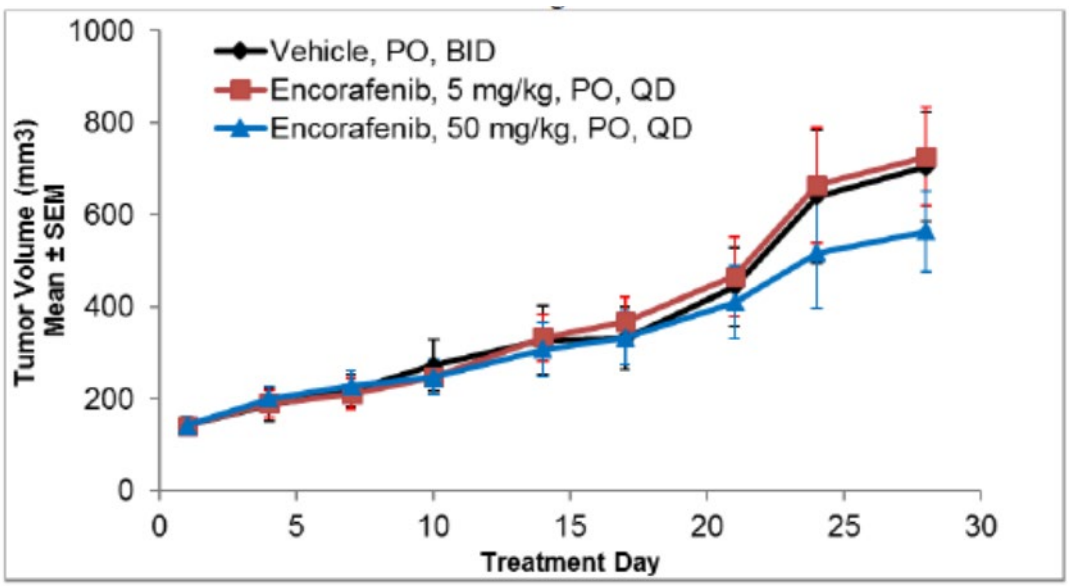
LGX818-NX was tested at two dose levels (5 and 50 mg/kg), and the PI3K inhibitor was tested at one dose level (32.7 mg/kg; equivalent to 30 mg/kg free base), on a daily oral treatment schedule for 28 days. Agents were tested individually and in four dual therapies that delivered the PI3K inhibitor within 1 h after LGX818-NX. Control mice received the vehicles for LGX818-NX (Vehicle 1; 0.5% carboxymethyl cellulose : 0.5% Tween 80 : 99% deionized water) and the PI3K inhibitor AA (Vehicle 2; 10% N-methylpyrrolidone : 90% polyethylene glycol 300). Paclitaxel as reference was omitted because the tumor engraftment rate was lower than anticipated.

Table 5: Efficacy of Single Agent Encorafenib in HT-29 Human BRAF-mutant CRC Xenograft Model in Nude Mice

Treatment	Dose (mg/kg)	Regimen	Tumour Responses		
			Mean T/ C (%)	Regression (%)	Mean Δ tumour volume (mm3)
Vehicle	0	PO, QD x 28d	100	-	562
Encorafenib	5	PO, QD x 28d	104	-	584
Encorafenib	50	PO, QD x 28d	75	-	422

T/C = Mean tumour volume in treated group /mean tumour volume in control group

Figure 5: Effects of Single Agent Encorafenib on Tumour Growth in HT-29 Human BRAF mutant CRC Xenograft Model in Nude Mice



Encorafenib was well tolerated at all dose levels and schedules with no significant body weight loss noted. No other signs of toxicity or mortality were observed. Tumors progressed satisfactorily in vehicle-treated Group 1 mice but LGX818-NX monotherapies at 5 and 50 mg/kg qd x 28 (Groups 2 and 3) were inactive.

Further results of this study were as follows: Monotherapy with PI3K inhibitor AA (Group 3) caused non-significant inhibition and negligible survival extension. LGX818-NX / PI3K inhibitor AA combination therapy at the 5:32.7 mg/kg ratio (Group 6) produced 31% T/C and significant ($P < 0.05$) inhibition, but improved non-significantly upon PI3K inhibitor AA monotherapy. LGX818-NX / PI3K inhibitor AA at the 50:32.7 mg/kg ratio (Group 7) yielded 14% T/C, significant ($P < 0.001$) inhibition, and significant improvements over the 50 mg/kg LGX818-NX ($P < 0.01$) and PI3K inhibitor AA ($P < 0.05$) monotherapies. The latter two groups caused the largest group mean body weight losses (8% and 6.4%, respectively).

Overall, LGX818-NX / PI3K inhibitor AA at the 5:32.7 and 50:32.7 ratios increased median TTE by 27% and 38%, respectively. The combination with the higher LGX818-NX dose yielded a significant survival extension ($P < 0.05$), but a non-significant improvement upon LGX818-NX monotherapy. Notably, during the first 1–2 weeks after dosing ended, median and mean tumor volumes increased more slowly in Groups 6 and 7 than in any other groups.

Encorafenib administered as single agent were inactive in this study; only the combination with the PI3K inhibitor AA caused significant tumor inhibition in the HT-29 cell line. But, this inhibition does not correlate with a sustained survival extension.

Dose and Schedule Dependence of LGX818-NX Activity and Response to in the LS411N Human Colon Carcinoma Nude Mouse Xenograft Model (Study LS411N-e202) (updated)

This study determined the dose and schedule dependence of LGX818-NX activity in the subcutaneous LS411N human colon carcinoma nude mouse xenograft model.

LGX818-NX was administered orally for four weeks and was tested at three dose intensities (10, 50, and 300 mg/kg/day), on twice daily and once daily treatment schedules. Control mice received the LGX818-NX vehicle, and a reference group received a standard preclinical paclitaxel regimen.

Treatment	Dose (mg/kg)	Regimen	Tumour Responses		
			Mean T/ C (%)	Regression (%)	Mean Δ tumour volume (mm^3)
Vehicle	0	PO, BID x 28d	100	-	1017
Encorafenib	5	PO, BID x 28d	56	-	574
Encorafenib	10	PO, QD x 28d	77	-	787
Encorafenib	25	PO, BID x 28d	48	-	490
Encorafenib	50	PO, QD x 28d	64	-	650
Encorafenib	150	PO, BID x 28d	34	-	342
Encorafenib	300	PO, QD x 28d	69	-	705
Paclitaxel	30	IV, QOD x 5	5	-	54

T/C = Mean tumour volume in treated group /mean tumour volume in control group

LGX818-NX p.o. b.i.d. x 28 at 5, 25, and 150 mg/kg (Groups 2, 4, and 6) produced 56%, 48%, and 34% T/C on D28, and extended survival by 36%, 38%, and 49%, respectively. This mean tumor growth during the dosing period indicated significant but weakly dose-dependent activity. The short-term and overall activities for b.i.d. LGX818-NX were significant at 5 mg/kg ($P < 0.05$), 25 mg/kg ($P < 0.05$), and 150 mg/kg ($P < 0.01$), respectively. Non-significant short-term and overall effects with LGX818-NX p.o. qd x 28 at 10, 50, and 300 mg/kg (Groups 3, 5, and 7) indicated that qd dosing was less effective than split doses administered twice daily. Statistically significant differences were not demonstrated between b.i.d. and qd regimens at the same dose intensity.

Overall, the BRAF inhibitor LGX818-NX at 5, 25, and 150 mg/kg produced weakly dose-dependent T/C and survival extension in the LS411N human colon carcinoma nude mouse xenograft model. At the same dose intensities, qd treatments produced non-significant T/C and survival extensions. Comparisons of b.i.d. and qd regimens indicated that improvements seen with b.i.d. dosing were not significant.

The effect on proliferation of combining the RAF inhibitor LGX818 with inhibitors of PI3K, EGFR, and cMET in BRAF mutant colorectal-derived cell lines (Study RD-2012-50088) (updated)

The study evaluated the effect of combining the RAF inhibitor LGX818 with either EGFR (Erlotinib (NVP-XBX005-NX-1), c-MET (NVP-INC280-AA), or PIK3Cα (BYL719-NX-11) inhibitors in a panel of 9 BRAF-mutant CRC cell lines. Analysis was carried out using cell proliferation assay and western blotting.

Table 6: Anti-proliferative Activity of Encorafenib and Erlotinib in CRC Cells In Vitro

Cell Line	Cancer Type	BRAF	PIK3CA	PTEN	Encorafenib IC_{50}[nM]	Erlotinib IC_{50}[nM]
SW1417	CRC	mut	wt	wt	235	2700
COLO-205	CRC	mut	wt	wt	5	2700
LS411N	CRC	mut	wt	wt	18	2700
CL-34	CRC	mut	wt	wt	30	2700
MDST8	CRC	mut	wt	mut	319	2700
HT-29	CRC	mut	mut	wt	49	2700
RKO	CRC	mut	mut	wt	1965	2700
SNU-C5	CRC	mut	mut	unknown	2700	2700
OUMS-23	CRC	mut	wt	mut	2700	2700

mut = V600E mutation
wt = wild-type IC_{50} = is the compound concentration which inhibits 50% of the viability signal

Table 7: Summary of Synergy Evaluations of Encorafenib When Combined with Erlotinib in CRC Cells In Vitro

Cell Line	Encorafenib + Erlotinib		
	SS	CI50	Effect Description
SW1417	4.56	0.13	Synergy
COLO-205	4.02	0.67	Additive/Synergy
LS411N	1.98	0.26	Additive/Synergy
CL-34	4.92	0.53	Additive/Synergy
MDST8	1.36	1.6	Additive
HT-29	3.99	0.29	Synergy
RKO	0.83	NC	Additive
SNU-C5	3.51	0.66	Additive/Synergy
OUMS-23	0.77	NC	Additive

NC = not calculated due to a lack of effect at 50% inhibition levels.
Effect description is a qualitative description of the combination effect observed, based on both the synergy score and best combination index. For combination effect descriptions, see Table 6.

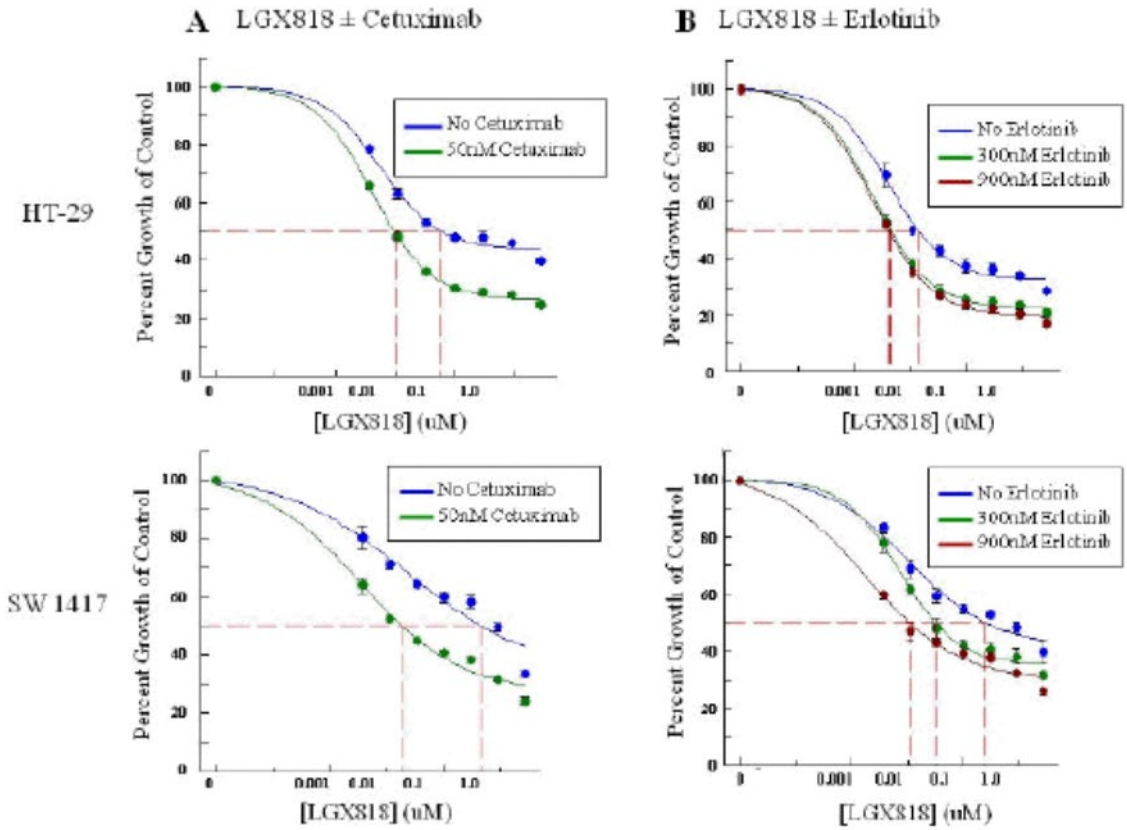
Table 8: Combination and Synergy Score Interpretation

Combination Index		*Synergy Score*	
CI = 0.5 -1	Dose additive	SS ~ 0	Dose additive
CI =0.3-0.5	Weak synergy	SS > 1	Usually indicating synergy
CI < 0.3	Synergy	SS > 2	Real synergy detected

All cell lines tested were insensitive to erlotinib as a single agent. In contrast 6/9 cell lines were sensitive to encorafenib as a single agent, displaying IC50 values below 500 nM (Table 4). The encorafenib/erlotinib combination synergistically inhibited the proliferation of 6/9 CRC cell lines (Table 5). Two cell lines were not sensitive to the encorafenib/erlotinib combination (MDST8 and OUMS-23).

The study further evaluated the combination effects of encorafenib (LGX818) with either cetuximab or erlotinib in HT-29 and SW 1417 cell lines showing that cetuximab and erlotinib had nearly identical effects on proliferation when combined with encorafenib (see figure 3).

Figure 6: Combination Effects of Encorafenib (LGX818) with Either Cetuximab or Erlotinib in HT-29 and SW 1417 Cell Lines



Shown are growth inhibition plots for the HT-29 and SW 1417 BRAF-mutant CRC cell lines following a 72 hr incubation with LGX818 ± cetuximab (A) or erlotinib (B). In all experiments LGX818 concentrations ranged from 0 – 2.7μM. LGX818 single agent results are graphed in blue, LGX818 combined with either 50nM cetuximab or 300nM erlotinib are depicted in green, and LGX818 with 900nM erlotinib are shown in red. For all curves the LGX818 concentration required for 50% growth inhibition is indicated with a dashed red line.

Cell proliferation assay: Eight of the nine cell lines were insensitive to INC280 at concentrations up to 2700nM. In contrast 6/9 cell lines were sensitive to LGX818 as a single agent, displaying IC50 values below 500nM. All cell lines tested were insensitive to Erlotinib. The LGX818/Erlotinib and LGX818/INC280 combinations synergistically inhibited the proliferation of 6/9 and 2/9 cell lines, respectively.

Proliferation was also studied with the two mechanistically distinct EGFR inhibitors erlotinib and cetuximab in combination with LGX818 in two cell lines (HT-29 and SW 1417). Both inhibitors had nearly identical effects on proliferation when combined with LGX818.

Combining LGX818 with the selective PIK3Cα BYL719 resulted in varying degrees of synergy in cells harboring both wt and activating alleles of PIK3Cα.

The triple combination of LGX818 with BYL719 and an RTK inhibitor exhibited a greater anti-proliferative effect compared to any of the pair-wise combination.

Western blotting: The effects of the inhibitors LGX818 and BYL719 were examined, as single agents, and in combination over a 48 hr time period in both the PI3Kα/BRAFV600E double mutant cell line HT-29 and the BRAFV600E single mutant SW 1417.

The triple combination mimicked the BYL719 single agent effects on p-AKT levels (suppression of p-AKT without effecting p-EGFR or p-ERK), and the effect of the LGX818/Erlotinib pair on p-ERK levels thereby providing robust suppression of both the PIK3Cα and MAPK pathways. When Cetuximab was used in place of Erlotinib in similar experiments virtually identical results were obtained (data not shown). Lastly, in both cell lines, treatment with LGX818 resulted in a reduction in the levels of total, but not phosphorylated, EGFR, particularly at the 24 and 48 time-points.

Overall, the sponsor concluded that the synergistic and greater overall effects observed for the triple combination likely resulted from the simultaneous suppression of both MAPK and PIK3Cα signaling. Thereby, it was concluded that the concept of combining the RAF inhibitor LGX818 with the EGFR inhibitor Cetuximab might support clinical application for the treatment of BRAFV600E tumors.

2.2.3. Ecotoxicity/environmental risk assessment

Updated ERAs have been provided for Braftovi and Mektovi to consider a type II variation to extend the indication of encorafenib/binimetinib in combination with binimetinib/encorafenib and cetuximab for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.

New ERAs are based on the ERAs of the initial marketing authorisation, which at that time had been considered complete and acceptable. No new experimental studies were provided for the present worksharing application but new initial $PEC_{surfacewater}$ values were calculated to be 0.0514 µg/l for Braftovi and 0.45 µg/l for Mektovi, respectively. Updated PEC/PNEC calculations showed that a risk to the aquatic and sediment compartment is not indicated. Assessments of the risk to the terrestrial compartment is considered not necessary.

Braftovi (active substance Encorafenib) – PEC/PNEC assessments			
	PEC (µg/L)	PNEC (µg/L)	PEC/PNEC
Microorganisms	0.052	100000	5.2 × 10-7
Surface water	0.052	21	2.5 × 10-3
Groundwater	0.013	21	6.2 × 10-4
	PEC (µg/kg dwt)	PNEC (µg/kg dwt)	PEC/PNEC
Sediment	12.5	5580	2.2 × 10-3

Mektovi (active substance Binimetinib) – PEC/PNEC assessments			
	PEC (µg/L)	PNEC (µg/L)	PEC/PNEC
Microorganisms	0.45	100000	4.5 × 10-6
Surface water	0.45	65	6.9 × 10-3
Groundwater	0.11	65	1.7 × 10-3
	PEC (µg/kg dwt)	PNEC (µg/kg dwt)	PEC/PNEC
Sediment	68.1	1000	6.8 × 10-2

However, both active substances have to be classified as very persistent (vP) in water/sediment systems as encorafenib showed a half-life (DT50) of 1000 days in sediment at 20 °C and DT50 of 203.7 - 468.6 days in the total system at 20 °C. Further, a transformation product of binimetinib formed in water – sediment systems shows a half-life (DT50) of 295 d (normalized to 12°C as average temperature in the EU).

Substance (INN/Invented Name): encorafenib					
CAS-number (if available): 1269440-17-6					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.6 (pH 7)			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	2.6			not B
Persistence	DT50 (20°C)	1,000 /468.6			vP
Toxicity	NOEC				not T
PBT-statement :	The compound is not considered as PBT nor vPvB.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$,refined	0.051	µg/L			> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 301/352 l kg^{-1} (sludge) K_{OC} = 1,786/794/941 l kg^{-1} (soil)			No soil assessment required
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	***System 1*** Parent: $DT_{50, water\ 20\ °C}$ = 44.4 d $DT_{50, sediment}$ = 1,000 $DT_{50, whole\ system\ 20\ °C}$ = 468.6 d NER = 15.2 % (test end) ***System 2*** Parent: $DT_{50, water\ 20\ °C}$ = 19.3 d $DT_{50, sediment}$ =1,000 d $DT_{50, whole\ system\ 20\ °C}$ = 203.7 d NER = 17.7 % (test end)			Encorafenib is classified as very persistent
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	750	µg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	210	µg/L	*Daphnia* magna
Fish, Early Life Stage Toxicity Test/*Danio rerio*	OECD 210	NOEC	10,000	µg/L	*Danio rerio*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1,000,000	µg/L	
Phase IIb Studies					

Sediment dwelling organism, *Chironomus riparius*	OECD 218	NOEC	558	mg/ kg	*Chironomus riparius,* (normalized to 10% Corg)
Substance (INN/Invented Name): binimetinib					
CAS-number (if available): 606143-89-9					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.1 (pH 4 and 7) 1.5 (pH 9)			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	1.5 – 2.1			not B
Persistence	DT50 (12°C) of main transformation product M-1	294.5 /106.5			vP
Toxicity	NOEC				not T
PBT-statement :	The compound is not considered as PBT nor vPvB.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default	0.45	µg/L			> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 122.7/162.3 l kg^{-1} (sludge) K_{OC} = 709.3/1280.7/1477.4 l kg^{-1} (soil)			No soil assessment required
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	***System 1*** Parent: $DT_{50,\ water\ 20\ °C}$ = 6.2 d $DT_{50,\ sediment}$ = n.d. $DT_{50,\ whole\ system\ 20\ °C}$ = 7.1 d M-1: $DT_{50,whole\ system,\ 20\ °C}$ =138 d % shifting to sediment = 11.1 (day 14) NER = 52.8% (test end) TP >10%: M-1 max. 64% at d14 ***System 2*** Parent: $DT_{50,\ water\ 20\ °C}$ = 5.2 d $DT_{50,\ sediment}$ = n.d. $DT_{50,\ whole\ system\ 20\ °C}$ = 5.6 d M-1: $DT_{50,whole\ system,\ 20\ °C}$ = 49.9 d % shifting to sediment = 10.5 (day 14)			Binimetinib is classified as very persistent (persistent transformation product M-1 DT_{50} = 295 d, normalized to 12°C)

		NER = 66.1 % (test end) TP >10%: M-1 max. 75% at d28			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	8400	µg/L	*Pseudokirchneriella subcapitata*
Daphnia magna. Reproduction Test	OECD 211	NOEC	650	µg/L	*Daphnia* magna
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	2200	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000 000	µg/L	
Phase IIb Studies					
Sediment dwelling organism, *Chironomus riparius*	OECD 218	NOEC	110	mg/ kg	*Chironomus riparius* (normalized to 10% Corg)

2.2.4. Discussion on non-clinical aspects

In order to support the new indication, previous data from *in vitro* and *in vivo* studies with encorafenib in combination with cetuximab and encorafenib as single agent have been re-analysed with the focus on the doublet combination.

In vivo studies where encorafenib was used as single agent were performed with three different BRAF mutant xenograft models. Different dose regimes and schedules were tested in the **LS411N** model showing that all dose regimens resulted in tumor growth inhibition and extended survival with weakly dose-dependency. Statistically significant differences could not be demonstrated between b.i.d. and qd regimens at the same dose intensity.

Encorafenib was further tested in the **HT-29** human colorectal tumor nude mouse xenograft model. Two dose levels (5 and 50 mg/kg) were used, on a daily oral treatment schedule for 28 days and both dose levels were shown to be inactive. This is in contrast to the results of study RD-2013-50350, where encorafenib was active (T/C 42% after administration of 20 mg/kg qd).

The effect of encorafenib on the **COLO 205** human colorectal adenocarcinoma nude mouse xenograft model was evaluated. Twice daily LGX818-NX at 5, 25, and 150 mg/kg once daily 10, 50, and 300 mg caused tumor reduction and extended survival. There were no significant advantages to b.i.d. versus qd dosing similar to the results obtained with the LS411N model.

Within the xenograft models in which encorafenib was used in combination with cetuximab, a statistically significant effect of the combination enco/cetuxi on tumor growth was only in the **HT-29** model. In both, the CRC563 and CRC769 models, an effect of combination could not be shown. Remarkable is the fact that cetuximab as single agent had no (**CRC563, CRC769**) respective, only a small effect on tumor growth (HT-29).

Administration of encorafenib plus erlotinib (as anti EGFR drug) in *in vitro* studies using different BRAF mutant cell lines resulted in synergistical inhibition of the proliferation of 6/9 CRC cell lines. Interestingly, all cell lines tested were insensitive to erlotinib as single agent similar to cetuximab as single agent in most of the xenograft models. Further *in vitro* studies evaluated the combination effects of encorafenib (LGX818) with either cetuximab or erlotinib in two cell lines: PI3Kα/*BRAF*V600E double mutant **HT-29** and BRAFV600E single mutant SW 1417. Both anti-EGFR drugs had nearly identical effects on

proliferation when combined with encorafenib. This is remarkable since HT-29 belongs to the BM2 subgroup of BRAF V600E mutant CRCs and **SW1417** to the BM1 subgroup**,** indicating that there might be no difference in behaviour between the subgroups with respect to EGFR- together with BRAF-inhibition. Western blots analysis showed that encorafenib reduced the levels of total, but not phosphorylated, EGFR, particularly at the 24 and 48 time-points in both the HT-29 and SW 1417 cell lines. Combining encorafenib with erlotinib resulted in a markedly better suppression of p-ERK levels than was accomplished by either inhibitor alone. Cetuximab behaved within this study equivalently to Erlotinib when combined with LGX818.

Administration of encorafenib as single agent in *in vivo* xenograft models resulted in tumor regression and extended survival independent of dose regimens and schedules (qd or bid). The combination of encorafenib and cetuximab led only in the HT-29 xenograft model to a significant effect on tumor growth. The HT-29 cell line was also the only one where cetuximab as single agent resulted in a distinct effect. Cetuximab as single agent had no effect in all other *in vivo* models. The HT-29 model was also part of the encorafenib evaluation in *in vitro* studies. Within these studies, the enco/cetuxi combination resulted in distinct tumor regression, similar to the xenograft models.

Overall, the preclinical data do not provide convincing evidence that the addition of cetuximab led to a superior effect in the treatment of CRC. In view of the fact that the data provided, rather, clearly demonstrate that cetuximab is ineffective in the models investigated, the submitted rationale for the clinical use of the double or triple combination is questionable. The non-clinical rationale for the addition of cetuximab to encorafenib in BRAFmut/RASwt models (preferably human colorectal carcinomas) is currently lacking.

2.2.5. Conclusion on the non-clinical aspects

Several studies with the combination of encorafenib, binimetinib and cetuximab were performed in different CRC cell lines to underline that the combination of encorafenib plus cetuximab had a positive impact on the new indication. The results however demonstrated

1. Cetuximab as single agent was inactive in the used models
2. Efficacious groups in the CRC tumor cell lines were the MEK162/LGX818 groups either as monotherapy or in combination with each other. The combination of LGX818 plus cetuximab or MEK162 plus cetuximab did not increase the efficacy of the single agents.
3. The results suggest that cetuximab was not only inactive as single agent but also in combination.

Therefore, from a preclinical point of view, the proposed positive influence of cetuximab through inhibition of the EGFR cannot be concluded from the results obtained.

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of binimetinib nor encorafenib.

Considering the above data, binimetinib and encorafenib are not expected to pose a risk to the environment.

Considering the above data, binimetinib and encorafenib should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the WSA.

The WSA has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Two new clinical studies support the new application in mCRC, the Phase Ib/II study CLGX818X2103 and the pivotal Phase III study ARRAY-818-302 (BEACON) and 2 new population PK and/or exposure response (ER) analyses are provided in support of this application (Reports CP19-013 and T2019-00141).

Study Code	Study Title	Formulation	Number of subjects	PK sampling
CLGX818X2103	A Phase 1b/2 Multicentre, Open Label, Dose Escalation Study of LGX818 and Cetuximab or LGX818, BYL719, and Cetuximab in Patients with BRAF Mutant Metastatic Colorectal Cancer	Capsule (encorafenib)	Whole study and PK dataset: 26 patients (Doublet, Phase Ib)	Rich (Phase 1)
			Phase 2: 50 (Doublet) PK dataset Phase 2: 28 patients (Doublet)	Rich and Sparse (Phase 2)
ARRAY-818-302 (BEACON CRC)	A Multicentre, Randomized, Open-label, 3-Arm Phase 3 Study of Encorafenib + Cetuximab Plus or Minus Binimetinib vs. Irinotecan/Cetuximab or Infusion of 5-Fluorouracil (5-FU)/Folinic Acid (FA) /Irinotecan (FOLFIRI)/Cetuximab with a Safety Lead-in of Encorafenib + Binimetinib + Cetuximab in Patients with BRAF V600E-mutant Metastatic Colorectal Cancer	Capsule (encorafenib)	CSLI: 37 patients (30 SLI, 7 JSLI) included in efficacy, PK and safety analyses Phase 3 Portion: 665 patients (224 Triplet arm, 220 Doublet arm, 221 Control arm) PK dataset: 230 patients (58 Triplet arm, 73 Doublet arm, 99 Control arm)	Limited in CSLI Phase and Sparse in Phase 3

Study Code	Short Tile	Number of subjects	Clinical studies included in dataset
CP19-013	External Visual Predictive Check of observed PK data from ARRAY-818-302 using historical models to evaluate potential interactions	230 patients (58 Triplet arm, 73 Doublet arm, 99 Control arm)	ARRAY-818-302
T2019-00141	Population pharmacokinetic and exposure-response analysis to support the ARRAY-818-302 study in patients with BRAF V600E mutant metastatic colorectal cancer	Total of 394 subjects received encorafenib, incl 15 healthy volunteers, 236 mCRC patients, 96 melanoma BRAF V600 mutation and 47 other tumours	ARRAY-162-105 CMEK162X2110 CLGX818X2103 ARRAY-818-302

In addition, a new updated popPK analysis based on the studies in the melanoma indication is provided (Report T2019-00140) which will be used as a point of comparison of encorafenib PK across indications.

2.3.2. Pharmacokinetics

Bioanalytical methods

- **Encorafenib**

Study Identifier	Method	Analyte	Method Performance		Incurred Sample reanalysis	Testing facilities	Clinical studies/Purpose
			Precision (%CV)	Accuracy (% Bias)			
Bioanalytical and Analytical Methods for Human Studies (corresponding reports in Section 5.3.1.4)							
Novartis report DMPK R1000595c-01	Enco-A	LGX818	NA	NA	NA	Novartis	Update to LTS and stock solution stability
WuXi AppTec Report R1300047-02 Also referred as 13BAS0110 Amendment 2	Enco-B	LGX818	NA	NA	NA	WuXi AppTec	Administrative and update to LTS
PPD Report AKCM2 included in AKCM2v2	Enco-C	LGX818	5.3% to 12.9%	-3.57% to 2.08%	NA	PPD	Method Validation – Plasma
PPD Report AKCM2 addendum 1 included in AKCM2v2	Enco-C	LGX818	NA	NA	NA	PPD	Update to LTS and stock solution stability
PPD Report AKCM2 addendum 2 Included in AKCM2v2	Enco-C	LGX818	NA	NA	NA	PPD	Update to LTS and stock solution stability
Novartis Report DMPK RCLGX818X2103	Enco-A	LGX818	4.0% to 7.0%	-7.5% to -4.3%	NA	Novartis	CLGX818X2103
WuXi AppTec Report 15BAS0446	Enco-B	LGX818	3.6% to 8.2%	-5.8% to 1.8%	Pass	WuXi AppTec	CLGX818X2103
WuXi AppTec Report 17BAS0309	Enco-B	LGX818	2.7% to 7.7%	-5.0% to 0.0%	Pass	WuXi AppTec	ARRAY-818-302

3 validated LC-MS/MS-based BA-methods using stable label internal standards were used to support the application in mCRC and were also used to support the initial MAA. All 3 methods for encorafenib in plasma had an LLOQ of 1 ng/mL.

Method Enco-A Amendment 01 (DMPK R1000595c-01) was an extension of long-term stability in plasma to 16 months (483 days) at -60°C.

Method Enco-B Amendment 02 (DMPK R1300047-02) was an extension of long-term stability in plasma to 46 months (1406 days) at -70°C.

Method Enco-C (Report AKCM2v2 including its 2 addendums, PPD) was cited in 17BAS0309 WuXi AppTec ARRAY-818-302 BA report to support long term sample stability for encorafenib in human plasma

at -20°C (up to 18 months) and to support encorafenib stability in whole blood on an ice bath and using non-refrigerated centrifuge. In human whole blood, encorafenib was demonstrated to be stable for up to 1.5 hours at room temperature.

PK samples generated in study CLGX818X2103 were analysed using method Enco-A and Enco-B (BA reports DMPK RCLGX818X2103 and 15BAS0446, respectively). All PK samples generated in study ARRAY-818-302 were analysed using method Enco-B.

- **Binimetinib**

Study Identifier	Method	Analyte	Method Performance		Incurred Sample reanalysis	Testing facilities	Clinical studies/Purpose
			Precision (%CV)	Accuracy (% Bias)			
Bioanalytical and Analytical Methods for Human Studies (corresponding reports in Section 5.3.1.4)							
WuXi AppTec Report DMPK R1300240-02 Also referred as 12BAS0106 Amendment 02	Bini-A	MEK162 and AR00426032	NA	NA	NA	WuXi AppTec	Administrative and update to LTS
WuXi AppTec Report DMPK R1300240-03 Also referred as 12BAS0106 Amendment 03	Bini-A	MEK162 and AR00426032	NA	NA	NA	WuXi AppTec	Administrative and wording LTS
PPD Report AKCN2	Bini-B	MEK162 and AR00426032	1.95% to 3.65% 2.45% to 6.21%	-4.65% to 4.05% -2.70% to 4.90%	NA	PPD	Method Validation – Plasma
PPD Report AKCN2_addendum 1	Bini-B	MEK162 and AR00426032	NA	NA	NA	PPD	Update to LTS and standard solution stability
WuXi AppTec Report 17BAS0309	Bini-A	MEK162 AR00426032	3.2% to 5.3% 4.1% to 7.9%	-5.7% to -4.0% -9.7% to -2.6%	Pass Pass	WuXi AppTec	ARRAY-818-302

%CV = Precision: coefficient of variation = 100 x standard deviation/mean; F/T = Freeze/Thaw; LTS = Long term stability; NA = Not applicable.

Three validated liquid chromatography with tandem mass spectrometry (LC-MS/MS)-based BA methods using stable label internal standards were used to support clinical development in mCRC and were also used to support the initial MAA. All 3 methods for binimetinib and its metabolite AR00426032 in plasma had an LLOQ of 1 ng/mL.

Method Bini-A (Method 12BAS0106, and amendment 01) was described in the initial MAA. Amendment 02 was an extension of long-term stability in plasma to 56 months (1687 days) at -70°C for both compounds. Amendment 03 was a change of sponsor from Novartis to Array BioPharma Inc. and some wording of the long-term storage stability section. All PK samples generated in study ARRAY-818-302 were analysed using method Bini-A.

Method Bini-B (PPD method AKCN2 and AKCN2 addendum 01) and Method Bini-C (QPS method 234-703) support whole blood stability on an ice bath and non-refrigerated centrifuge, and were cited in report 17BAS0309, i.e. the ARRAY-818-302 BA report describing clinical sample analysis.

Binimetinib and AR00426032 in plasma were demonstrated to be stable for up to 68 months when stored below -20°C and up to 56 months when stored at -70°C. In human whole blood, binimetinib and AR00426032 were demonstrated to be stable at 4°C for up to 45 min.

- **Cetuximab**

Study Identifier	Method	Analyte	Method Performance		Incurred Sample reanalysis	Testing facilities	Clinical studies/Purpose
			Precision (%CV)	Accuracy (% Bias)			
Bioanalytical and Analytical Methods for Human Studies (corresponding reports in Section 5.3.1.4)							
WuXi AppTec Report 15BAS0095	Cetux-A	Cetuximab	5.6% to 12.1%	-5.6% to 2.1%	NA	WuXi AppTec	Method Validation – Serum
WuXi AppTec Report 15BAS0095 Amendment 01	Cetux-A	Cetuximab	NA	NA	NA	WuXi AppTec	Update to LTS and F/T stability
WuXi AppTec Report 17BAS0403	Cetux-A	Cetuximab	7% to 183%	-3% to 30%	Pass	WuXi AppTec	ARRAY-818-302

The bioanalytical method used to quantify cetuximab in combination with binimetinib and encorafenib for ARRAY-818-302 was an indirect enzyme-linked immunosorbent assay (ELISA), developed and validated in human serum by WuXi AppTec.

The method is based on the Cetuximab present in calibration standard curve and sample controls bound to EGFR which is coated on the surface of the plate, and then use a primary Ab (mouse anti-Cetuximab mAb) to bind to the Cetuximab which had bounded to the EGFR. Finally, the bound mouse anti-Cetuximab mAb is then detected by adding a goat anti-mouse IgG (H+L) conjugated with horseradish peroxidase (The bound Cetuximab is detected indirectly at the same time). After addition of TMB working solution, the peroxidase on detection antibody will generate OD signals. As stopped by sulfuric acid, the resulting OD signal is directly proportional to the amount of bound Cetuximab by measured with the plate reader at 450 nm (reference wavelength 620 nm).

The linearity of the analytical method (4-parameter logistic regression) for analysis of cetuximab in serum was validated in the range of 40 to 4000 ng/mL (report 15BAS0095 and amendment 01). The method demonstrated specificity in serum plasma with no significant interferences observed in the biological matrix. The inter-day accuracy and precision of the method were evaluated as the mean bias and precision of quality control (QC) samples analysed during 6 validation days. The bias and the precision at the lower limit of quantitation (LLOQ) were 2.1% and 5.6%, respectively. The bias and the precision at the upper limit of quantitation (ULOQ) were -5.6% and 12.1%, respectively. Between the LLOQ and the ULOQ, the biases were within the range of -0.3% to 2.1% and the precisions were within the range of 7.7% to 9.1%. Accuracy of dilution was demonstrated for 160-fold dilution.

Cetuximab in serum was stable for up to 42 months when stored below -70°C or at -20°C, and was stable for up to 8 days when stored at room temperature or at 4°C. Cetuximab in human serum was stable for up to 6 freeze/thaw cycles at both -20±5°C and -70±10°C. Incurred sample reproducibility of quantitation has been demonstrated for cetuximab in serum samples from patient population collected during the oncology study used to support treatment in mCRC.

- **Molecular screening**

Patients were eligible for the study based on identification of a BRAFV600E mutation in the tumour as determined by the central laboratory as part of Molecular Prescreening for the trial or by a local assay result obtained any time prior to Screening. Only polymerase chain reaction (PCR) and next generation sequencing (NGS)-based local assays results were acceptable. If the patient was enrolled based on local assay results, the BRAF mutation status must have been confirmed by the central laboratory no later than 30 days from first dose of study treatment.

Central testing has been performed in central labs complying with international *in vitro* diagnostic quality standards. The analytical performance and clinical validity of BRAF central testing method with a Qiagen-developed real-time PCR BRAF V600E clinical trial assay developed for this study was detailed, as well the

analytical performance and clinical validity of KRAS central testing method with IVD/CE-marked therascreen KRAS RGQ PCR Kit.

Pharmacokinetic sampling

In Phase Ib/II Study **CLGX818X2103** rich serial PK samples (predose, 0.5, 1, 2, 4, 6, 8 and 24 hours post dose on Cycle 1 Day 1 and C2D1) were collected to estimate PK parameters for the Doublet combination of encorafenib + cetuximab. Samples were collected from all patients in the dose-escalation phase and in the first 10 patients in the Phase 2 portion of the study; the remainder of patients on the Phase 2 portion of the study had sparse PK sampling (predose, and between 0.5 to 2, 2 to 4 and 4 to 10 hours on C1D1 and C2D1). Planned predose PK samples were also collected on C3D1 through C10D1 in both the dose escalation portion and the Phase 2 portion of the study. A complete treatment cycle was defined as 28 days.

Only encorafenib was analysed in the Doublet portion of the study and no PK samples for cetuximab analysis were collected in this study.

In **phase III study ARRAY-818-302 (BEACON)** PK sampling in the Safety Lead-In (SLI) portion was performed according to the following scheme:

	Cycle 1 Day 1					**Cycle 2 Day 1**				
Time after dosing on designated dosing days (h)	0 (predose)	1	2	4	6	0 (predose)	1	2	4	6
PK Sample[a]	X	X	X	X	X	X	X	X	X	X

Abbreviations: h = hours; PK = pharmacokinetic.

[a] PK samples were collected from all SLI patients on Cycle 1 Day 1 and Cycle 2 Day 1 only at the following time points: predose (just prior to dose of encorafenib/binimetinib) and pre-infusion (just prior to infusion of cetuximab), post dose/post-infusion at 1 h (± 10 min), 2 h (± 10 min), 4 h (± 30 min), 6 h (± 30 min). Blood samples for encorafenib/binimetinib PK were collected predose and postdose at the times indicated above and processed to plasma. Blood samples for cetuximab PK were collected pre-infusion and post-infusion at the times indicated above and processed to serum.

PK sampling in the randomized phase 3 portion was performed as follows:

	Cycle 1 Day 1		**Cycle 2 Day 1**	
Time after dosing on designated dosing days (h)	2	6	0 (predose)	2
PK Sample Triplet Arm[a] Doublet Arm[b] Control Arm[c]	X	X	X	X

Abbreviations: h = hours; PK = pharmacokinetic.

[a] Triplet Arm: PK samples were collected for the first ~50 patients enrolled in the Triplet Arm on Cycle 1 Day 1 postdose (encorafenib/binimetinib) and post-infusion (cetuximab) at 2 h (± 10 min) and 6 h (± 30 min). PK samples will be collected on Cycle 2 Day 1 predose (just prior to encorafenib/binimetinib dose) and pre-infusion (just prior to infusion of cetuximab) and postdose/post-infusion at 2 h (± 10 min). Blood samples for encorafenib/binimetinib PK were processed to plasma. Blood samples for cetuximab PK were processed to serum.

[b] Doublet Arm: PK samples were collected from the first ~50 patients enrolled in the Doublet Arm on Cycle 1 Day 1 postdose of encorafenib and post-infusion of cetuximab at 2 h (± 10 min) and 6 h (± 30 min). PK samples were collected on Cycle 2 Day 1 predose of encorafenib and pre-infusion of cetuximab, and postdose/post-infusion at 2 h (± 10 min). Blood samples for encorafenib PK were processed to plasma. Blood samples for cetuximab PK were processed to serum.

[c] Control Arm: Cetuximab PK samples were collected from the first ~100 patients enrolled in the Control Arm on Cycle 1 Day 1 post-infusion at 2 h (± 10 min) and 6 h (± 30 min). PK samples were collected on Cycle 2 Day 1 just prior to infusion and post-infusion at 2 h (± 10 min). Blood samples for cetuximab PK were processed to serum.

Pharmacokinetic and statistical data analysis

PK parameters were determined using non-compartmental (NCA) methods, based on individual plasma/serum concentration-time data. In addition, the metabolite to parent exposure ratios were calculated on C1D1 and C2D1 for AR00426032, while the accumulation ratios were calculated for all analytes on C2D1.

PK samples collected outside the allowed time windows were flagged in the concentration data listings and excluded from all associated tables and mean figures, but retained in the individual concentration-time plots and estimation of PK parameters.

Concentration data was summarized at each nominal time point with the following descriptive statistics: n, Mean, SD, CV%, Median, Min, Max, GeoMean, and GeoCV%.

Common PK and statistical analysis methods were applied.

Population PK models

PopPK report T2019-00141

Population PK and exposure-response analyses were performed based on five clinical studies in healthy subjects, patients with unresectable or metastatic BRAF V600 mutant melanoma and patients with BRAF V600E-mutant mCRC from the following clinical trials:

Patients with BRAF V600E-mutant mCRC

- Study BEACON (ARRAY-818-302): triple combi (binimetinib/encorafenib/cetuximab) or dual combi (encorafenib/cetuximab or irinotecan/cetuximab or folfiri/cetuximab)
- Study CLGX818X2103: dual combi (encorafenib/cetuximab)

Patients with BRAF V600 mutant advanced solid tumors

- Study CMEK162X2110: dual combi (binimetinib/encorafenib)
- Study CLGX818X2101: single agent encorafenib

Healthy subjects

- Study ARRAY-162-105 single agent binimetinib or encorafenib

Doses used were:

- Binimetinib: 45 mg BID,
- Encorafenib: 50, 100, 300, 450, 600 or 900 mg QD,
- Cetuximab: 250 or 400 mg/m2

Given that PK data from patients with mCRC in studies ARRAY-818-302 and CLGX818X2103 are limited or sparse sampling data, rich sampling data of encorafenib and binimetinib from healthy subjects (ARRAY-162-105) were included into the full dataset. In addition, data from studies CMEK162X2110 and CLGX818X2101 were used to document the analysis in patients with rich sampling data, to bring information about dose and time dependent PK of encorafenib and evaluate differences between patients with melanoma and with mCRC.

Concentration-time profiles of encorafenib and binimetinib were previously modeled based on PK data collected in five clinical trials. The final population PK model of encorafenib consisted of a two-compartment model with a first order absorption rate, a lag-time and a time-varying clearance to account for enzymatic auto-induction. The final population PK model of binimetinib consisted of a two-compartment model with linear elimination with a zero-order rate of absorption and a lag time. Relevant covariates were included such as body weight, age, and concomitant administration of CYP3A inhibitors. Those structural population PK models were the starting point to characterize the PK profiles of

encorafenib and binimetinib in patients with mCRC in BEACON and CLGX818X2103 studies (for encorafenib only). Models were refined to optimize the quality of fit.

A population PK model of cetuximab was previously developed based on 1,253 concentration samples collected in 96 patients with confirmed stage IV colorectal adenocarcinoma with unresectable metastases. Cetuximab PK profiles were best described by a two-compartment model with combined first- and zero-order elimination processes. Albumin and BSA were identified as predictors of volume and elimination processes. The structural model was used as a starting point to develop a population PK model with the PK data of cetuximab collected in patients with mCRC in BEACON and CLGX818X2103 studies.

- **Encorafenib**

The final population PK model of encorafenib consisted of a two-compartment model with a first order absorption rate, a lag-time and a time-varying clearance to account for enzymatic auto-induction. Time-dependent clearance is expressed with a sigmoid function with a maximum time effect (Emax) and time to reach 50% of Emax (T50). Those structural population PK models were the starting point to characterize the PK profiles of encorafenib and binimetinib in patients with mCRC in BEACON and CLGX818X2103 studies (for encorafenib only). Models were refined to optimize the quality of fit. A total of 394 subjects received encorafenib either as monotherapy (ARRAY-162-105 and CLGX818X2101), in combination only with binimetinib (CMEK162X2110), in combination with cetuximab and in combination with binimetinib and cetuximab (BEACON). A total of 236 (59.9%) patients had BRAF V600E-mutant with mCRC and 96 (24.4%) patients had melanoma with a BRAF V600 mutation. Oral encorafenib dose levels varied from 25 to 900 mg with single dose administration, or repeated QD or BID administrations.

The previous structural model of encorafenib was re-evaluated with the dataset updated with PK data collected in BEACON and CLGX818X2103 studies. Of a total of 4348 samples, 43 (<1%) were excluded from the analysis (outliers, measurable concentrations before the 1st dose and during unscheduled visit). Additional structural models were evaluated by adding BSV on lag time of absorption (ALAG) (Enco2), BSV on ALAG, Emax and T50 (refer to Enco3) and BSV on ALAG, CL/2 and V2/F (Enco3), but important shrinkage was obtained on most PK parameters (i.e., >30%). The model was re-estimated without log-transformation on concentrations (model Enco5) and with a 3rd compartment but no improvement in goodness-of-fit was observed. The previous model with BSV on Ka, CL/F and V/F with time-dependent effect on CL/F was found to better describe the data (Enco01). Shrinkages of PK parameters were low (24.7% for ka, 16.3& for Vc/F and 14.8% for Cl/F).

Baseline characteristics of encorafenib patients is shown in table 1.

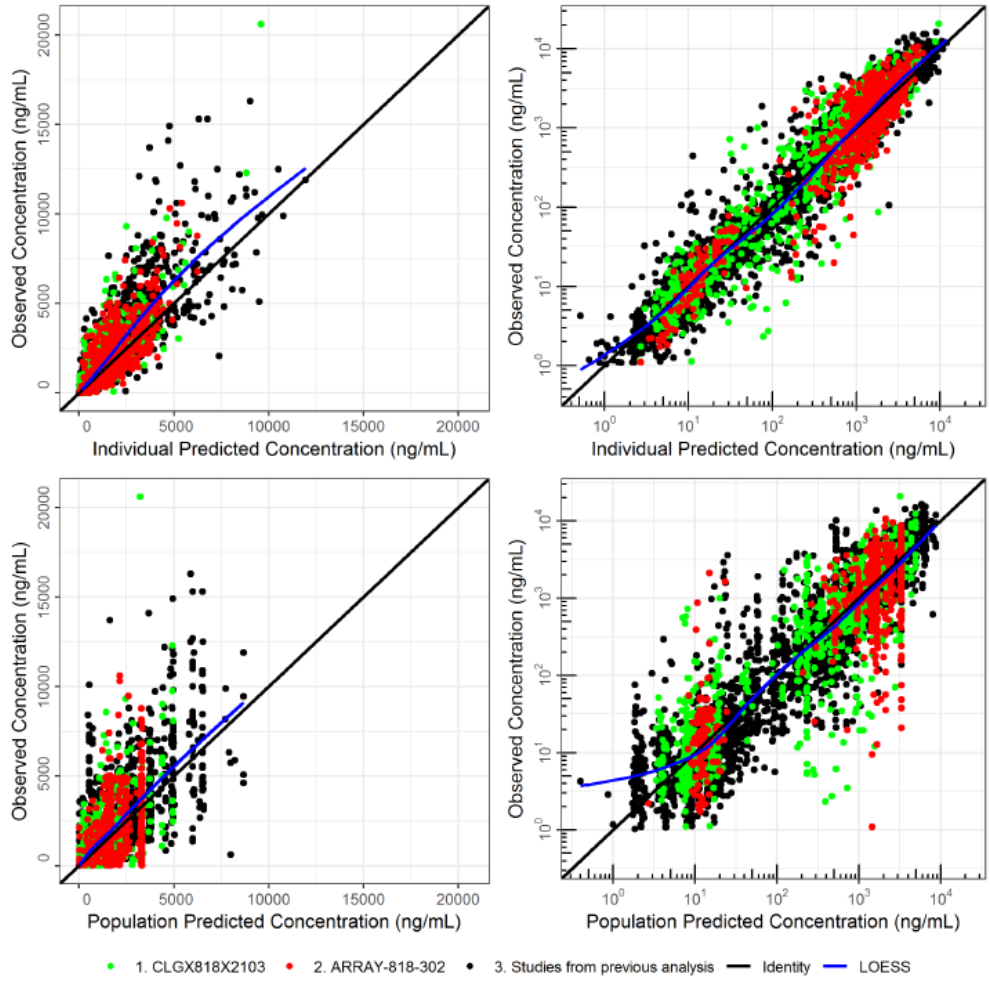
Table 1 Baseline Characteristics of Encorafenib Population by Tumor Type-Categorical Data

Covariates	Healthy Subjects (N=15)	Melanoma (N=96)	mCRC (N=236)	Other Tumor (N=47)	Overall (N=394)
Sex					
Male	11 (73.3%)	60 (62.5%)	102 (43.2%)	25 (53.2%)	198 (50.3%)
Female	4 (26.7%)	36 (37.5%)	134 (56.8%)	22 (46.8%)	196 (49.7%)
Race					
White	8 (53.3%)	87 (90.6%)	199 (84.3%)	42 (89.4%)	336 (85.3%)
Black	7 (46.7%)	0 (0%)	3 (1.3%)	0 (0%)	10 (2.5%)
Native American	0 (0%)	1 (1.0%)	0 (0%)	0 (0%)	1 (0.3%)
Asian	0 (0%)	4 (4.2%)	30 (12.7%)	5 (10.6%)	39 (9.9%)
Other	0 (0%)	4 (4.2%)	3 (1.3%)	0 (0%)	7 (1.8%)
Unknown	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	1 (0.3%)
ECOG at Baseline					
Healthy Subjects	15 (100%)	0 (0%)	0 (0%)	0 (0%)	15 (3.8%)
0	0 (0%)	56 (58.3%)	103 (43.6%)	25 (53.2%)	184 (46.7%)
1	0 (0%)	37 (38.5%)	130 (55.1%)	22 (46.8%)	189 (48.0%)
2	0 (0%)	3 (3.1%)	3 (1.3%)	0 (0%)	6 (1.5%)
Renal Impairment Group Based on CRCL Levels at Baseline					
Normal Renal Function	13 (86.7%)	72 (75.0%)	136 (57.6%)	30 (63.8%)	251 (63.7%)
Mild Impairment Function	2 (13.3%)	21 (21.9%)	76 (32.2%)	12 (25.5%)	111 (28.2%)
Moderate Impairment Function	0 (0%)	3 (3.1%)	22 (9.3%)	5 (10.6%)	30 (7.6%)
Missing	0 (0%)	0 (0%)	2 (0.8%)	0 (0%)	2 (0.5%)
Prior Use of CYP3A Inducers					
Absence or Presence of Weak	15 (100%)	96 (100%)	100 (42.4%)	47 (100%)	258 (65.5%)
Presence of Moderate	0 (0%)	0 (0%)	136 (57.6%)	0 (0%)	136 (34.5%)
Prior Use of CYP3A Inhibitors					
Absence or Presence of Weak	15 (100%)	89 (92.7%)	197 (83.5%)	43 (91.5%)	344 (87.3%)
Presence of Moderate	0 (0%)	5 (5.2%)	29 (12.3%)	4 (8.5%)	38 (9.6%)
Presence of Strong	0 (0%)	2 (2.1%)	10 (4.2%)	0 (0%)	12 (3.0%)

CRCL= creatinine clearance; ECOG= Eastern Cooperative Oncology Group status; mCRC= metastatic colorectal cancer; N= number of subjects; PK= pharmacokinetic

Note 1: ECOG -= 0 for fully active, able to carry on all pre-disease performance; ECOG= 1 for restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; ECOG= 2 for ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of walking hours

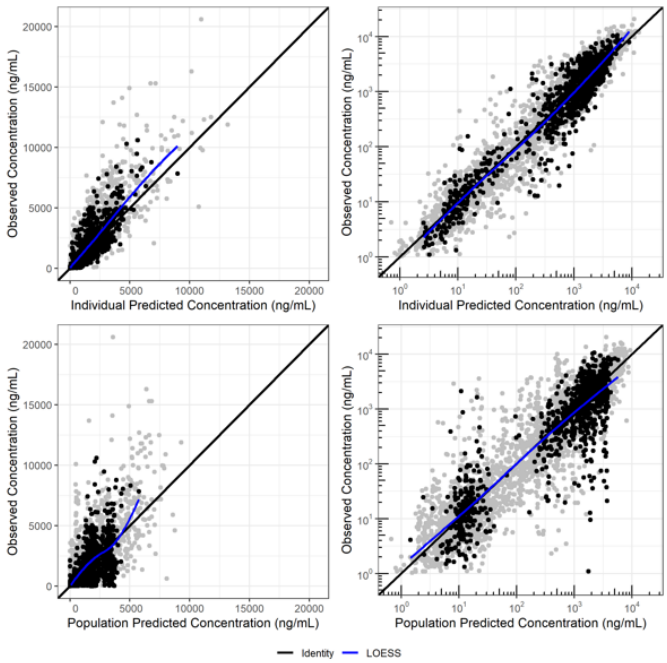
11.10. Structural Population PK Model of Encorafenib – Goodness-of-Fits



LOESS = locally weighted scatter plot smoothing; PK= pharmacokinetic
Note 1: Blue lines represent LOESS and black lines represent the identity line
Note 2: To improve data visualization, one concentration (DV= 39600 ng/mL, subjid #CMEK162X2110-5000-104) in Study CMEK162X2110 was removed

Figure 3: Goodness-of-Fit Plots – Patients with Cancer– Encorafenib 300 mg – Individual Predicted Concentrations versus Observed Concentrations (top) and Population Predictions versus Observed Concentrations (bottom)

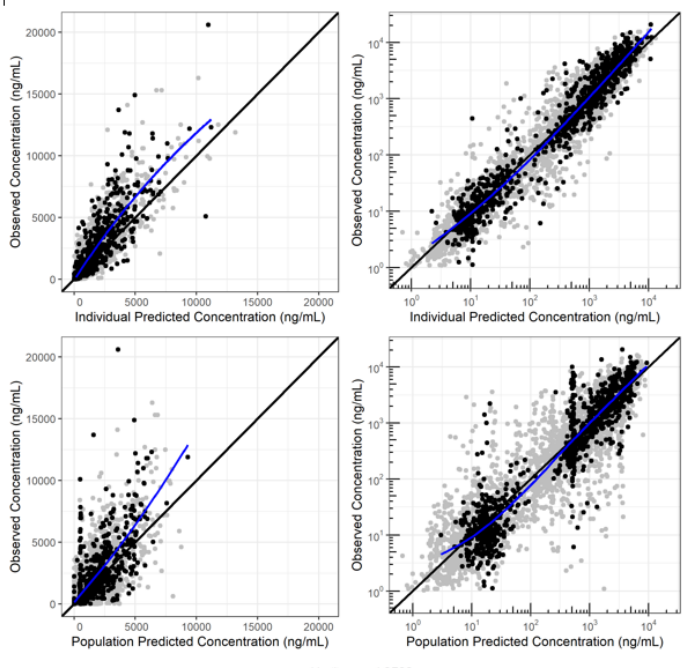
The plots are presented with linear scales (left) and log scales (right).



Source: T2020-00051 Amendment 1 Figure 3. LOESS = locally weighted scatter plot smoothing; PK= pharmacokinetics
Note 1: Blue lines represent LOESS and black lines represent the identity line. Grey symbols represent individual values from al the population and black symbols represent individual values for cancer patients after 300 mg. LOESS lines are based on the black symbols.

Figure 5: Goodness-of-Fit Plots – Patients with Cancer– Encorafenib 450 mg – Individual Predicted Concentrations versus Observed Concentrations (top) and Population Predictions versus Observed Concentrations (bottom)

The plots are presented with linear scales (left) and log scales (right).



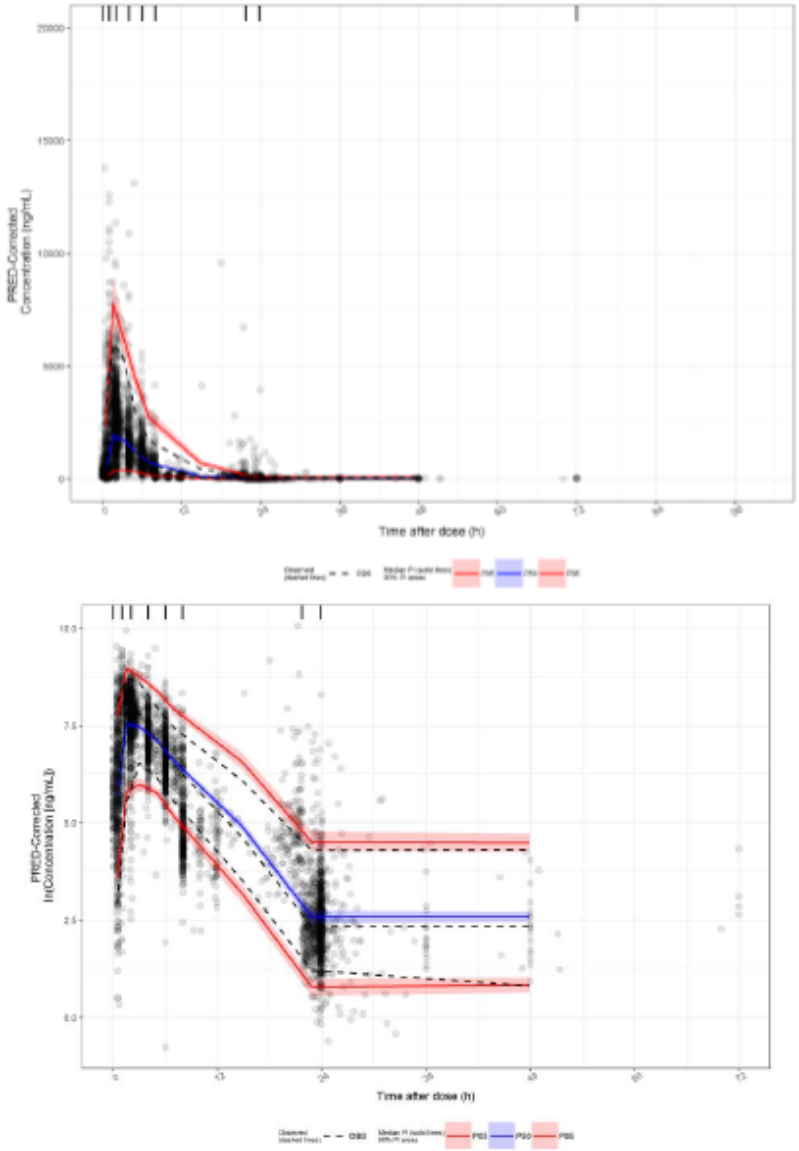
Source: T2020-00051 Amendment 1 Figure 4. LOESS = locally weighted scatter plot smoothing; PK= pharmacokinetics
Note: Blue lines represent LOESS and black lines represent the identity line. Grey symbols represent individual values from al the population and black symbols represent individual values for cancer patients after 450 mg. LOESS lines are based on the black symbols.

Sources of variability were explored to visually assess the effect of continuous and categorical covariates on PK parameters of encorafenib. Based upon a full model approach, the final model included the following covariates

- Ka: age as a continuous covariate
- CL/F: disease status (mCRC patients vs patients with melanoma vs patients with other tumors vs healthy subjects), ECOG status (1 and 2), CYP3A4 inhibitors (strong (not significant based on 95% CI) and moderate), renal function (mild and moderate, not significant based on 95% CI) as categorical covariates, and AST (not significant based on 95% CI), TPROT, BIL, LDH, age and body weight as continuous covariates
- Emax: dose
- V/F: age as a continuous covariate (not significant based on 95% CI)

All PK parameters were estimated with a good precision with RSE varying from 1.5% to 41.2%. Based on the 95% CI, the effects of AST, renal impairment and strong CYP3A4 inhibitors on CL/F and the effect of age on V/F were not statistically significant (i.e., 95% CI included the null hypothesis). All other covariates included in the final population PK model have significant effects on the PK behavior of encorafenib, being age on ka, disease status, ECOG status, moderate CYP3A4 inhibitors, TPROT, BIL, LDH, age and bw on CL, dose on Emax.

11.62. Final Population PK Model of Encorafenib - Goodness of Fit – Prediction Corrected Visual Predictive Check (Linear and Log – Scales)



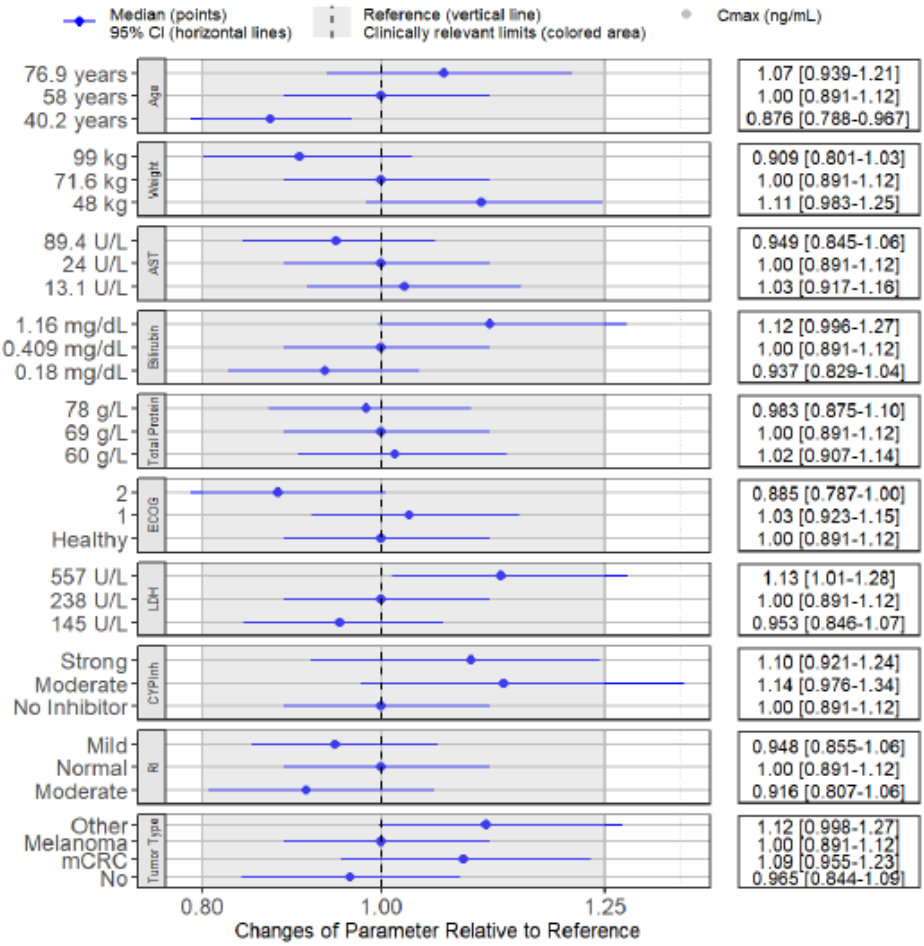
PI= prediction interval; PRED-corrected= population prediction corrected
Blue shade area: 95% PI of simulated median within each bin.
Red shade area: 95%PI of simulated 5th and 95th percentiles within each bin.

Table 4 Final Population PK Parameters of Encorafenib

Parameters	Estimates	BSV(%)	%RSE	95% CI*	Shrinkage (%)
Ka (h^{-1})	0.303	29.6%	4.8	0.283-0.339	22.7%
× $(Age/58)^{theta}$	-0.051		36.2	-0.120- -0.0254	
Absorption Lag (h)	0.431		3.5	0.411-0.459	
CL/F (L/h)	16.4	35.3%	4.3	14.9-17.5	18.7%
× $(WT/72)^{theta}$	0.220		23.8	0.195-0.517	
× $(Age/58)^{theta}$	-0.432		16.8	-0.537- -0.278	
× $(TPROT/69)^{theta}$	0.163		40.8	0.035-0.301	
× $(BIL/0.409)^{theta}$	-0.133		21.9	-0.170- -0.0642	
× $(AST/24)^{theta}$	0.064		41.2	-0.00512- 0.0838	
× $(LDH/238)^{theta}$	-0.176		19.3	-0.230- -0.104	
× for Mild CRCL	1.06		3.5	0.981-1.12	
× for Moderate CRCL	1.08		6.6	0.969-1.24	
× for Healthy Subjects	1.12		3.8	1.01-1.14	
× for Patients with mCRC	0.868		3.8	0.808-0.939	
× for Patients with Other Tumor	0.883		3.6	0.838-0.971	
× Moderate CYP3A4 Inhibitors	0.849		6.9	0.709-0.978	
× Strong CYP3A4 Inhibitors	0.870		6.4	0.798-1.04	
× ECOG=1	0.938		1.5	0.929-0.989	
× ECOG=2	1.15		5.1	1.04-1.27	
Emax	-1.70		6.4	-1.94- -1.51	
× $(DOSE/300)^{theta}$	0.248		24.1	0.179-0.489	
T50 (h)	67.3		22.7	52.0-123.5	
V/F (L)	17.0	226%	17.3	10.6-21.0	16.3%
× $(Age/58)^{theta}$	-0.188		39.9	-0.322- 0.00948	
CL2/F (L/h)	1.37		8.8	1.12-1.57	
V2/F (L)	38.0		16.9	27.1-54.0	
Residual Error	**Estimates**				
Log-additive Error	0.700				

*Bootstrap were performed on 553 resampling runs for final population PK model.
AST = aspartate aminotransferase (U/L); BIL= bilirubin (mg/dL); BSV= between subject variability; CI = confidence intervals; CL/F= apparent clearance; CL2/F= apparent inter-compartmental clearance; CRCL= creatinine clearance; ECOG= eastern cooperative oncology group; Emax= maximum time effect; Ka= first order rate of absorption; LDH = lactate dehydrogenase (U/L); mCRC= metastatic colorectal cancer; RSE = relative standard error; T50= time to reach 50% of the maximum time effect; Tlag= lag time of absorption; TPROT= total protein (g/L); V/F= apparent central volume of distribution; V2/F= apparent peripheral volume of distribution; WT = body weight (kg).
Note: Time effect on CL/F was implemented using the following equation : 1-Emax*t/(T50+t))

Figure 2 Forest Plot – Covariate Effects on Encorafenib Exposure (Cmaxss)



Simulations were performed based on bootstrap outputs of the final population PK model and oral administration of 300 mg QD at steady-state conditions. The dots and the horizontal segments represent bootstrap-derived mean and 95% CI of covariate effect relative to the reference patient (i.e., a 58 years old, fully active patient with melanoma and normal renal function, having a bogy weight of 71.6 kg, an AST level of 24 U/L, bilirubin of 0.409 mg/dL, LDH of 238 U/L, total protein level of 69 g/L and not treated with CYP inhibitor). The shaded area represents effect size of 80% -125%.
AST= aspartate aminotransferase; CI= confidence interval; Cmax/Cmaxss= maximum concentration at steady-state; ECOG= Eastern Cooperative Oncology Group status; LDH=lactate dehydrogenase; mCRC= metastatic colorectal cancer; RI=renal impairment.
Note: missing values were not considered in the distribution.

In terms of categorical covariates, medians and 95% CI of the following covariate effects on AUCss and Cmaxss were within 80% and 125% relative to the reference patient: ECOG (1 vs 0), disease status and/or tumor type (mCRC vs no tumor vs melanoma) and renal function (mild vs normal). Lower limits of 95% CI of ECOG 2 effect were less than 80% for the relative changes in AUCss and Cmaxss with medians within 80%-125%. Upper limits of 95% CI of the effects of moderate renal impairment function, of other tumor types and of co-administration of moderate CYP inhibitor were higher than 125%, although all medians were within 80% - 125%.

In terms of continuous covariates, upper limits of 95% CI of BIL and LDH effects were higher than 125% for the relative changes of AUCss and Cmaxss, assuming high levels of BIL (i.e., 1.16 mg/dL) and of LDH (i.e., 557 U/L). Similarly, upper limit of 95% CI of WT effect on AUCss was higher than 125% for a WT of 48 kg. Medians and 95% CI of TPROT and AST on AUCss and Cmaxss were within 80% and 125% relative to the reference patient. For forest plots for AUCss please refer to section on special populations.

The covariates included in this new analysis are similar to the covariates included in the improved model of encorafenib (CP19-016/T2019-00140)9 and the previous ones (CP17-004 and CP17-004A1)8,10 except for the age which was included in the previous improved model CP19-016/T2019-00140)9 as a covariate on Ka and V/F and for the CRCL covariate which is included in the current model as a

categorical covariate rather than a continuous one. Impacts of the current covariates on PK parameters are similar to and no more impactful as shown in the previous models.

The auto-induction of clearance had the following impact: After a single dose, the population estimates of CL/F for encorafenib was 16.4 L/h for patients with melanoma and 14.2 L/h for patients with mCRC. Based on the population PK model, half-life values associated with the distribution (t1/2α) and elimination (t1/2ß) phases of encorafenib after a single dose in patients with mCRC were 0.754 and 21.2 h, respectively. The population estimate of CL/F was 1.70-fold higher after several days of dosing due to the enzymatic auto-induction of encorafenib, resulting in t1/2α and t1/2ß values of 0.297 and 19.9 h, respectively. The estimated time to achieve 50% of the maximum CL/F (T50) is 67.3 h after the 1st dose, which leads to a 90% of the maximal effect at 605.7 h (25 days ~3 weeks). This is also consistent with the physiological mechanism of enzymatic induction. To adequately characterize the magnitude and time-dependent effects of enzyme auto-induction after multiple doses of encorafenib, the Emax for the auto-induction on CL/F showed an increase with encorafenib that was both dose- and time-dependent, consistent with concentration effect in the induction physiology. For example, with a dose of 300 mg, the CL/F at steady-state condition would be 1.70-fold higher than after a single dose, whereas with a dose of 450 mg, the CL/F at steady-state would be 1.87-fold higher than after a single dose.

Final population PK models were used to derive rich concentration-time profiles and exposure parameters were derived according to the randomized dose in patients enrolled in all studies.

Simulations were derived based on steady-state conditions. Mean and median AUCss of encorafenib at 300 mg and 450 mg QD were similar to those predicted in COLUMBUS study at steady-state after repeated administration of combination encorafenib + binimetinib9 (mean and median AUCss were 7.96 µg.h/mL and 7.37 µg.h/mL at 300 mg QD and 10.2 µg.h/mL and 9.70 µg.h/mL at 450 mg QD, respectively) as well as mean and median Cmaxss (1847 ng/mL and 1827 ng/mL at 300 mg QD and 2549 ng/mL and 2544 ng/mL at 450 mg QD, respectively), and mean and median Cminss (22 ng/mL and 9.02 ng/mL at 300 mg QD and 17.0 ng/mL and 10.4 ng/mL at 450 mg QD, respectively). Same conclusions can be drawn comparing with exposure metrics predicted at steady-state after repeated administration of encorafenib monotherapy. Although the two effects are confounded, this suggests no clear difference between the two types of tumors and between combinations cetuximab + encorafenib + binimetinib and encorafenib + binimetinib.

- **Binimetinib**

In a first model, based on six clinical trials (ARRAY 162-111, CMEK162X2201, CMEK162X1101 CMEK162X2101J, CMEK162A2301 and ARRAY 162-0602) binimetinib PK was described with a two-compartment model with first order absorption and a lag time. Covariates on clearance were moderate and mild renal impairment, patient status (HV/patient), total bilirubin, sex and age. This model had been updated including additional studies ARRAY 162-205, CMAK162X2110, CMEKB2301, CLGX818 and CLGX2109. In this updated model the absorption component was changed to a zero-order rate of absorption with lag time. As covariates on clearance similar to the previous analysis, bilirubin and sex were significant but not renal impairment, age and patient status. Instead, body weight and albumin showed significant effects on clearance additionally. On volume of distribution body weight, albumin and patient status were significant covariates. This structural population PK model was the starting point to characterize the PK profile of binimetinib in patients with mCRC in BEACON study.

In the current popPK analysis for binimetinib, data from the following studies were included: ARRAY818-302 (BEACON), CMEK162X2110 and ARRAY -162-105. A total of 181 subjects received binimetinib either as monotherapy in ARRAY-162-105, in combination only with encorafenib in CMEK162X2110 study, in combination with encorafenib and cetuximab in BEACON study. A total of 93 (51.4%) patients had BRAF V600E-mutant with mCRC from BEACON study and 73 (40.3%) patients had melanoma with a BRAF V600

mutation from Study CMEK162X2110. With the exception of the single dose in healthy subjects (N=15) in Study ARRAY-162-105, binimetinib was orally administered BID at 45 mg. A total of 11 PK samples were excluded from the analysis due to unscheduled visit and measurable concentrations before the 1st dose.

The model was refined in a first step by excluding BSV on peripheral PK parameters due to the high shrinkage (i.e., >30%) including the effect of body weight on CL/F (Bini02). The structural model resulted in adequate goodness-of-fit, and overall the predictive power of the model was deemed adequate to evaluate the relations between PK parameters and covariates.

All PK parameters were estimated with a good precision, with RSE varying from 4.32% to 39.3%, at the exception of AST effect on CL/F with RSE of 85.9%. Based on the 95% CI, effects of AST, renal impairment and tumor type (mCRC vs melanoma) on CL/F and effect of tumor type (mCRC vs melanoma) on V/F were not statistically significant (i.e., 95% CI included the null hypothesis). Thus, the final model included the following covariates

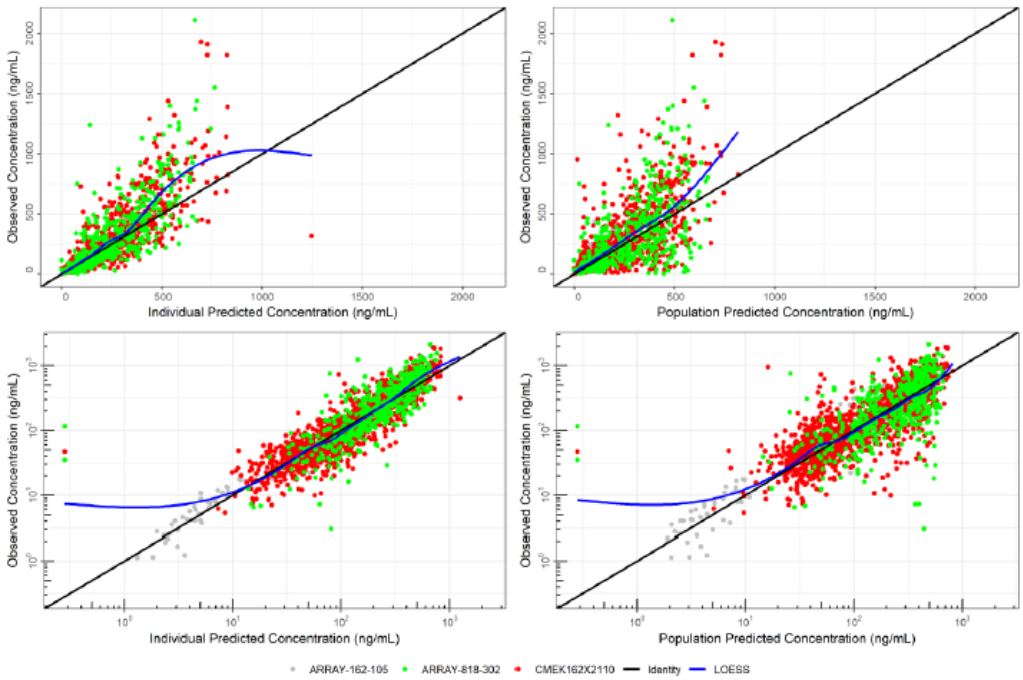
CL/F: disease status (mCRC patients vs patients with melanoma vs healthy subjects), and renal function as categorical covariates, and age, body weight, AST, bilirubin as continuous covariates

V/F: disease status (mCRC patients vs patients with melanoma vs healthy subjects) as categorical and body weight as continuous covariates

The full model with the covariate effect was refined by re-evaluating the model using different initial values for V/F, by testing with first-order rate of absorption instead of zero order rate of absorption and by optimizing the OMEGA matrix. The model with Ka and correlation between CL/F and V/F was found to better describe the data (Full7).

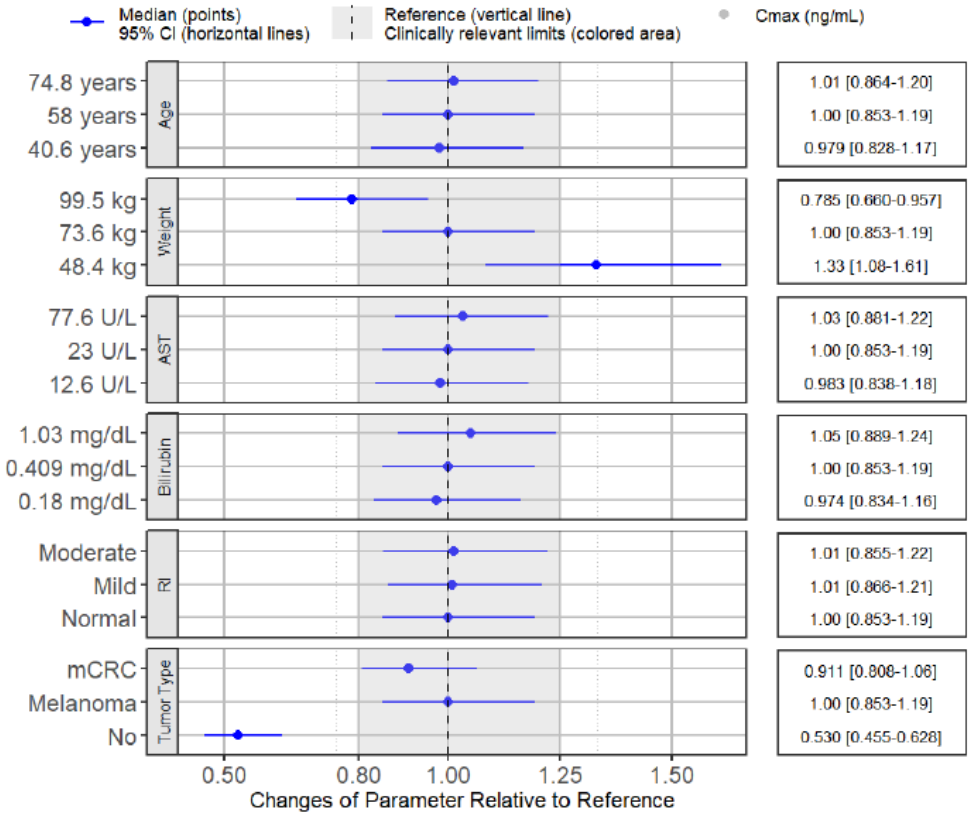
Goodness-of-fit of the final population PK model of binimetinib is presented in Figure 6.

Figure 6 Final Population PK Model of Binimetinib - Goodness-of-Fits



LOESS = locally weighted scatter plot smoothing; PK= pharmacokinetics;
Note: Blue lines represent LOESS and black lines represent the identity line

Figure 5 Forest Plot – Covariate Effects on Binimetinib Exposure (Cmaxss)



Simulations were performed based on bootstrap outputs of the final population PK model and oral administration of 45 mg BID at steady-state conditions. The dots and the horizontal segments represent bootstrap-derived mean and 95% CI of covariate effect relative to the reference patient (i.e., a 58 years old patient with melanoma, normal renal function, having a bogy weight of 73.6 kg, an AST level of 23 U/L and bilirubin of 0.409 mg/dL). The shaded area represents effect size of 80% -125%.
AST= aspartate aminotransferase; CI= confidence interval; Cmax/Cmaxss= maximum concentration at steady-state; mCRC= metastatic colorectal cancer; RI=renal impairment

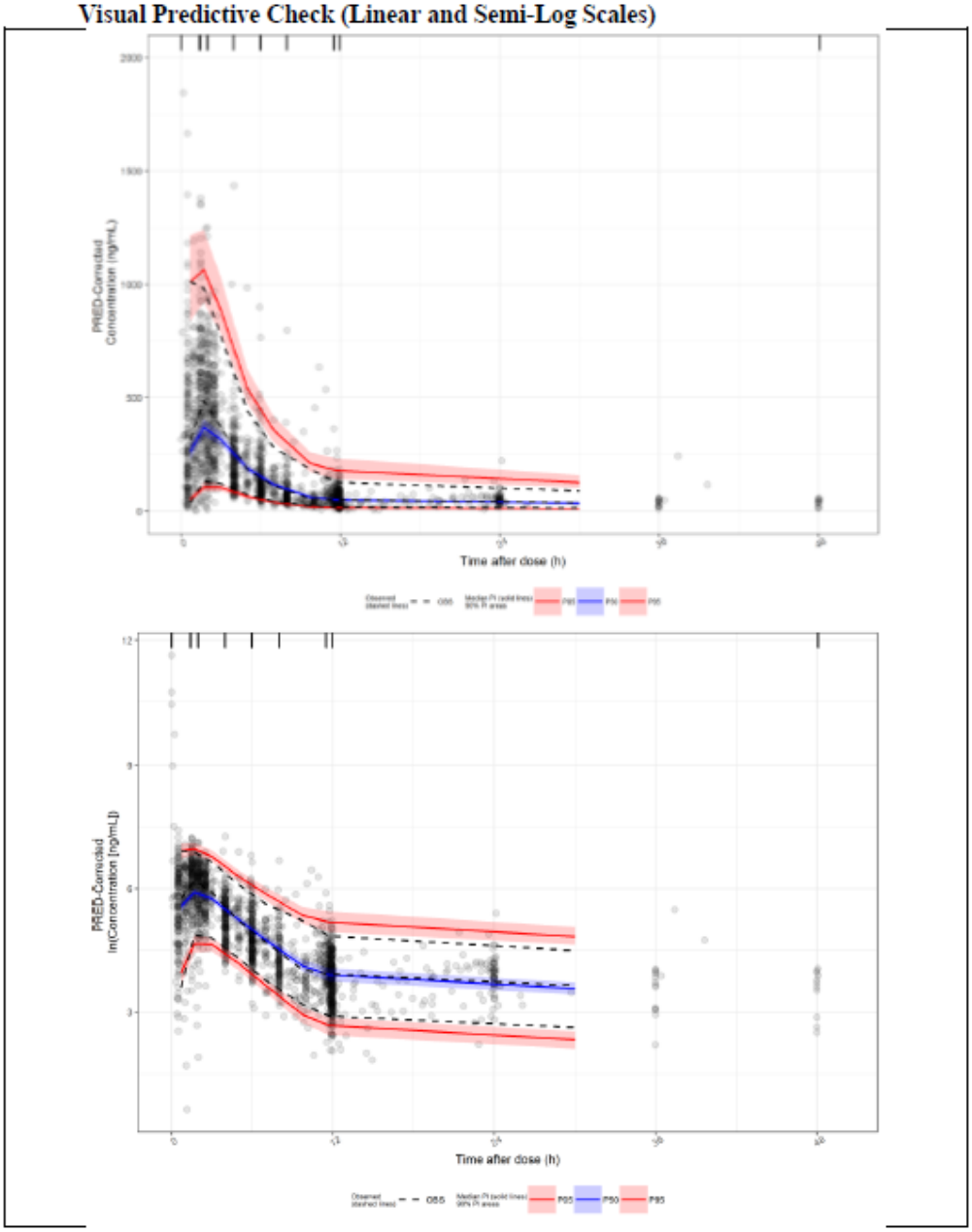
Forest plots for AUCss can be found in section on special populations.

In terms of categorical covariates, medians and 95% CI of renal function (moderate vs mild vs normal) and tumor type (mCRC vs melanoma) were within 80% and 125% relative to the reference patient. Healthy subjects would have significantly lower exposures comparing to reference with point estimates lower than 80% (i.e., point estimate equal to 76% for AUCss and 53% for Cmaxss).

In terms of continuous covariates, medians and 95% CI of the following covariate effects on AUCss and Cmaxss were within 80% and 125% relative to the reference patient: age, AST and BIL. Exposures of binimetinib (AUCss an Cmaxss) would significantly change with the body weight range included in BEACON study (i.e., 48.4 – 99.5 kg) with magnitude of effect greater than 20%; patients of 48.4 kg would have 29% and 33% higher AUCss and Cmaxss respectively relative to the reference patient whereas for patients of 99.5 kg, only Cmaxss of binimetinib is significantly affected with a point estimate of 0.785 for lower Cmaxss relative to the reference patient. However the 95%CI of these estimates are inclusive of the 80% - 125%, suggesting a lack of clinical significance. In addition no trends were observed in individual PK parameters (CL/F, V/F and Ka) regarding the race/ethnic covariates.

The covariates included in this new binimetinib population PK analysis are similar to the covariates included in the previous ones (CP17-004, CP17-004A1 and CP16-001) except for the albumin which was included on CL/F and V/F in the previous model, age also included on V/F in the previous model and AST on CL/F included in the current model. These modifications are deemed minor as they show low impact on PK parameters. In addition, the magnitude of the current covariates on PK parameters is close and not more impactful as in the previous model.

12.54. Final Population PK Model of Binimetinib - Goodness of Fit – Prediction Corrected Visual Predictive Check (Linear and Semi-Log Scales)



Bins are nominal time
Blue shade area: 95% confidence interval (CI) of simulated median within each bin.
Red shade area: 95% CI of simulated 5th and 95th percentiles within each bin.

The final population PK model was used to derive rich concentration-time profiles and exposure parameters were derived according to the randomized dose in patients enrolled in all studies. Simulations were derived based on steady-state conditions.

In the current analysis, lower Cmaxss and Cminss were observed. In the previous analysis, mean and median of Cmaxss were 692 ng/mL and 677 ng/mL, respectively and mean and median of Cminss were 38.3 ng/mL and 36.0 ng/mL, respectively. Higher predicted Cmaxss in the previous analysis (i.e., ~63% higher than the current analysis) may be explained by the structure of the absorption model which was a zero-order rate of absorption.

- **Cetuximab**

A population PK analysis was performed on cetuximab concentration data in order to evaluate any effect of encorafenib and binimetinib on cetuximab PK profiles and to provide predicted individual exposures for exposure-response analyses. A total of 261 patients with mCRC received intravenous (IV) administration of cetuximab in control, in doublet and triplet arms in BEACON study. In control groups, cetuximab was administered with irinotecan or Folfiri (folinic acid, fluorouracil and irinotecan), in doublet with 300 mg QD of encorafenib and in triplet with 300 mg QD of encorafenib and 45 mg BID of binimetinib. Initial IV administration of cetuximab was a 120-min IV infusion of 400 mg/m2 followed by 60-minute IV infusion of 250 mg/m2 once weekly.

The PK population included 136 (52.1%) male and 125 (47.2%) female patients, mainly of White origin (83.1%). Over the 261, 99 (37.9%) patients were treated with cetuximab in control arms, 69 (26.4%) patients were treated with cetuximab combined with encorafenib and 93 (35.6%) were treated with the triplet therapy of cetuximab combined to encorafenib and binimetinib. Amongst patients in BEACON study, 116 (44.4%) had a fully active life (i.e., ECOG score of 0) and 145 (55.6%) patients had a restricted physical activity (i.e., ECOG score of 1). A total of 136 subjects (52.1%) had normal renal function (CRCL ≥ 90 mL/min), while 98 (37.5%) patients presented mild renal impairment (CRCL from 60 to 89 mL/min), 25 (9.6%) patients moderate renal impairment (CRCL from 30 to 59 mL/min). The population PK model previously developed for cetuximab was a two-compartment linear disposition model with saturable elimination rate with a zero-order elimination constant.

A total of 15 PK samples were excluded due to unscheduled visit, measurable concentrations before the 1st dose and deviation on the PK sample collection. Due to the sparse PK samples collected in most of the patients in BEACON study, typical values of peripheral compartment (i.e., CL2 and V2) were fixed the values estimated by Azzopardi et al. Re-estimation of K0 value with the BEACON data significantly improved the overall fits (cetu2) and was thus retained as the structural model. The source of cetuximab (i.e., European versus US sources) was tested on CL but was not relevant. Variability on the peripheral parameters was not retained due to important shrinkage (i.e., >30%). The structural model resulted in adequate goodness of- fit, with three outlier concentrations observed on IPRED. Nevertheless, the model was deemed adequate by the company to evaluate the relations between PK parameters and covariates.

The final model included the following covariates
- CL: BSA and sex
- Vc: BSA and sex

The stability of the final population PK model was tested by using the non-parametric bootstrap approach where 600 samples were statistically evaluated. All covariates were statistically significant with null hypothesis excluded from the 95%CI, at the exception of BSA on V. No residual trend was observed with the final model of cetuximab. Population PK parameters of cetuximab derived with the final population PK model are presented in Table 12.

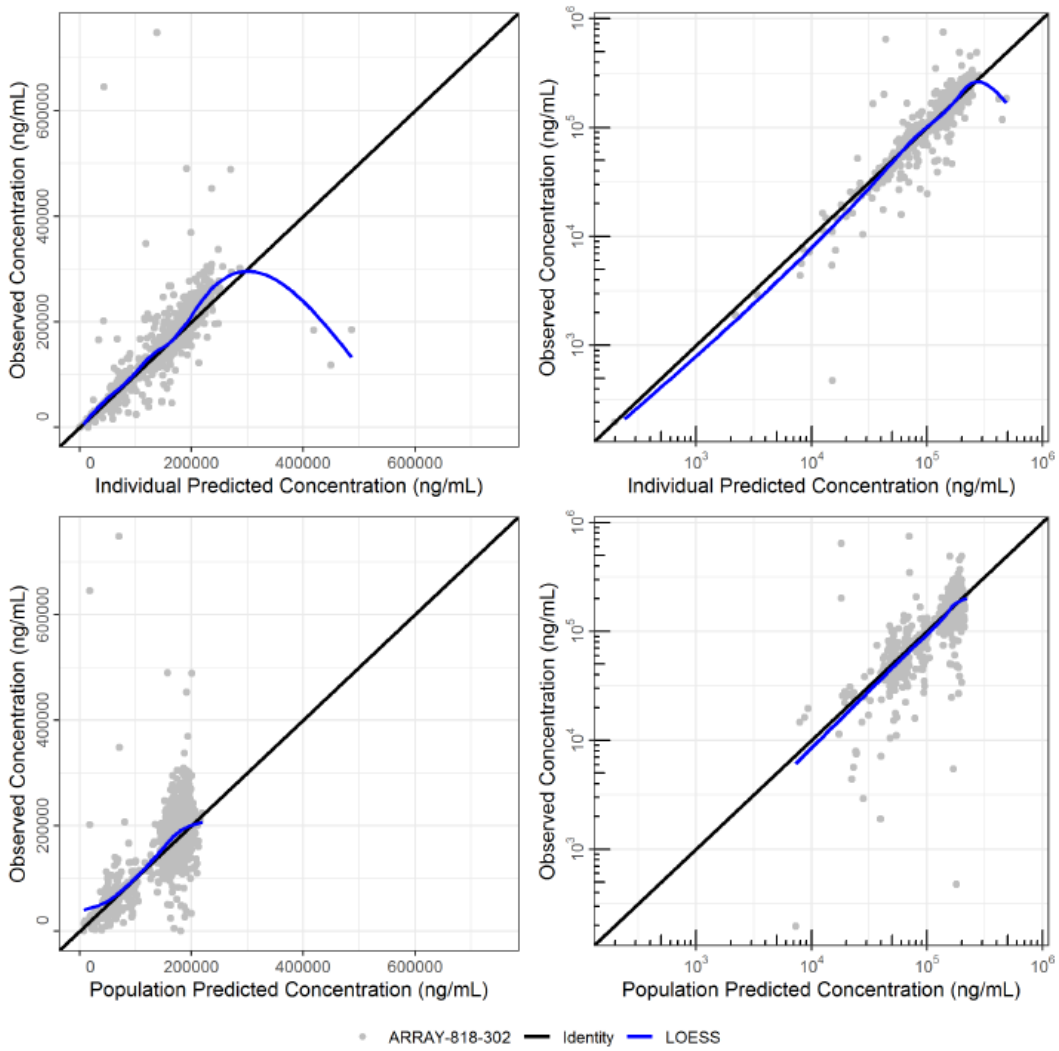
Table 12 Final Population PK Parameters of Cetuximab

Parameters	Estimates	%RSE	95% CI	
CL (L/h)	**0.0154**	**17.3**	**0.0114-0.0225**	
x $(BSA/1.8)^{theta}$	1.60	25.5	0.801-2.45	
x for Male Patients	1.33	7.79	1.15-1.55	
Vc (L)	**3.52**	**3.21**	**3.30-3.74**	
x $(BSA/1.8)^{theta}$	0.655	46.9	-0.00228-1.24	
x for Male Patients	1.14	5.23	1.03-1.26	
V2 (L)	**4.65**	-	-	
CL2 (L/h)	**0.0348**	-	-	
K0 (µg/h)	**631**	**34.1**	**0.380-896**	
Random effects	**Estimates (%)**	**%RSE**	**95% CI**	**Shrinkage (%)**
BSV on CL	33.9	21.2	0.0623-0.153	32.9
BSV on Vc	32.2	43	0.0309-0.181	18.6
Residual error	**Estimates**	**%RSE**	**95% CI**	
Log-additive Error	0.317	-	-	

*Bootstrap were performed on 600 resampling runs for final population PK model.
Note: 95%CI were derived from the bootstrap results.
BSA= body surface area; CI = confidence interval; CL = clearance; CL2 = inter-compartmental clearance; K0= zero-order elimination constant; RSE = relative standard error; Vc = central volume of distribution; V2 = peripheral volume of distribution

Goodness-of-fit of the final population PK model of cetuximab is presented in Figure 8.

Figure 8 Final Population PK Model of Cetuximab - Goodness-of-Fits

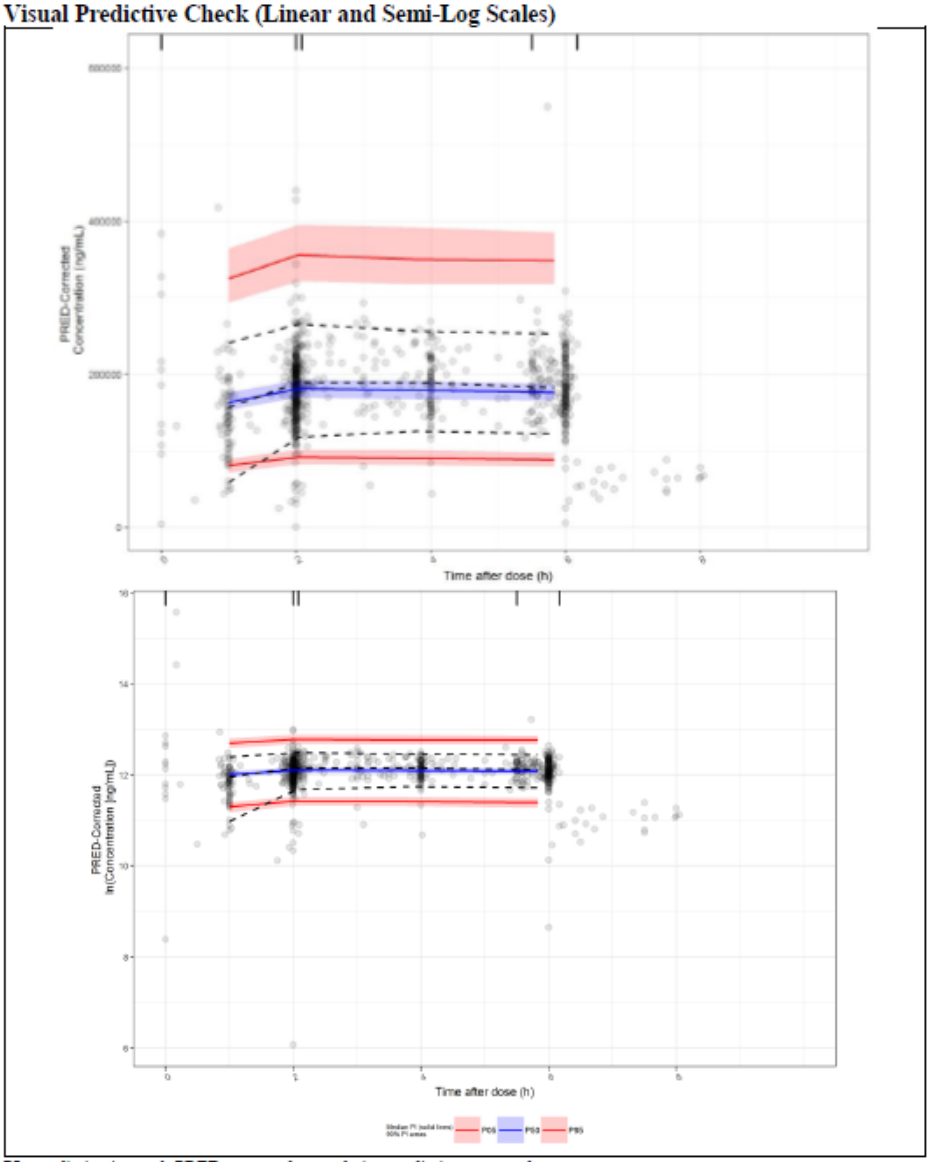


LOESS = locally weighted scatter plot smoothing; PK= pharmacokinetics;
Note: Blue lines represent LOESS and black lines represent the identity line

A small bias for three PK samples of cetuximab with high IPRED and lower DV. With the exception of those points, for the overall range of cetuximab, the overlay of the LOESS fit for the observed, individual predicted and population predicted support the agreement with the model predicted and observed data.

A pcVPC for the final model is shown in figure 13.50.

13.50. Final Population PK Model of Cetuximab - Goodness of Fit – Prediction Corrected Visual Predictive Check (Linear and Semi-Log Scales)

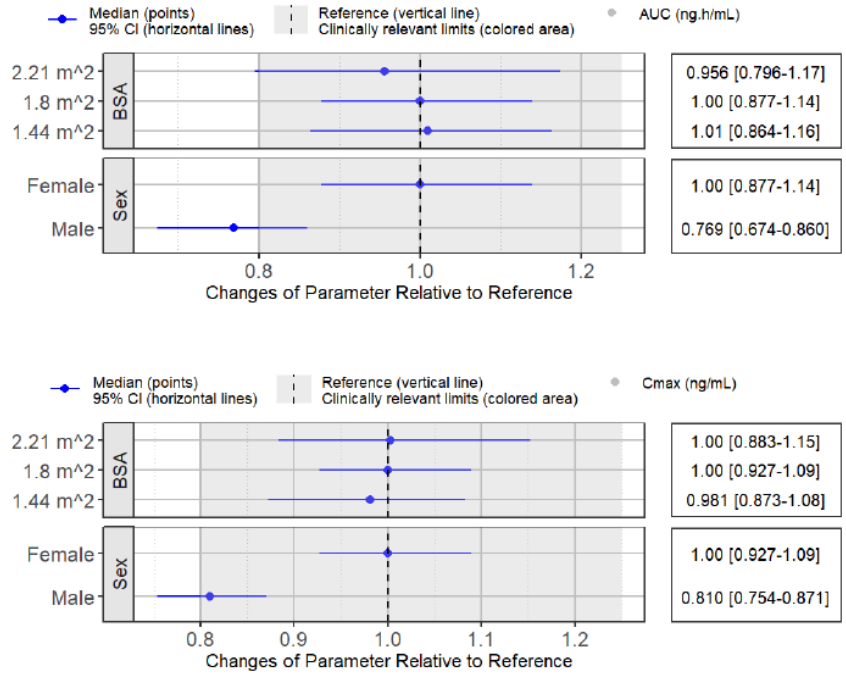


PI= prediction interval; PRED-corrected= population prediction corrected
Blue shade area: 95% PI of simulated median within each bin.
Red shade area: 95%PI of simulated 5th and 95th percentiles within each bin.

Distributions of estimates in covariate effects derived with the bootstrap were used to evaluate the relevance of covariate effects (mean and 95% CI) on the relative changes in exposures of cetuximab at steady-state (AUCss and Cmaxss) based on the demographic data in BEACON study relative to the reference patient (i.e., a female patient with body surface area of 1.8 m^2).

The magnitude of effect of each covariate on CL based on the final model is depicted using a tornado plot and the magnitude and covariate effects on AUCss and Cmaxss in patients from BEACON study are presented in Figure 7.

Figure 7 Forest Plot –Covariate Effects on Cetuximab Exposures (AUCss and Cmaxss)



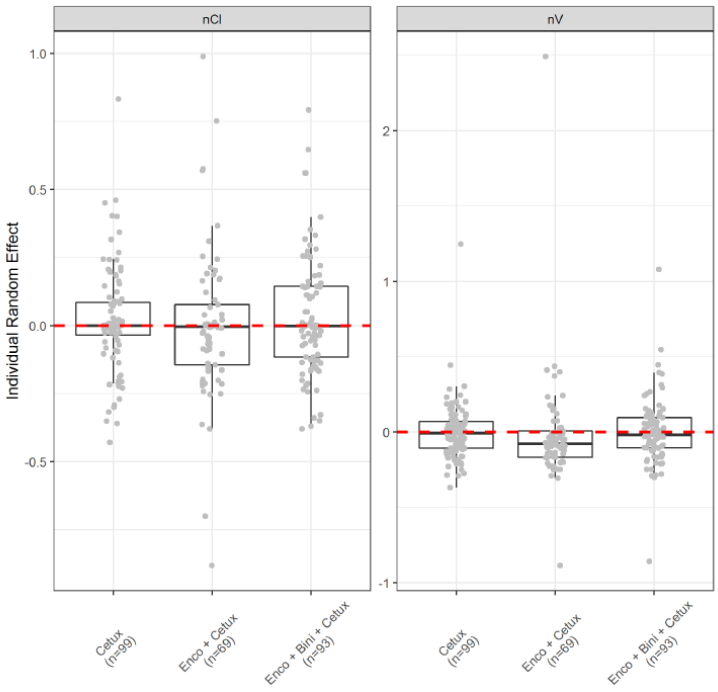
Simulations were performed based on bootstrap outputs of the final population PK model and 1-h IV infusion of 250 mg/m^2 at steady-state conditions. The dots and the horizontal segments represent bootstrap-derived mean and 95% CI of covariate effect relative to the reference patient (i.e., a female patient with a body surface area of 1.8m^2). The shaded area represents effect size of 80% -125%.
AUC/AUCss= area under the concentration-time curve at steady-state; BSA= body surface area; CI= confidence interval; Cmax/Cmaxss= maximum concentration at steady-state

In terms of categorical covariates, male patients would have significantly lower cetuximab exposures to the reference patient with point estimates lower than 80% (i.e., 76.9% lower for AUCss).

In terms of continuous covariates, medians and 95% CI of BSA effects on AUCss and Cmaxss were within 80% and 125% relative to the reference patient.

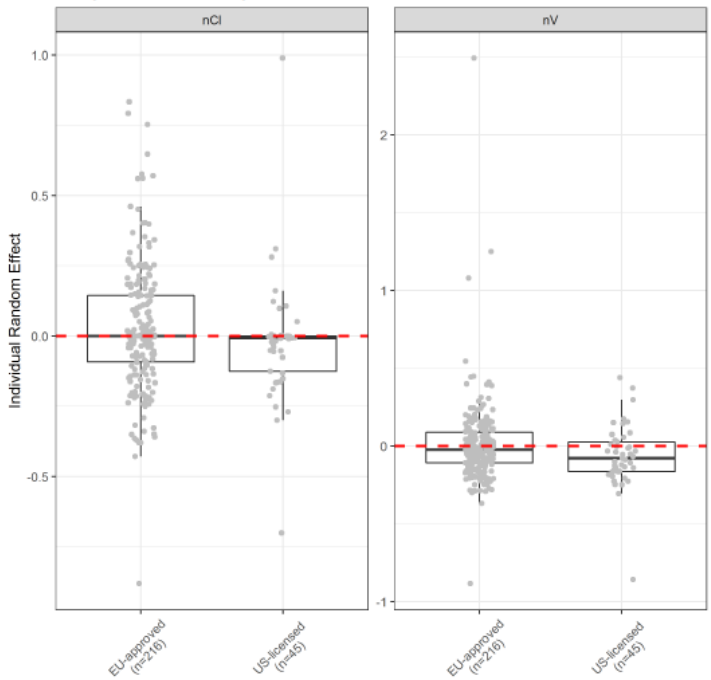
Relationships between individual and individual random effects of PK parameters derived with the final population PK model of cetuximab versus covariates are presented in a scatter matrix plots and boxplots.

13.31. Final Population PK Model of Cetuximab - Sources of Variability – Categorical Covariates (Drug-Drug Interaction)



Bini=binimetinib; Cetux=cetuximab; Enco=encorafenib; n=number of subjects; nCl= individual random effect of apparent clearance; nV= individual random effect of apparent central volume of distribution; PK= pharmacokinetic

13.30. Final Population PK Model of Cetuximab - Sources of Variability – Categorical Covariates (Cetuximab Source)



n=number of subjects; nCl= individual random effect of apparent clearance; nV= individual random effect of apparent central volume of distribution; PK= pharmacokinetic

Pharmacokinetics in target population

- **Encorafenib**

Study CLGX818X2103

Geometric mean exposure parameters increased with an increased dose, with moderate to high inter-subject variability. On Cycle 2 Day 1, the AUC_{tau} accumulation ratio (R_{AUC}) of encorafenib was below 1 across all dose ranges (except the lowest dose 100 mg QD), which is consistent with the auto-induction of encorafenib clearance.

Table 2 Pharmacokinetics of encorafenib in combination with cetuximab after single and multiple QD doses

Dose and Regimen (N)	Pharmacokinetic Parameter on Cycle 1 Day 1[a]						
Parameter Unit	C_{max} (ng/mL)	T_{max} (h)	AUC_{tau} (ng.h/mL)	$T_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)	
100 mg QD (2)	1110 (44.9)	2.00 [1.98, 2.02]	5930 (22.5)	4.28 (5.86)	16.6 (21.9)	102 (28.0)	
200 mg QD (6) Phase Ib	3460 (55.3)	1.99 [0.97, 2.05]	19300 (63.9)	3.72 (28.3)	10.2 (64.4)	54.9 (53.5)	
200 mg QD (17) Phase II	2970 (38.8)	2.00 [0.93, 6.12]	16300 (41.5)	3.33 (23.7)	12.2 (41.9)	58.6 (41.3)	
400 mg QD (9)	5130 (53.2)	2.03 [1.00, 4.00]	36700 (40.1)	3.59 (8.51)	11.2 (41.5)	57.7 (42.9)	
450 mg QD (7)	6360 (74.9)	2.17 [1.00, 5.97]	39700 (54.4)	3.15 (25.6)	11.2 (54.1)	51.0 (59.3)	
Dose and Regimen (N)	**Pharmacokinetic Parameter on Cycle 2 Day 1 (28-day Cycle)**						
Parameter Unit	**$C_{max,ss}$ (ng/mL)**	**$T_{max,ss}$ (h)**	**$AUC_{tau,ss}$ (ng.h/mL)**	**$T_{1/2,ss}$ (h)**	**CL/F (L/h)**	**V_z/F (L)**	**R_{AUC}**
100 mg QD (2)	1410 (57.4)	1.51 [1.00, 2.02]	7440 (35.8)	3.41 (14.2)	13.4 (35.8)	66.1 (20.9)	1.25 (61.9)
200 mg QD (5) Phase Ib	1500 (45.8)	2.00 [1.00, 4.03]	6830 (42.5)	2.96 (39.5)	29.3 (42.5)	125 (39.0)	0.299 (40.7)
200 mg QD (11) Phase II	2120 (56.9)	1.15 [0.98, 5.93]	7430 (33.6)	2.86 (29.3)	26.9 (33.6)	111 (38.3)	0.481 (38.8)
400 mg QD (6)	3590 (21.7)	1.98 [0.97, 4.00]	12700 (7.04)	2.26 (47.1)	31.6 (7.04)	103 (46.6)	0.297 (39.5)
450 mg QD (7)	4210 (62.9)	1.98 [1.05, 2.05]	15700 (37.2)	3.02 (20.1)	28.7 (37.2)	125 (59.1)	0.594 (36.8)

Dose proportionality was assessed over the encorafenib dose range of 100 mg to 450 mg QD administered with cetuximab. On C2D1, encorafenib exposure increased in a less than proportional manner for AUCtau.

Table 3 Dose proportionality analysis for encorafenib in combination with cetuximab

Dose Range	Visit	PK Parameter (unit)	N[1]	Estimate of Beta	90% Confidence Interval
100 mg to 450 mg	Cycle 1 Day 1	AUCtau (h*ng/mL)	22	1.15	(0.797, 1.51)
		Cmax (ng/mL)	24	0.962	(0.551, 1.37)
	Cycle 2 Day 1	AUCtau,ss (h*ng/mL)	16	0.606	(0.311, 0.900)
		Cmax,ss (ng/mL)	20	0.896	(0.536, 1.26)

Study ARRAY-818-302

PK Data from 267 subjects were available from the BEACON CRC study, with 37 subjects from the Safety Lead-in portion and 230 subjects from the randomized portion. Data were analysed with non-compartmental analysis (**report CP19-14**), and included in the popPK model T2019-00141.

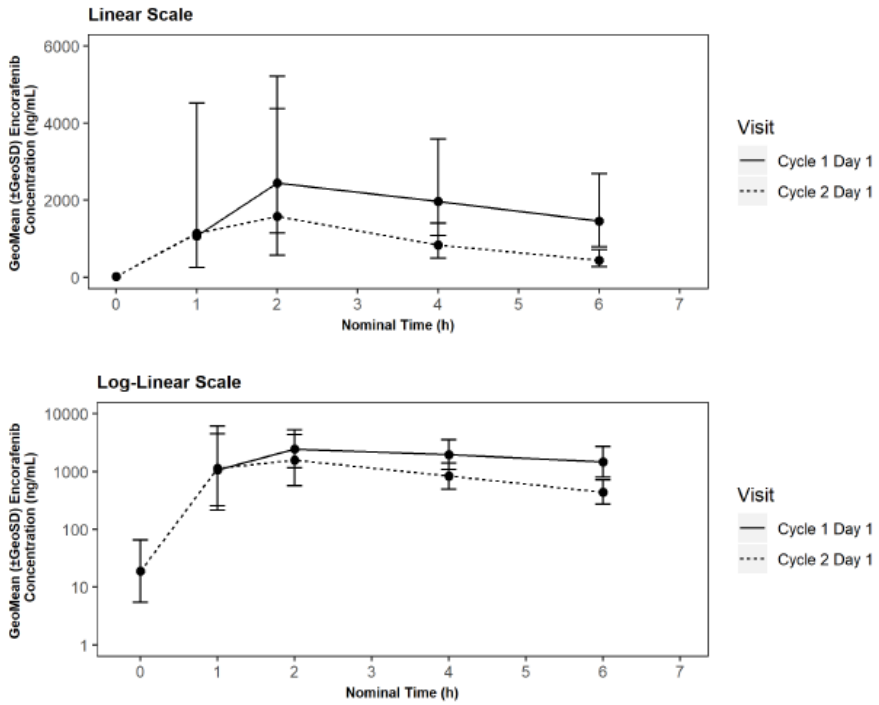
The GeoMean plasma/serum concentration-time profiles from the safety lead-in part for each analyte and visit are presented below. With variability taken in consideration, GeoMean concentrations were similar between the two visits (C1D1 and C2D1) for binimetinib and cetuximab and slightly lower at C2D1 for AR00426032 and encorafenib. Due to the limited sampling schedule, the elimination phase was not well characterized for many subjects. The elimination phase dependent results (ie. AUCinf, LambdaZ, Half-life) only reflect less than half of the cohort, at best, and any conclusions based on this data should take this into consideration [data not shown].

Table 4 Summary of Main PK Parameters – Combined Safety Lead In

Visit	Analyte	Statistics	C_{max}	AUC_{last}	T_{max}
			ng/mL	hr*ng/mL	hr
C1D1	Binimetinib	n	35	35	35
		GeoMean (Geo CV%)	654 (50.8)	1960 (43.6)	1.98 [0.883-5.67]*
	AR00426032	n	35	35	35
		GeoMean (Geo CV%)	59.9 (50.8)	206 (46.7)	2.00 [0.883-5.78]*
	Encorafenib	n	34	34	34
		GeoMean (Geo CV%)	3360 (65.1)	11300 (61.5)	2.00 [0.883-6.25]*
	Cetuximab	n	34	34	34
		GeoMean (Geo CV%)	195000 (22.2)	841000 (22.2)	3.77 [1.83-6.05]*
C2D1	Binimetinib	n	26	26	26
		GeoMean (Geo CV%)	524 (70.1)	1540 (44.7)	1.04 [0.900-4.00]*
	AR00426032	n	26	26	26
		GeoMean (Geo CV%)	20.5 (119)	70.0 (95.5)	1.58 [0.933-6.52]*
	Encorafenib	n	29	29	29
		GeoMean (Geo CV%)	2490 (75.6)	6660 (61.7)	2.00 [0.950-5.73]*
	Cetuximab	n	32	32	32
		GeoMean (Geo CV%)	199000 (26.8)	970000 (20.6)	3.05 [1.00-6.17]*

AUC_{last} = area under the plasma concentration-time curve from zero to the last measurable time point; C_{max} = maximum concentration; GeoCV% = geometric coefficient of variation; GeoMean = geometric mean; T_{max} = observed time of C_{max}.
Source: Appendix I section 3

Encorafenib



Source: Report CP19-014, Fig. 2

For the randomized Phase 3 at C2D1, the GeoMean (GeoCV%) concentration of encorafenib at 2 hours post-dose, i.e. ~Tmax, in the Doublet was 1550 ng/mL(143%). In the Triplet, the GeoMean concentration was 969 ng/mL (273%). GeoMean predose concentrations were 12.4 ng/mL (139%) in the doublet and 23.3 ng/mL (375%) in the triplet.

Table 5 Exposure Parameters of Encorafenib by Dose and Study in Patients with mCRC after Repeated Administration of Encorafenib QD

PK Parameters	BEACON	CLGX818X2103		
	300 mg (N=164)	200 mg (N=42)	400 mg (N=9)	450 mg (N=8)
AUCss (µg.h/mL)				
Mean (CV%,SD)	7.96 (29.2%, 2.32)	6.06 (37.6%, 2.28)	10.2 (26.7%, 2.72)	12.1 (42.9%, 5.21)
Median [Min, Max]	7.58 [1.55, 16.7]	5.32 [3.13, 11.9]	9.45 [6.70, 14.3]	11.1 [7.75, 23.6]
GeoMean (GeoCV%)	7.64 (30.2%)	5.70 (36.3%)	9.84 (27.3%)	11.4 (38.5%)
Maximum Concentration at steady-state (ng/mL)				
Mean (CV%,SD)	1556 (33.0%, 514)	1147 (41.1%, 472)	2056 (38.0%, 782)	2414 (57.6%, 1390)
Median [Min, Max]	1592 [195, 3428]	1066 [265, 2017]	2145 [1045, 3037]	2103 [1026, 5561]
GeoMean (GeoCV%)	1452 (42.9%)	1042 (49.4%)	1916 (42.6%)	2148 (53.2%)
Minimum Concentration at steady-state (ng/mL)				
Mean (CV%,SD)	17.9 (138%, 24.7)	15.6 (106%, 16.6)	14.2 (49.0%, 6.96)	23.1 (81.7%, 18.9)
Median [Min, Max]	11.4 [0.296, 194]	8.50 [1.93, 87.9]	13.6 [6.21, 26.9]	14.5 [6.38, 55.5]
GeoMean (GeoCV%)	12.2 (94.7%)	10.3 (110%)	12.8 (51.2%)	17.1 (101%)

AUCss= area under the concentration-time curve at steady-state; CV = coefficient of variation; GeoCV = geometric coefficient of variation; GeoMean = geometric mean; QD= once daily; Max= maximum; Min= minimum; N= number of subjects; PK= pharmacokinetic; SD= standard

Note: Descriptive statistics of subjects with dose of 100 mg (N=2) are not presented

Source: popPK report T2019-00141, Tab. 5

- **Binimetinib**

In the SLI phase a small decrease in exposure at steady state was noted and is not considered meaningful due to moderately high variability that accompanies these results. At C2D1 in Phase 3, the 2 hours post-dose GeoMean concentration was 268 ng/mL (77.8%), the GeoMean predose concentration was 48.8 ng/mL (112%).

Lower exposure parameter values were observed for AR00426032 at Cycle 2, with lower exposures following multiple doses compared to a single dose (lower right figure).

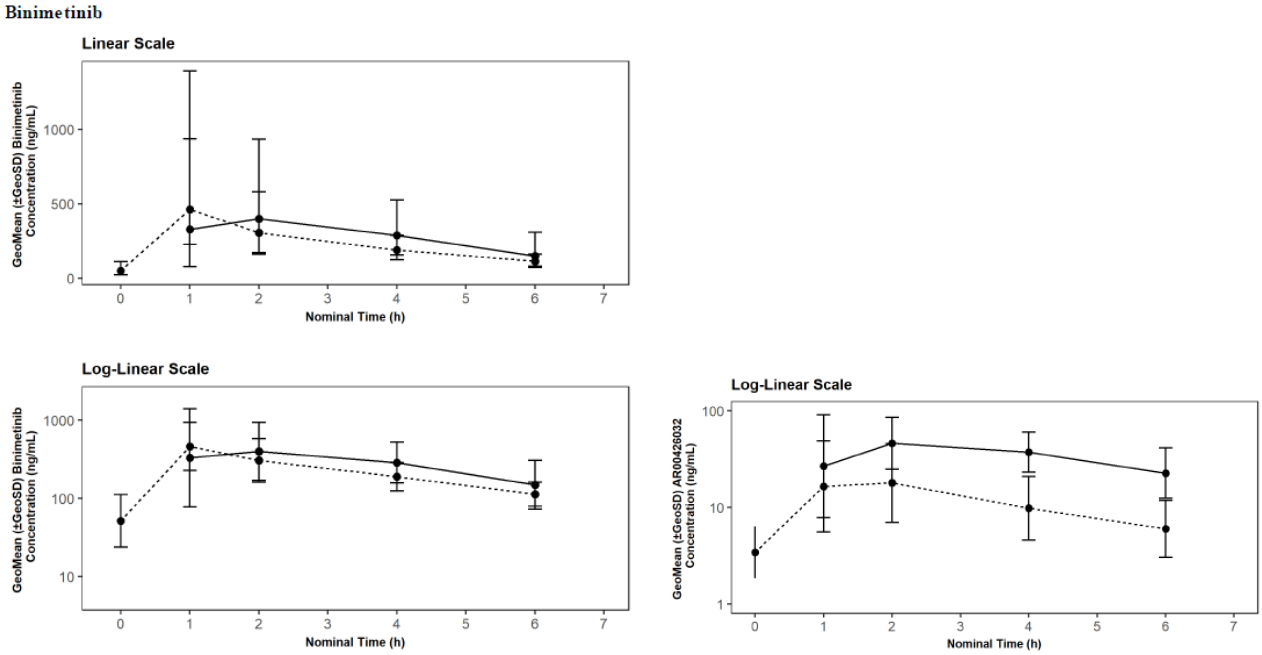


Table 6 Exposure Parameters of binimetinib by Dose and Study in Patients with mCRC after Repeated Administration

Exposure Parameters	BEACON (N=93)
AUCss (µg.h/mL)	
Mean (CV%,SD)	2.55 (30.2%, 0.768)
Median [Min, Max]	2.39 [1.23, 5.48]
GeoMean (GeoCV%)	2.44 (29.2%)
Maximum Concentration at steady-state (ng/mL)	
Mean (CV%,SD)	424 (35.1%, 149)
Median [Min, Max]	414 [66.9, 717]
GeoMean (GeoCV%)	393 (44.3%)
Minimum Concentration at steady-state (ng/mL)	
Mean (CV%,SD)	22.9 (57.4%, 13.2)
Median [Min, Max]	18.4 [5.21, 75.3]
GeoMean (GeoCV%)	19.9 (57.6%)

AUCss= area under the concentration-time curve at steady-state; BID= twice daily; CV = coefficient of variation; GeoCV = geometric coefficient of variation; GeoMean = geometric mean;Max= maximum; Min= minimum; N= number of subjects; PK= pharmacokinetic; SD= standard

Source: popPK report T2019-00141, Tab. 9

- **Cetuximab**

Cetuximab's mean concentrations were slightly higher at C2D1 with approximately 15% compared to C1D1, with the total loading dose amount given at C1D1 was higher than the maintenance dose at C2D1 (400 mg/m^2 and 250 mg/m^2, respectively). The GeoMean Cmax was relatively similar between the two visits. Geometric mean Cmax [199 µg/mL (26.8%)] in the CSLI portion was comparable to the mean value reported in Tabernero, 2010 [210 µg/mL (54%)]. Cmin for the Phase 3 at C2D1 was 46200 ng/mL

(66.6%) in the control, 54500 ng/mL (103%) in the doublet and was 52800 ng/mL (47.2%) in the triplet arm.

The population estimates of CL and Vc for cetuximab were 0.0154 L/h (i.e., 0.370 L/day) and 3.52 L, respectively. Based on the population PK model, half-life values associated with t1/2α and t1/2β phases of cetuximab were 34.4 h and 17.7 days, respectively. Total volume of distribution was 8.17 L (i.e., 3.52 + 4.65 L).

Cetuximab

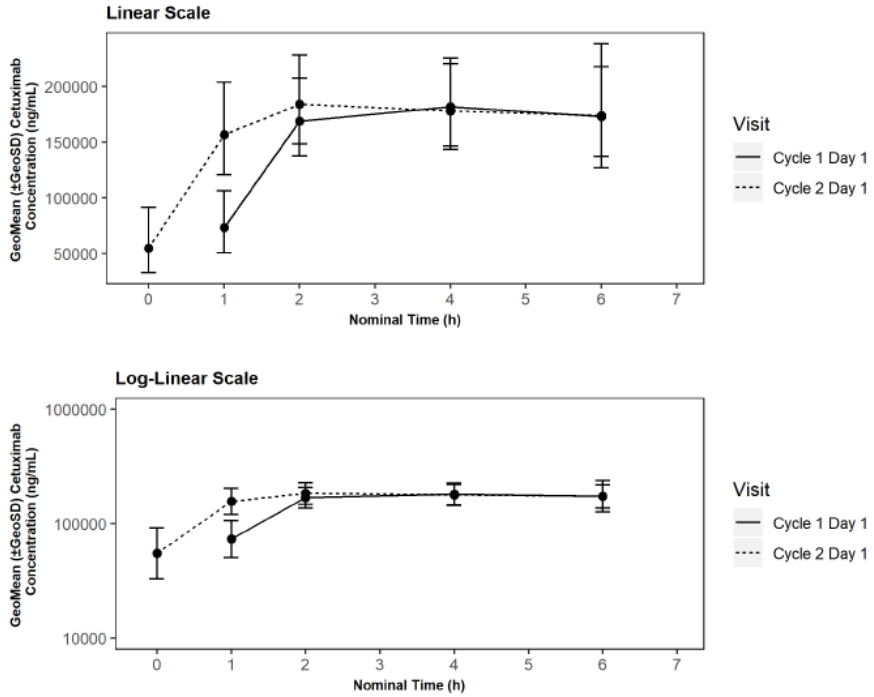


Table 7 Exposure Parameters of cetuximab by Dose and Study in Patients with mCRC after Repeated Administration

Exposure Parameters	Safety Lead-In	Phase III		
	ENCO+ BINI + CETUX (N=37)	ENCO+ BINI + CETUX (N=56)	ENCO+ CETUX (N=69)	CETUX (N=99)
AUCss (µg.h/mL)				
Mean (CV%,SD)	12382 (39.4%, 4879)	13139 (32.0%, 4205)	13484 (43.5%, 5862)	13795 (38.4%, 5302)
Median [Min, Max]	12980 [3.36e-06, 23925]	13678 [3143, 32075]	12723 [2058, 36788]	12580 [3845, 32370]
GeoMean (GeoCV%)	3807 (NC)*	12459 (35.7%)	12338 (46.3%)	12958 (36.3%)
Maximum Concentration (µg/mL)				
Mean (CV%,SD)	118 (31.2%, 36.8)	135 (26.8%, 36.2)	137 (33.7%, 46.1)	134 (25.5%, 34.1)
Median [Min, Max]	121 [1e-08, 171]	137 [75.2, 314]	137 [21.2, 375]	127 [58.8, 261]
GeoMean (GeoCV%)	34.8 (NC%)*	131 (24.8%)	129 (38.0%)	130 (24.5%)
Minimum Concentration (µg/mL)				
Mean (CV%,SD)	10.1 (81.6%, 8.27)	10.0 (83.2%, 8.35)	11.4 (101%, 11.5)	11.8 (95.0%, 11.2)
Median [Min, Max]	9.92 [1e-08, 32.1]	10.2 [1e-08, 52.3]	8.66 [1e-08, 58.8]	8.94 [1e-08, 64.9]
GeoMean (GeoCV%)	1.34 (NC%)	1.36 (NC%)	1.10 (NC%)	3.82 (NC%)

AUCss= area under the concentration-time curve at steady-state; Bini=binimetinib; Cetux=cetuximab; CV = coefficient of variation; Enco=encorafenib; GeoCV = geometric coefficient of variation; GeoMean = geometric mean; Max= maximum; Min= minimum; N= number of subjects; NC=not calculated; PK= pharmacokinetic; SD= standard

Note : GeoCV% were set to NC due to two subjects (ARRAY-818-302-4503-1013, ARRAY-818-302-5402-1025) who were treated with small dose of cetuximab.

Source: popPK report T2019-00141, Tab. 13

PopPK report CP19-013

External visual predictive checks (VPC) for encorafenib, binimetinib and cetuximab were performed to evaluate a potential drug-drug interaction between the binimetinib-encorafenib combination with cetuximab, as well as to assess differences between the mCRC and melanoma populations. The median, 5th and 95th percentiles of observed concentrations from the ARRAY-818-302 study and simulated concentrations using a published model (cetuximab) and prior models generated with a population of patients with melanoma (binimetinib and encorafenib) are in good agreement. No major differences in the observed data, relative to the simulated data, suggest that a clinically relevant interaction between binimetinib, encorafenib and cetuximab is unlikely. Additionally, there are no major differences observed in the colorectal population in BEACON-CRC relative to the model that was constructed from a majority of melanoma patients simulated as part of the external VPC. These results support the conclusion that there is no clinically relevant disease effect on the PK of binimetinib, AR00426032 or encorafenib.

Special populations

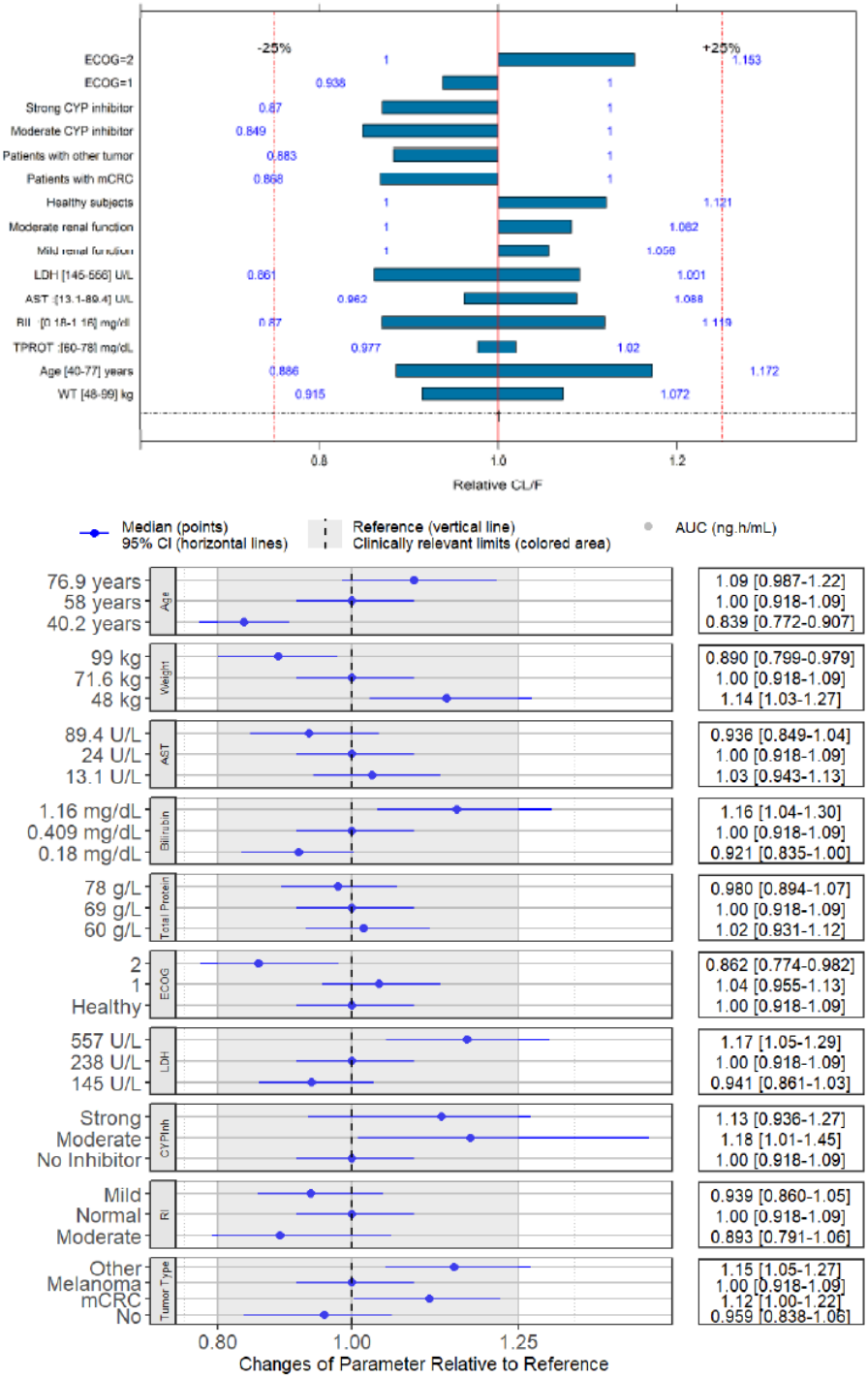
PopPK modelling report T2019-00141

When comparing with the encorafenib models performed in patients with melanoma, most of the covariates included in this new analysis are similar to the covariates included in the improved model of encorafenib (T2019-00140) and the previous one (T2017-01151) except for the body weight which was not included on Ka and V/F in the current model and potential effect of disease status (mCRC vs melanoma vs other tumours vs healthy) which was quantified. Based on the 95% CI calculated by bootstrap, all the included covariate effects were statistically significant except the effects of AST, renal impairment and strong CYP3A4 inhibitors on CL/F and the effect of age on V/F.

- **Encorafenib**

In the final model CYP3A4 inhibitor effects and age accounted for the largest contribution of variability in CL/F. All covariate effects had no significant impact on PK exposures (AUC_{ss} and C_{maxss}) of encorafenib with point estimates within 80% and 125% relative to the reference patient. None of the included covariates appear to be clinically relevant based on this analysis since all point estimates were lower than 20%.

Figure 1 Final PopPK Model: Range of Covariate Effects on CL/F and AUC of Encorafenib



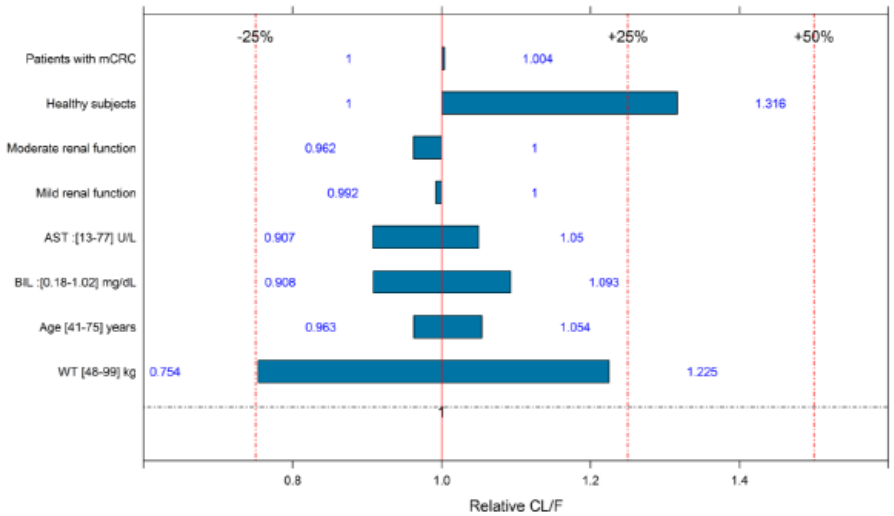
The dots and the horizontal segments represent bootstrap-derived mean and 95% CI of covariate effect relative to the reference patient (i.e., a 58 years old, fully active melanoma patient with normal renal function, having a bogy weight of 71.6 kg, an AST level of 24 U/L, Bilirubin of 0.409 mg/dL, LDH of 238 U/L, total protein level of 69 g/L and not treated with CYP inhibitor). The shaded area represents effect size of 80% -125%.
AST= aspartate aminotransferase; AUC= area-under the curve under steady-state; CI= confidence interval; ECOG= Eastern Cooperative Oncology Group status; LDH=lactate dehydrogenase; mCRC= metastatic colorectal cancer; RI=renal impairment.
Note: missing values were not considered in the distribution.

- **Binimetinib**

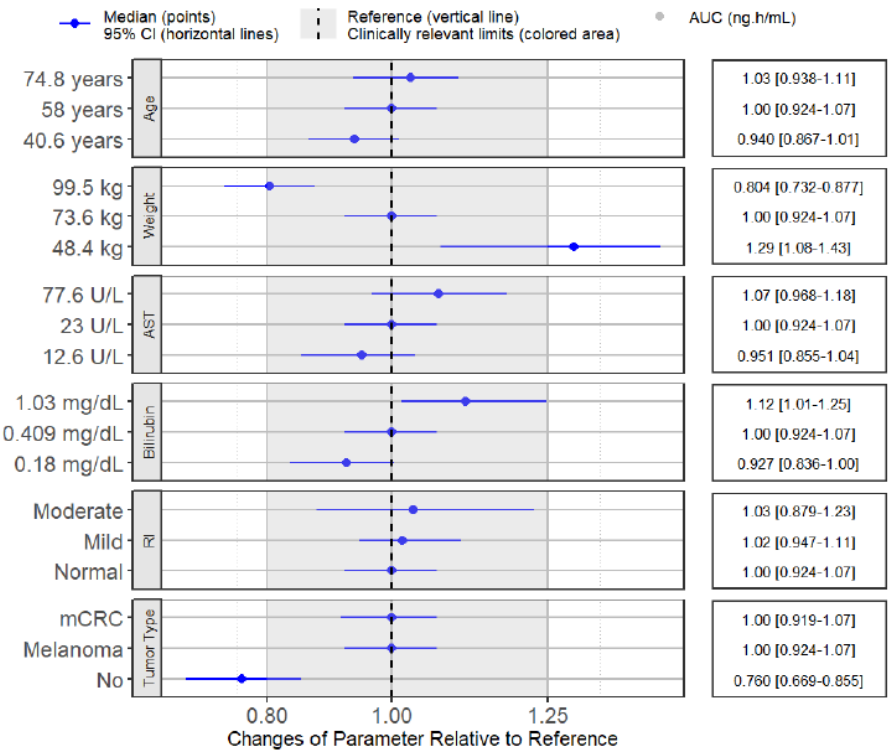
In terms of continuous covariates, medians and 95% CI of the following covariate effects on AUC_{ss} and C_{maxss} were within 80% and 125% relative to the reference patient: age, AST and BIL. Exposures of binimetinib (AUC_{ss} and C_{maxss}) would significantly change with the body weight range included in BEACON study: patients of 48.4 kg would have 29% and 33% higher AUC_{ss} and C_{maxss} respectively relative to the

reference patient; whereas patients of 99.5 kg, only C_{maxss} of binimetinib is significantly affected with a point estimate of 0.785 for lower C_{maxss}. However, the 95%CI of these estimates are inclusive of the 80% - 125%, suggesting a lack of clinical significance.

Figure 2 Final PopPK Model: Range of Covariate Effects on CL/F and AUC of Binimetinib



AST = aspartate aminotransferase (U/L); BIL= bilirubin (mg/dL); CL/F = Apparent clearance; mCRC= metastatic colorectal cancer; WT = body weight (kg).
Note 1: blue distribution represent the typical effect of each covariate for each category or each percentile



The dots and the horizontal segments represent bootstrap-derived mean and 95% CI of covariate effect relative to the reference patient (i.e., a 58 years old, fully active melanoma patient with normal renal function, having a bogy weight of 71.6 kg, an AST level of 24 U/L, Bilirubin of 0.409 mg/dL, LDH of 238 U/L, total protein level of 69 g/L and not treated with CYP inhibitor). The shaded area represents effect size of 80% -125%.
AST= aspartate aminotransferase; AUC= area-under the curve under steady-state; CI= confidence interval; mCRC= metastatic colorectal cancer; RI=renal impairment
Note: missing values were not considered for the distribution.

- **Cetuximab**

In terms of categorical covariates, male patients would have significantly lower cetuximab exposures to the reference patient [female patient with a body surface area of 1.8m^2] with point estimates lower than 80% (i.e., 76.9% for AUCss).

- **Impaired renal function**

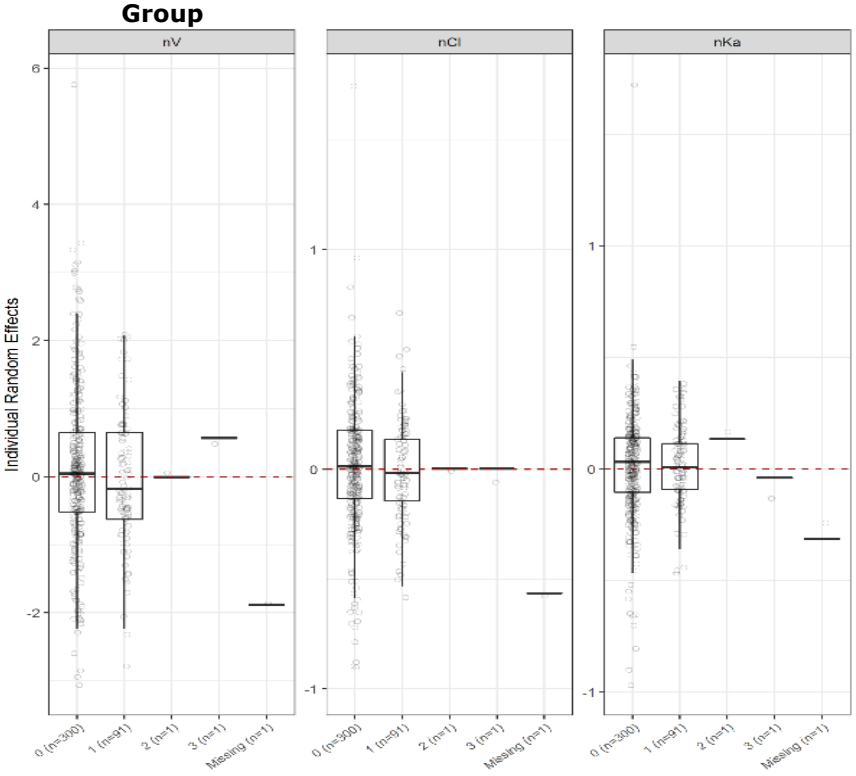
In the population PK performed with patients with mCRC (**T2019-00141**), mild (n=111) and moderate (n=30) renal impairment was assessed as a categorical covariate using Creatinine clearance (CLCR) calculated with Cockcroft-Gault method. Based on Forest plots, limited increase in **encorafenib** AUC and C_{max} were observed in patients with mild (CRCL from 60 to 89 mL/min) and moderate (CRCL from 30 to 59 mL/min) renal impairment (maximum difference of 11 %) compared to patients with normal renal function (n=251, CRCL ≥90 mL/min). No dose adjustment is recommended/required for subjects with mild or moderate renal impairment based on the population PK analyses. A recommended dose has not been established for subjects with severe renal impairment, and so encorafenib should be used with caution in these patients.

Based on Forest plots, no increase in **binimetinib** AUC and C_{maxss} was evident in patients with mild or moderate /severe (< 30 mL/min) renal impairment compared to subjects with normal renal function. No binimetinib dose adjustment is recommended/required for subjects with renal impairment.

- **Impaired hepatic function**

In the population PK analysis (**T2019-00141**), the covariate of hepatic impairment indicated no significant trend in **encorafenib** CL/F or V/F when comparing healthy subjects (N=300) with mild hepatic impairment subjects (N=91). Given the limited number of subjects available in the moderate and severe hepatic impairment categories (N=1 in each category), no evaluation could be performed in these groups.

Figure 3 Final PopPK Model of Encorafenib - Sources of Variability –NCI Organ Dysfunction Group

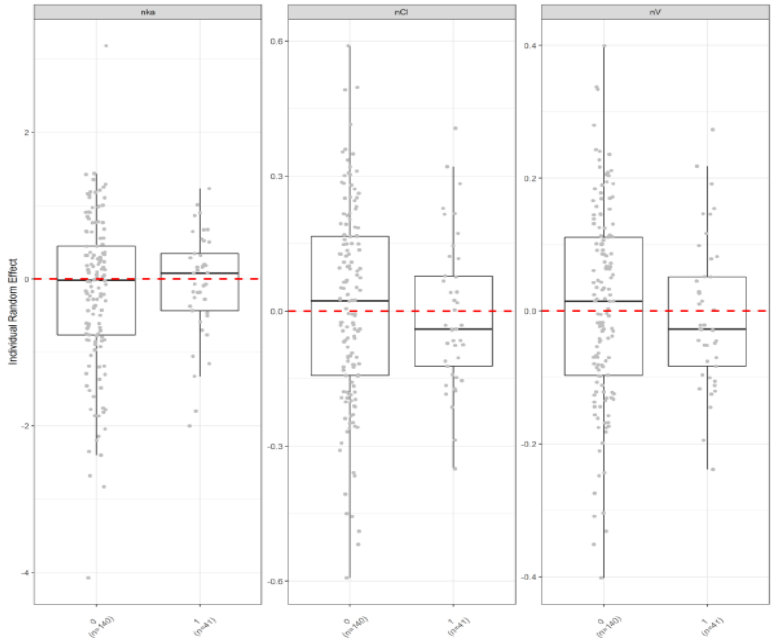


NCI : 0 = BIL ≤ ULN & AST ≤ ULN; 1 = (BIL ≤ ULN & AST > ULN) or (ULN < BIL ≤ 1.5 x ULN); 2 = 1.5 ULN < BIL ≤ 3 x ULN
AST= aspartate aminotransferase (U/L); BIL= bilirubin (mg/dL); n=number of subjects; NCI= National Cancer Institute Organ Dysfunction Working criteria; nCl= individual random effect of apparent clearance; nKa= individual random effect of first order rate of absorption; nV= individual random effect of apparent central volume of distribution; PK= pharmacokinetic; ULN= upper limit of normal

Based on the comparable safety and tolerability observed between mild HI patients and patients with normal hepatic function, encorafenib can be administered to mild HI patients with the same precautionary measures and at the same dose of 300 mg QD as in the melanoma indication. In the absence of clinical data, encorafenib is not recommended in patients with moderate or severe hepatic impairment in all indications.

In the popPK analysis for **binimetinib**, no data were available for moderate and severe hepatic impairment. 41 patients over 181 exhibited a mild hepatic impairment. Based upon this information, no residual covariate effect of mild impairment can be shown on binimetinib CL/F and V/F in the final model. Taken together, no dose adjustment is proposed in subjects with mild hepatic impairment (Child Pugh A).

Figure 4 Final PopPK Model of Binimetinib - Sources of Variability –NCI Organ Dysfunction Group



NCI : 0 = BIL ≤ ULN & AST ≤ ULN; 1 = (BIL ≤ ULN & AST > ULN) or (ULN < BIL ≤ 1.5 x ULN)
AST= aspartate aminotransferase (U/L); BIL= bilirubin (mg/dL); n=number of subjects; NCI= National Cancer Institute Organ Dysfunction Working criteria; nCl= individual random effect of apparent clearance; nV= individual random effect of apparent central volume of distribution; PK= pharmacokinetic; ULN= upper limit of normal

In order to provide similar exposure to patients with normal hepatic function, the dose in moderate and severe hepatic impairment should be adjusted to 15 mg BID. However, as encorafenib is not recommended in patients with moderate (Child Pugh B) or severe hepatic impairment (Child-Pugh C), administration of binimetinib is not recommended in these patients.

In addition, EMA CHMP requested as a post authorisation measure (PAM), to assess the PK and the safety of encorafenib when administered in combination with binimetinib in cancer patients with moderate or severe hepatic impairment. A clinical study is planned (W00090GE101) to fulfil this requirement and results are due by December 2023.

- **Gender**

Sex was not retained as a covariate in the final model for encorafenib and binimetinib. Based on a visual inspection of the residual plots of post-hoc CL/F and V/F with sex, no sex-specific trends on encorafenib CL/F or V/F were observed. Based on this no encorafenib and binimetinib dose adjustment based on sex is recommended necessary.

- **Race/Ethnic origin**

Comparison between the two cohorts (Japanese and non-Japanese) in the SLI portion does not indicate any significant difference in exposure of all analytes at steady state. Even though geometric ratios were at some occasions lower or higher than 1.00 (0.95-1.19) for dose-normalised Cmax and AUClast at C2D1, the variability in results (reflected by large CIs) hinders any conclusive difference and suggest a lack of substantial differences between the Japanese and non-Japanese patients.

Descriptive statistics for Asian and non-Asian cohorts were compared at steady state C2D1 for exploratory purposes, as discussed in PK report CP19-14. For binimetinib and encorafenib, all trough concentrations appear to be slightly higher in the Asian population, while post-dose concentrations at 2 hours are slightly lower (Table 8). Trough and concentrations at 2 hours for AR00426032 were higher

for Asian population. However, a high GeoCV% is observed with these results across all analytes, indicating that concentrations are widely distributed compared to the mean and inter-subject variability is significant. A difference in total number of subjects for each cohort is also observed, having only 4 to 6 subjects in the Asian population in the doublet and triplet arms, thus impacting definitive conclusions between Asians and non-Asians in these arms. No important difference was observed for cetuximab, either for trough concentrations or at 2 hours post dose.

Table 8 Comparison of Concentrations (ng/mL) between Asian and Non-Asian Cohorts for the Randomized Portion based on GeoMean (GeoCV%)

Analyte	Arm	Time (hr)	Non-Asian		Asian	
			N	GeoMean (GeoCV%)	N	GeoMean (GeoCV%)
Binimetinib	ENCO + BINI + CETUX	0	32	47.7 (120)	4	58.8 (50.0)
		2	30	279 (81.9)	4	201 (35.9)
AR00426032	ENCO + BINI + CETUX	0	32	3.47 (83.8)	4	8.88 (87.2)
		2	30	12.0 (104)	4	22.7 (31.6)
Encorafenib	ENCO + BINI + CETUX	0	36	22.2 (392)	4	34.8 (319)
		2	35	1040 (289)	4	506 (140)
	ENCO + CETUX	0	41	12.4 (152)	6	12.6 (68.4)
		2	39	1490 (149)	5	2130 (96.3)
Cetuximab	ENCO + BINI + CETUX	0	37	54900 (44.1)	5	39100 (63.5)
		2	25	154000 (52.5)	5	158000 (19.4)
	ENCO + CETUX	0	46	54900 (112)	6	51800 (25.7)
		2	40	161000 (46.6)	5	206000 (11.4)
	CONTROL	0	49	46700 (69.6)	9	47100 (48.1)
		2	42	167000 (32.6)	9	171000 (23.5)

C2D1 = cycle 2 day 1; hr = hour; GeoMean = geometric mean; GeoCV% = geometric coefficient of variation.
Source: Appendix 1 Section 2

In the popPK model, no clear trend were observed in individual PK parameters (CL/F, V/F and Ka) regarding the race/ethnic covariates.

Taken together, neither ethnic origin nor race are considered clinically relevant for encorafenib and binimetinib PK when administered in combination with cetuximab, and as a result no dose adjustments are proposed based on race/ethnicity.

- **Weight**

Body weight was found to be a significant covariate for encorafenib CL/F and binimetinib CL/F and V/F and therefore retained in the final model (see above). However, given the small magnitude of changes in encorafenib PK parameters predicted in the models, weight is unlikely to be clinically relevant. Based on this, no dose adjustment based on body weight is recommended.

- **Elderly**

The influence of age was evaluated in the population PK analysis (Report T2019-00141). Age as a covariate was retained in the final model on the **encorafenib** CL/F, V/F and Ka terms. Although small sample size in older groups gave limited information, the residual on the post-hoc derived AUC or Cmax and age in the Forest plot showed no definitive trend between the 5th and 95th percentiles of age (40.2 years and 76.9 years) compared to the median (58 years).

Table 9 PK Exposure Levels of encorafenib by Age – Study ARRAY-818-302

PK Parameters	< 65 years (N = 99)	65 - 74 years (N=51)	75 – 84 years (N=13)	≥ 85 years (N=1)	Overall (N=164)
AUCss (µg.h/mL)					
Mean (CV%,SD)	7.61 (29.0%, 2.21)	8.65 (30.4%, 2.63)	8.02 (16.1%, 1.29)	NC	7.96 (29.2%, 2.32)
Median [Min, Max]	7.21 [4.04, 16.4]	8.52 [1.55, 16.7]	8.32 [5.52, 9.79]	NC [7.21, 7.21]	7.58 [1.55, 16.7]
GeoMean (GeoCV%)	7.33 (27.4%)	8.21 (36.7%)	7.91 (17.4%)	NC	7.64 (30.2%)
Cmax (ng/mL)					
Mean (CV%,SD)	1485 (32.3%, 479)	1693 (34.2%, 578)	1557 (28.4%, 442)	NC	1556 (33.0%, 514)
Median [Min, Max]	1514 [322, 3247]	1728 [195, 3428]	1694 [505, 2034]	NC [1541, 1541]	1592 [195, 3428]
GeoMean (GeoCV%)	1395 (39.6%)	1561 (49.7%)	1471 (40.9%)	NC	1452 (42.9%)
Cmin (ng/mL)					
Mean (CV%,SD)	15.1 (117%, 17.7)	24.0 (147%, 35.2)	16.7 (111%, 18.6)	NC	17.9 (138%, 24.7)
Median [Min, Max]	9.73 [2.58, 129]	13.7 [0.296, 194]	11.4 [5.32, 77.5]	NC [8.71, 8.71]	11.4 [0.296, 194]
GeoMean (GeoCV%)	11.1 (80.5%)	14.6 (127%)	12.8 (70.3%)	NC	12.2 (94.7%)

AUCss= area-under the curve under steady-state; CV = coefficient of variation; Max= maximum; Min= minimum; N= number of subjects; PK= pharmacokinetic; SD= standard deviation
Source: Report T2019-00141 Appendix 1 Sections 11.67 and 11.68

Age was retained as a significant covariate in the final model on the **binimetinib** CL/F term, however the residual on the post-hoc derived AUC or Cmax in the Forest plots showed no definitive trend. Similarly, no major influence of age on binimetinib PK was identified in the previous population PK analyses integrating the melanoma patient population as monotherapy or in combination with encorafenib (Reports CP16-001 and CP17-004).

Table 10 PK Exposure Levels of binimetinib by Age–Study ARRAY-818-302

Exposure Parameters	< 65 years (N=60)	65 -74 years (N=28)	75 -84 years (N=4)	>85 years (N=1)	Overall (N=93)
AUCss (µg.h/mL)					
Mean (CV%,SD)	2.44 (31.0%, 0.755)	2.74 (29.2%, 0.801)	2.62 (18.1%, 0.474)	NC	2.55 (30.2%, 0.768)
Median [Min, Max]	2.28 [1.23, 5.09]	2.51 [1.83, 5.48]	2.59 [2.20, 3.09]	NC [3.46,3.46]	2.39 [1.23, 5.48]
GeoMean (GeoCV%)	2.33 (30.2%)	2.65 (26.3%)	2.58 (18.4%)	NC	2.44 (29.2%)
Maximum Concentration (ng/mL)					
Mean (CV%,SD)	416 (36.8%, 153)	443 (33.0%, 146)	365 (13.0%, 47.5)	NC	424 (35.1%, 149)
Median [Min, Max]	407 [66.9, 706]	446 [171, 717]	374 [299, 411]	NC [640, 640]	414 [66.9, 717]
GeoMean (GeoCV%)	382 (47.5%)	416 (40.2%)	362 (13.7%)	NC	393 (44.3%)
Minimum Concentration (ng/mL)					
Mean (CV%,SD)	21.6 (61.2%, 13.2)	25.3 (53.6%, 13.6)	23.1 (40.6%, 9.37)	NC	22.9 (57.4%, 13.2)
Median [Min, Max]	17.5 [5.21, 69.2]	21.0 [11.2, 75.3]	21.8 [14.8, 33.9]	NC [33.6,33.6]	18.4 [5.21, 75.3]
GeoMean (GeoCV%)	18.4 (61.9%)	22.8 (47.7%)	21.7 (43.2%)	NC	19.9 (57.6%)

AUC_{ss}= area-under the curve at steady-state; CV = coefficient of variation; Max= maximum; Min= minimum; N= number of subjects; NC=not calculated; PK= pharmacokinetic; SD= standard deviation
Source: Report T2019-00141 Appendix 2 Section 12.61

Given the small magnitude of PK parameters change predicted in the models, age is unlikely to be clinically relevant. Based on this, no dose adjustment of encorafenib and binimetinib based on age is recommended.

Pharmacokinetic interaction studies

No new clinical studies were performed for evaluation of drug-drug interactions for either encorafenib or binimetinib.

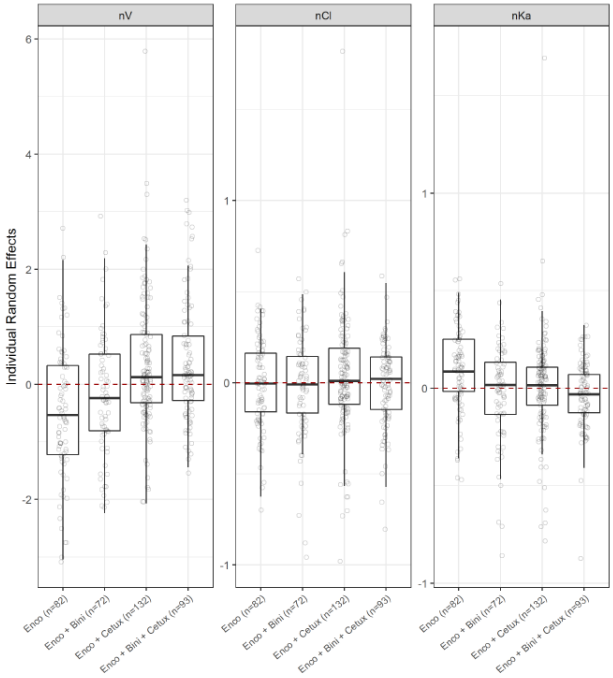
DDI between the combination partners

PopPK report CP19-013 evaluated the potential of DDI of cetuximab on the PK of encorafenib and binimetinib by external VPCs. No major differences in the observed data, relative to the simulated data, suggest that a clinically relevant interaction between binimetinib, encorafenib and cetuximab is unlikely. Additionally, there are no major differences observed in the colorectal population in BEACON-CRC relative to the model that was constructed from a majority of melanoma patients simulated as part of the external VPC. These results support the conclusion that there is no clinically relevant disease effect on the PK of binimetinib, AR00426032 or encorafenib.

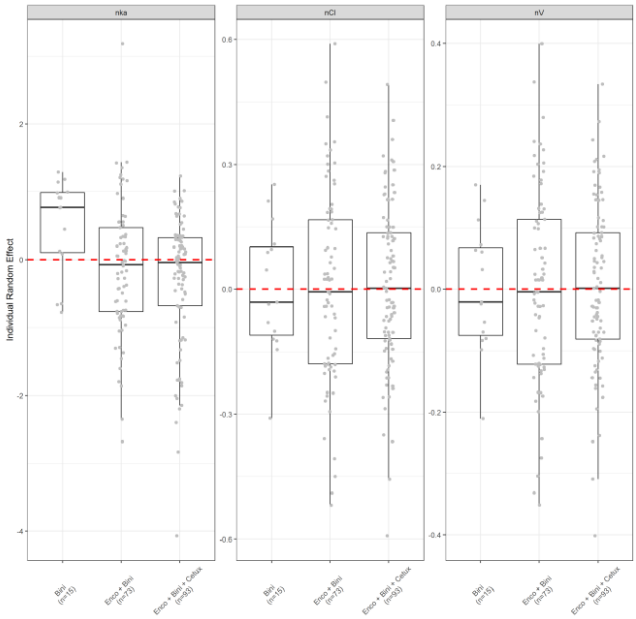
Within **popPK model T2019-00141,** as categorical covariates, DDI between the combination partners have been analysed as sources of variability on Cl and V, and rate of absorption (Ka) in patients.

Figure 5 Final Population PK Model - Categorical Covariate Drug-Drug Interaction

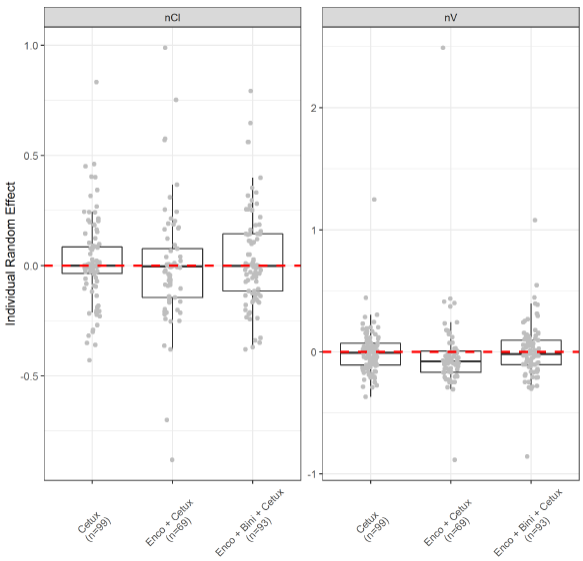
A) encorafenib



B) binimetinib



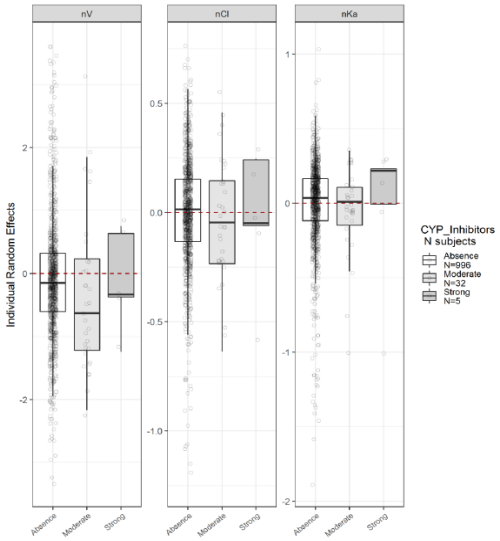
C) cetuximab



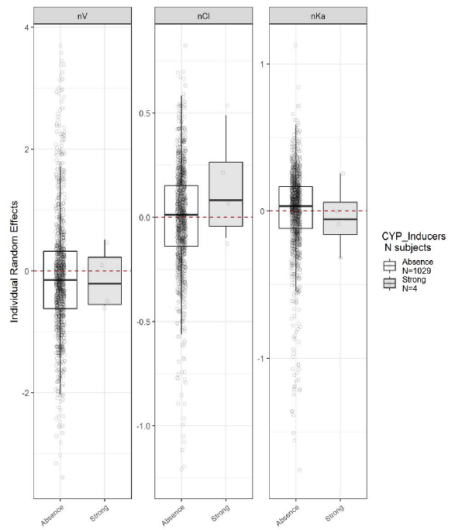
CYP3A4 inhibitors and inducers

With the submitted updated previous popPK model **T2019-00140**, CYP3A4 inhibitors and inducers have been analysed as sources of variability on Cl and V of encorafenib.

Figure 6 Final PopPK Model T2019-00140 of encorafenib, melanoma population – Categorical Covariates: CYP3A4 Inhibitors (left), CYP3A4 inducers (right)



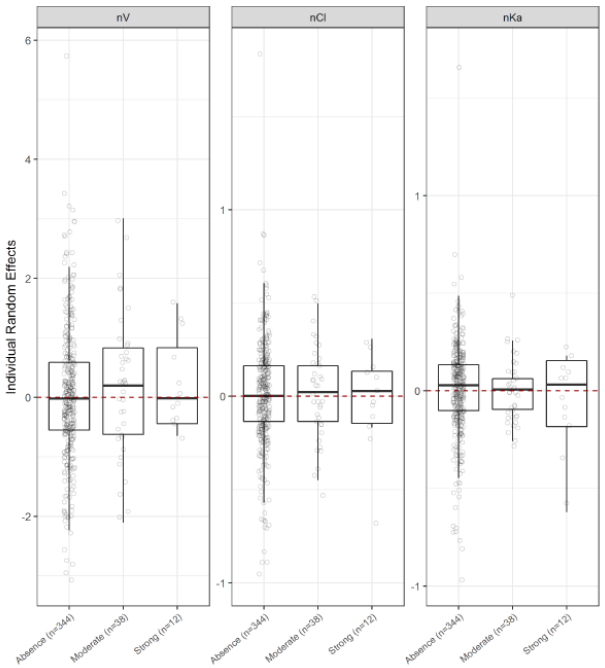
N=number of subjects; nCl= individual random effect of apparent clearance; nKa= individual random effect of first order rate of absorption; nV= individual random effect of apparent central volume of distribution; PK= pharmacokinetic.
Note: Concomitant administration of CYP3A inhibitors was considered present if at least one of the PK samples was collected during concomitant administration of CYP3A inhibitors

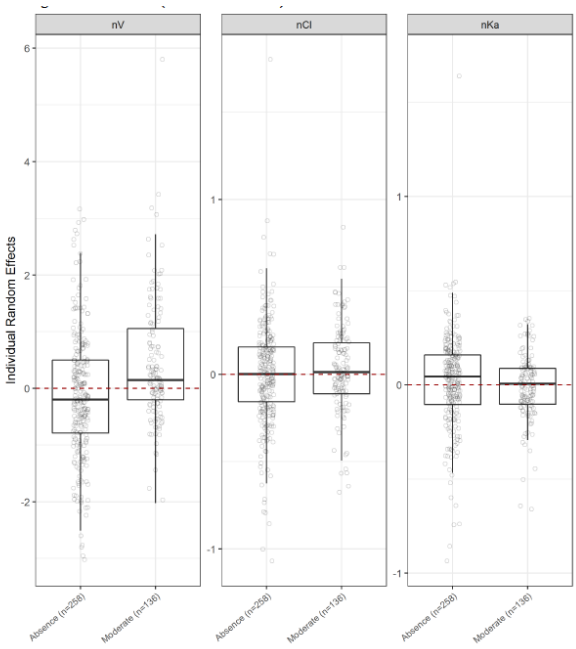


N=number of subjects; nCl= individual random effect of apparent clearance; nKa= individual random effect of first order rate of absorption; nV= individual random effect of apparent central volume of distribution; PK= pharmacokinetic.
Note: Concomitant administration of CYP3A inducers was considered present if at least one of the PK samples was collected during concomitant administration of CYP3A inducers

Within **popPK model T2019-00141** the mCRC population was analysed. CYP3A4 inhibitors and inducers have been analysed as sources of variability on Cl and V.

Figure 7 Final PopPK Model T2019-00141 of encorafenib, CRC population – Categorical Covariates: CYP3A4 Inhibitors (left), CYP3A4 inducers (right)





2.3.3. Pharmacodynamics

Cardiac safety

No supplementary exposure-cardiac electrophysiology analyses were conducted to support this new mCRC indication.

Given that no drug drug interactions were evidenced between **binimetinib** and cetuximab, no impact of the combination with cetuximab on a QT prolongation is expected. Taken all together, these results suggest that binimetinib in combination with encorafenib and cetuximab does not cause clinically meaningful QT prolongation or HR changes at the proposed therapeutic doses.

Biomarkers

Tumour Marker and Biomarker Results

In Phase 3, median Baseline **Carcinoembryonic Antigen** (CEA) values were higher in the Triplet arm (29.4 µg/L) than the Doublet and Control arms (18.0 and 23.3 µg/L, respectively). Baseline CEA values >5 µg/L were reported in a greater proportion of patients in the Triplet and Control arms (79.9% and 80.5%, respectively) than the Doublet arm (69.5%). In these patients, the median percent decrease from Baseline to nadir CEA value was greater in the Triplet and Doublet arms (-87.3% and -86.1%, respectively) than the Control arm (-34.5%).

In Phase 3, median Baseline **Carbohydrate Antigen 19-9** (CA19-9) values were higher in the Triplet and Doublet arms (224.3 and 221.2 U/mL, respectively) than the Control arm (187.6 U/mL). Baseline CA19-9 values >35 U/mL were reported in a comparable proportion of patients in each treatment arm (71.0% Triplet arm, 67.7% Doublet arm, 70.6% Control arm). In these patients, the median percent decrease from Baseline to nadir CA19-9 value was greater in the Triplet and Doublet arms (-89.1% and -91.5%, respectively) than the Control arm (-40.1%).

Genomic and Proteomic Biomarkers

An exploratory objective of the study was to assess blood- and tissue-based biomarkers that may be predictive of biological activity. Analyses for this exploratory biomarker objective are not included in this report. The Sponsor plans to conduct laboratory testing for biomarkers after all sample collection (including the EOT samples) is completed

2.3.1. PK/PD modelling

Exposure-response analyses

E/R analyses in the target mCRC population were discussed in popPK report T2019-00141. Exposure-response relationships were performed using the ARRAY-818-302 study data on a PK dataset pooling patients from the CSLI part and a subset of patients of the Phase 3 portion on whom blood samples were collected for purposes of PK and exposure-responses analyses. The exposure efficacy dataset included 92 patients for the Triplet, 68 patients for the Doublet and 99 patients for the Control arm. Given that the exposure-efficacy relationships were developed on a subset of patients of the whole dataset of study ARRAY-818-302, the exposure-efficacy analysis was considered as exploratory.

The PK set comprises only one third of the FAS, of which the control arm (~45%) is better represented than the Triplet and Doublet arms. Especially the Triplet is underrepresented with only 26% of patients having contributed with sparse-sampling PK data in the randomised phase III part; see Table 17 from CSR:

Table 17: Analysis Sets

	Randomized and CSLI (Pooled)	CSLI	Randomized Portion			
	ENCO + BINI + CETUX (N = 261)	ENCO + BINI + CETUX (N = 37)	ENCO + BINI + CETUX (N = 224)	ENCO + CETUX (N = 220)	CONTROL (N = 221)	Phase 3 Total (N = 665)
Full Analysis Set[a]	261 (100.0)	37 (100.0)	224 (100.0)	220 (100.0)	221 (100.0)	665 (100.0)
Safety Set[b]	259 (99.2)	37 (100.0)	222 (99.1)	216 (98.2)	193 (87.3)	631 (94.9)
Phase 3 Response Efficacy Set[c, d]	111 (42.5)	0 (0.0)	111 (49.6)	113 (51.4)	107 (48.4)	331 (49.8)
Per Protocol Set[c, e]	209 (80.1)	0 (0.0)	209 (93.3)	199 (90.5)	178 (80.5)	586 (88.1)
Pharmacokinetic Set[f]	95 (36.4)	37 (100.0)	58 (25.9)	73 (33.2)	99 (44.8)	230 (34.6)
Dose-determining Set[g, h]	34 (13.0)	34 (91.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SLI Efficacy Set[g, i]	36 (13.8)	36 (97.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Exposure-efficacy analyses

Exposure-efficacy relationships were explored between the individual predicted exposure metrics at steady state (AUCss, Cmax,ss and Cmin,ss) and OS, PFS and ORR endpoints through descriptive Kaplan-Meier (KM) plots for OS and PFS (derived by high/low exposures relative to the median) and single descriptive logistic regression for ORR. Cox regression model was performed with PFS and OS endpoints to evaluate the effects of each drug and risk factors by pooling all the information. A logistic regression model was evaluated between the drug exposure metrics and the ORR endpoints and risk factors. Parametric time-to-event regression models were performed with PFS and OS outcomes using time-varying average concentrations (Cavg) in order to account for dose reductions and interruptions.

New exploratory exposure efficacy analyses for the Doublet and Control arms show the benefit of the combination encorafenib + cetuximab through the positive interaction terms of encorafenib and cetuximab AUC in the OS Cox Hazard Model and through a reduction in the rate of death or progression (PFS) with cetuximab and encorafenib Cavg using a parametric time to event regression model. These analyses further support the efficacy of the combination of encorafenib with cetuximab in the treatment of patients with mCRC with BRAF V600E mutation.

Exposure-efficacy analyses were revised for Doublet and Control arms upon request. They showed the benefit of E+C through the positive interaction terms of encorafenib and cetuximab AUCs in the OS Cox Hazard Model, and through a reduction in the rate of death or progression (PFS) with cetuximab and encorafenib Cavg using a parametric time to event regression model. No such relationship was found for ORR.

Exposure-safety analyses

Exposure-response relationships between model-derived exposures (encorafenib, binimetinib and cetuximab) in patients in BEACON and CLGX818X2103 studies and the probability of the following AEs were explored: arthralgia/musculoskeletal pain (grade≥2), diarrhoea (grade≥2), blood creatinine elevation (all grades), creatine phosphokinase elevation (all grades), skin adverse events (grade≥2) and retinal events (grade≥2).

E/R relationships were explored as a function of exposure levels of each drug based on PK exposure levels derived with randomized dose at treatment assignment assuming steady-state conditions.

Negative significant relationships were observed between the probability of arthralgia/musculoskeletal pain (grade≥2) and AUCss and Cmaxss of encorafenib. Negative significant relationship ($p<0.05$) was observed between the probability of skin adverse events (grade≥2) and cetuximab PK parameters (i.e., AUCss, Cmaxss, Cminss). Positive significant relationship ($p<0.05$) between the probability of retinal events (grade≥2) and binimetinib Cmaxss.

No statistical significant relationships with diarrhoea, blood creatinine elevation and creatine phosphokinase elevation were found. Given that the diarrhoea adverse events were the most observed AE in BEACON study, the lack of relationships between diarrhoea AE and encorafenib, binimetinib or cetuximab exposures could be explained by confounding effects between the 3 drugs.

In the requested second analysis the exposure-safety relationships were explored by arm and by analyte using data from Study ARRAY-818-302 only.

2.3.2. Discussion on clinical pharmacology

Pharmacokinetics

Two new clinical studies in support of the application in mCRC provide new PK data, the Phase Ib/II study CLGX818X2103 and the pivotal Phase III study ARRAY-818-302 (BEACON). The data were also included in 2 new population PK and/or exposure response (ER) analyses. This is considered acceptable for the current variation.

The PK sampling schemes to determine binimetinib, encorafenib and cetuximab seem adequate, when considering that in the lead-in-part of the mCRC study rich sampling for encorafenib was performed and basic popPK models for binimetinib and encorafenib were already available from the initial MAA in melanoma patients. Cetuximab PK was, however, only analysed in the phase III study portion.

For molecular screening of presence of BRAF-V600E mutation [and absence of RASmut] for study eligibility only PCR and NGS-based methods were allowed and needed confirmation by the central lab.

The Population PK analyses were performed based on five clinical studies in healthy subjects, patients with unresectable or metastatic BRAF V600 mutant melanoma and patients with BRAF V600E-mutant mCRC from the following clinical trials: BEACON (ARRAY-818-302), Study CLGX818X2103, CMEK162X2110, CLGX818X2101 and ARRAY-162-105.

The popPK model previously developed for encorafenib was a two-compartment model with first order absorption and time-dependent clearance described with a dose-dependent Emax model. Different changes to the model were tested but finally the previous model was considered to be appropriate.

The final model included the following covariates: age on ka, disease status, ECOG status, moderate CYP3A4 inhibitors, TPROT, BIL, LDH, age and bw on CL, dose on Emax.

The concomitant medication with CYP inducers does not seem to have had a significant effect on the PK of encorafenib.

Since all point estimates were within 80% and 125% relative to the reference patient the company considered that the covariates, except for comedication with CYP 3A4 inhibitors, which is already mentioned in the SmPC, did not have a clinically relevant effect on the PK parameters of encorafenib.

The auto-induction of clearance was implemented as a time-dependent function and the height of the maximal clearance was dose-dependent due to the covariate dose on Emax. The estimated time to achieve 50% of the maximum CL/F (T50) was 67.3 h after the 1st dose (2-3 days) and based on this calculated time to reach 90% of the maximal effect is 605.7 h (25 days i.e 3.6 weeks).

The MAH explained the strategy chosen for data selection in order to generate a manageable, meaningful database for the model. Exclusion of study data was justified. In total, 96 patients with metastatic melanoma (~ 25 % of the full dataset) and 236 patients with mCRC (~ 68% of the full dataset) were included in the dataset for a full population analysis in mCRC and melanoma populations. With this dataset, computational run times of the model were acceptable. GOF plots and VPCs were provided for the 200mg, 300 mg and 450 mg doses, separately. The MAH provided individual GOF plots of the rich sampling profiles of Study ARRAY-818-302 (BEACON) and Study CLGX818X2103. The MAH provided VPCs for all studies included in the PopPK analysis, separately (studies ARRAY-818-302, CLGX818X2103, CMEK162X2110, CLGX818X2101 and ARRAY-162-105). The provided plots reveal that overall, model performance is acceptable. GOF plots for population and individual predictions were provided.

One aim of the PopPK analysis for cetuximab was to evaluate any effect of encorafenib and binimetinib on cetuximab PK profiles. According to the model results, no difference in cetuximab clearance and volume of distribution could be found when combined with encorafenib or encorafenib + binimetinib.

The source of cetuximab (i.e., European versus US sources) was tested on CL since US-licensed cetuximab provides approximately 22% higher exposure than EU-approved cetuximab. This effect did not show significance. In addition, the different sources were investigated comparing the relations between individual PK parameters and individual random effects of CL and V. This evaluation also did show no differences. PcVPCs show that typical values are slightly underpredicted and variability considerably overpredicted.

Encorafenib PK was time-dependent and less than dose-proportional also in the newly studied combination(s). CL/F was increased to 2.5-3-fold at C2D1 which is consistent with the encorafenib-mediated auto-induction of its main metabolic enzyme CYP3A4. Ctrough in the triplet was comparable to what was measured in Part 2 of the COLUMBUS study in melanoma patients with 300mg for the E+B combo.

It is noted that steady-state %CV was huge for encorafenib PK in the triplet, especially in the randomised phase III part. In previous studies %CV was usually below 100% whereas here it was observed with 140-375%. This high inter-subject variability in PK resulted from PK sampling data unaccounted for time of drug intake.

From the popPK, binimetinib AUCss was comparable to that observed previously with the 300mg E+B combo. However, lower Cmaxss and Cminss were observed in the current analysis and are suggested by the MAH to be explained by the structure of the absorption model. The appropriateness of the current model for binimetinib was questioned, but not further pursued due to withdrawal of binimetinib.

For the active metabolite AR00426032 lower exposure was observed in steady state.

No obvious pharmacokinetic impact of encorafenib or binimetinib on the PK of cetuximab was seen and mean Cmax was comparable with the value for steady-state given in the EU-Erbitux SmPC. PopPK modelling and evaluation of external VPCs supported absence of clinically relevant, mutual drug interactions of E, B and C.

The US-FDA label of Erbitux states that the systemic exposure of US-sourced cetuximab was 22% (90% CI: 6%, 38%) higher than that of another (= EU-sourced) cetuximab product. Therefore, randomisation was stratified [beside others] according to cetuximab source (US vs. EU). Ca. 18-20% of the study population received US-sourced cetuximab and indeed, mean AUC of the US source were 25%, 13 % and 20 % higher than the EU source for the Triplet, Doublet and Control arm, respectively.

Special populations

Impact on PK in special populations were analysed largely by popPK modelling. Clinically relevant differences between melanoma and mCRC patients were not observed.

Male patients were modelled to have significantly lower cetuximab exposures than the female reference patient [BSA of 1.8m^2] with 76.9% for AUCss. No such information is given in the EU-Erbitux SmPC but the US label provides congruent information of a 25% lower intrinsic clearance in females. No dose adaptions are recommended up to to-date and thus the clinical relevance in the targeted combination is also considered of minor importance.

In the final encorafenib model CYP3A4 inhibitor effects and age accounted for the largest contribution of variability in CL/F, whereas exposures of binimetinib would relevantly change with the body weight range: patients of 48.4 kg would have 29% and 33% higher AUCss and Cmaxss respectively relative to the reference patient. As binimetinib was withdrawn from the applied indication, this was not further pursued.

In line with previous data, renal impairment has low impact on PK of both drugs. Hence, no dose adjustment is recommended/required in mCRC patients with mild or moderate renal impairment. A recommended dose for encorafenib has not been established for subjects with severe renal impairment.

Encorafenib is proposed for mild HI patients at the same 300 mg QD dose as in the melanoma indication, i.e. no special dose reduction is proposed here, based on comparable safety in mCRC patients with mild HI and those with normal hepatic function. This is acceptable. In the absence of clinical data, encorafenib is not recommended in patients with moderate or severe hepatic impairment in all indications.

As a post authorisation measure from the initial MAA, a clinical study is planned (W00090GE101) to assess PK and safety of encorafenib in combination with binimetinib in cancer patients with moderate or severe HI, with results due by December 2023.

Binimetinib and encorafenib trough concentrations appeared to be slightly higher in the Asian population whereas Cmax was slightly lower. A high geoCV% was mainly observed for encorafenib for the non-Asian subgroup; however, due to the small sample size in the Asian population, definitive conclusions between Asians and non-Asians in these arms cannot reliably be drawn.

Only small PK changes were predicted for age effects, although in the final encorafenib model age was one of 2 covariates accounting for the largest contribution of variability in CL/F. No dose adjustments of encorafenib and binimetinib based on age are recommended which is acceptable based on current knowledge.

In the paediatric population no data are currently available for both drug substances. As part of the PIP (EMEA 001588-PIP01-13) a study in paediatric mBRAF-melanoma patients is planned.

The dosing recommendations given in the SmPC are in line with the MAH's conclusions drawn from the new clinical data.

Drug interactions

The covariate effect of CYP3A4 inducers may have been inadequately evaluated in the submitted popPK model(s) of encorafenib. The population baseline characteristics show that in the group "absence of CYP3A4 inducers" also patients with weak inducers were included. As most mCRC patients are probably receiving a glucocorticoid (e.g. dexamethasone) as a commonly recommended cetuximab pre-medication and this is a known CYP3A4 inducer, the broad variability of Ka, CL and V could potentially also be resultant from weak CYP3A4 induction. Re-classification of glucocorticoids to weak inducers and re-modelling showed low clinically relevant interaction potential, especially as the pre-medication is only given once weekly.

DDI with other common recommended cetuximab pre-medications, such as diphenhydramine (CYP2D6 inhibitor) or e.g. prednisone (CYP2C inducer are neither of clinical importance, as these enzymes do not concern major metabolic pathways of encorafenib.

Pharmacodynamics

The MAH discussed that EGFR signalling has the potential to bypass mBRAF inhibition and by that lead to therapeutic resistance in BRAFV600E CRC. Thus, a BRAFi in combination with an EGFR inhibitor (i.e., inhibiting the activated oncogene and the dominant reactivated receptor), could optimise the MAPK pathway suppression and could lead to improved efficacy in BRAFV600E-mutant CRC compared to a BRAF inhibitor only.

In addition, as most resistance signals in BRAF-mCRC occur in the MAPK pathway upstream of MEK, this suggested that the addition of a MEK inhibitor to BRAF plus EGFR inhibitors could lead to an improved and more durable suppression of ERK signalling and therefore to improved response rates.

No new data have been obtained in the new indication with regard to cardiac safety. The PI texts of both products have thus not been amended. This is considered acceptable.

Exposure-efficacy analyses were revised for Doublet and Control arms. They showed the benefit of E+C through the positive interaction terms of encorafenib and cetuximab AUCs in the OS Cox Hazard Model, and through a reduction in the rate of death or progression (PFS) with cetuximab and encorafenib Cavg using a parametric time to event regression model. No such relationship was found for ORR.

Exposure-safety relationships were explored by arm and by analyte using data from Study ARRAY-818-302 only. The most relevant E-R result was that the estimated probability of anaemia (grade≥2) increased from 9.18% to 13.8% from the lowest to the highest quartiles of encorafenib AUC.

On the contrary, increasing encorafenib exposure reduced the probability of the cetuximab ADR acneiform dermatitis (grade≥2) from 11.6% to 0.86%.

No other statistically significant relationships between encorafenib exposure and the events of interest (renal failure, diarrhoea, arthralgia/muscuskeletal pain) have been identified.

2.3.3. Conclusions on clinical pharmacology

The clinical pharmacology data submitted to support the use of encorafenib in combination with cetuximab for the treatment of BRAF V600E-mutant metastatic colorectal cancer is considered acceptable. From a clinical pharmacology point of view the application is approvable.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Dose-response analyses were not conducted. Evaluations of dose proportionality were submitted within the initial Marketing authorisation application Supporting the melanoma indication.

Phase Ib part of study CLGX818X2103 is labelled as a dose finding study and is investigating cetuximab in combination with increasing encorafenib doses. However, this part of trial 2103 is investigating PK but not response.

2.4.2. Main study(ies)

Title of Study

BEACON CRC Study (ARRAY-818-302): a multicenter, randomized, open-label, 3-arm phase 3 study of encorafenib + cetuximab plus or minus binimetinib vs. irinotecan/cetuximab or infusional 5-fluorouracil (5-fu)/folinic acid (FA)/irinotecan (FOLFIRI)/cetuximab with a safety lead-in of encorafenib + binimetinib + cetuximab in patients with BRAF V600E-mutant metastatic colorectal cancer.

Methods

Study dates:

Date of First Informed Consent: 09 October 2016

Date of Data Cutoff: **11 February 2019**

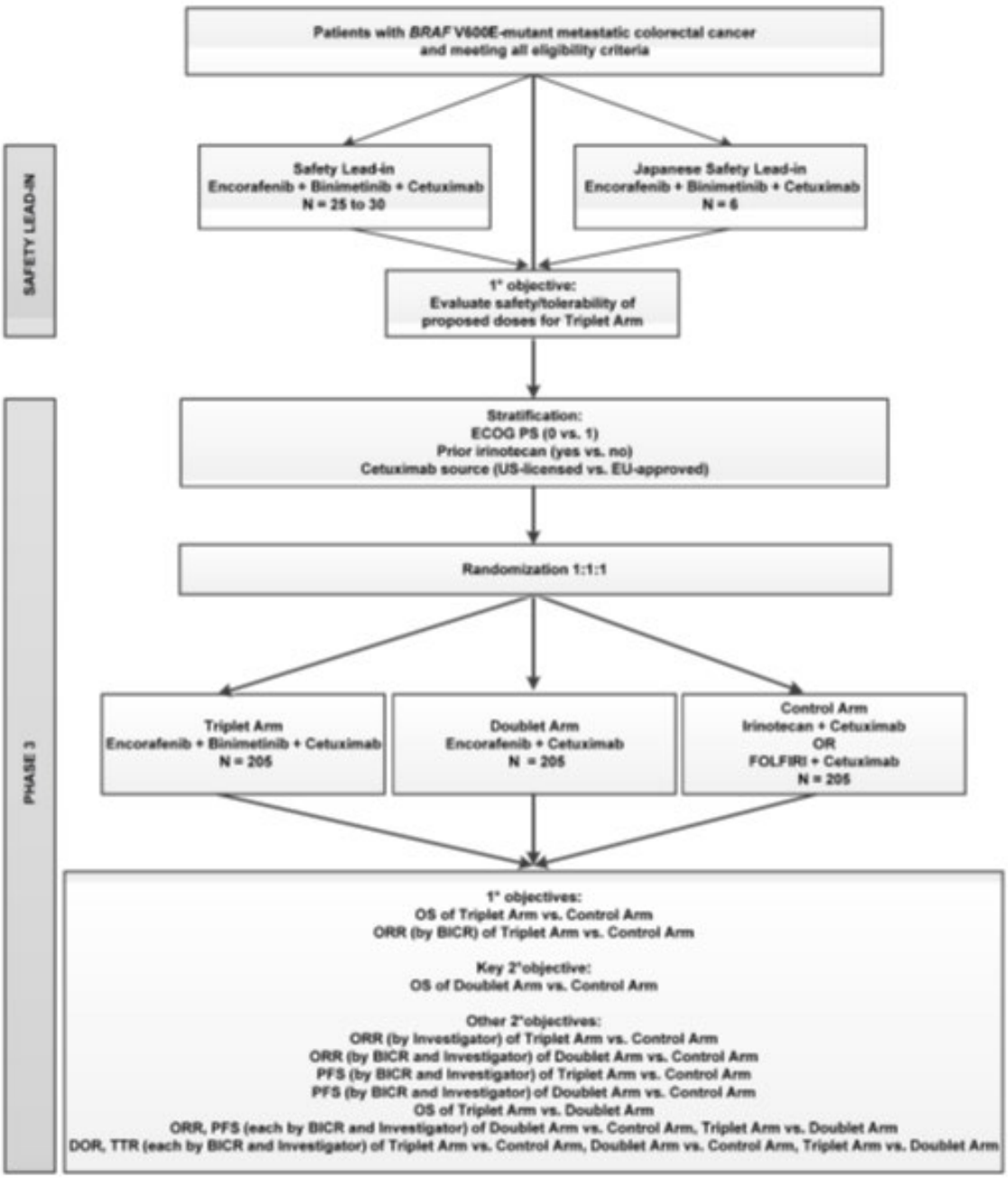
Date of CSR: 12 September 2019

Date of Data Cutoff (**update**) **15 August 2019**

Date of updated efficacy and safety analysis 20 January 2020

A schema of the study design is presented in Figure 1.

Figure 1: Study Design



Abbreviations: BICR = blinded independent central review; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PS = performance status; TTR = time to response

Note: The study was initiated with the SLI cohort (US/EU), in which the safety and tolerability of the Triplet combination of encorafenib + binimetinib + cetuximab were assessed prior to initiation of the randomized Phase 3 portion of the study. The JSLI cohort (Japan) was conducted later and prior to initiation of randomization in Japan.

Methods

In the Phase III portion of the study, a total of approximately 615 eligible patients with BRAF V600E-mutant mCRC who had progressed on 1 or 2 prior metastatic regimens were to be randomized in a 1:1:1 ratio to one of the following 3 treatment arms:

- **Triplet arm**: encorafenib 300 mg QD + binimetinib 45 mg BID + standard cetuximab (400 mg/m^2

followed by 250 mg/m2 IV QW)

- **Doublet arm**: encorafenib 300 mg QD + standard cetuximab (400 mg/m2 followed by 250 mg/m^2 IV QW)
- **Control arm**: Investigator' s choice of either irinotecan/cetuximab or FOLFIRI/cetuximab, with the choice to be declared prior to randomization

The number of third-line patients (those who had received 2 prior regimens) was limited per protocol to 35% of the total randomized Phase III population, after which only patients with 1 prior regimen were to be randomized. Patients with 2 prior regimens who had entered Screening at the time that the limit had been reached were to be permitted to continue into the study if they were otherwise determined to be eligible.

Randomization was stratified according to the following factors:

- Baseline ECOG PS (0 vs. 1),
- Prior use of irinotecan (yes vs. no),
- Cetuximab source (US-licensed vs. EU-approved).

To confirm tolerability, the DMC reviewed the available safety information after the first 30 patients in the randomized Phase 3 portion of the study (i.e., approximately 10 patients in each arm) had the opportunity to complete at least 1 (28-day) cycle of treatment. During the remainder of the study, the DMC was to review safety data at regular intervals.

An initial analysis of the Phase III portion of the study was to be performed when all 3 of the following criteria were met:

- Approximately 9 months after randomization of the 330th patient (i.e., approximately 110 patients per arm), to allow a majority of responders among the 330 Phase III patients to have had the opportunity to be followed for approximately 6 months or longer after their first response
- At least 188 OS events had occurred in the Triplet and Control arms combined (i.e., approximately 70% information)
- At least 169 OS events had occurred in the Doublet and Control arms combined (i.e., approximately 50% information)

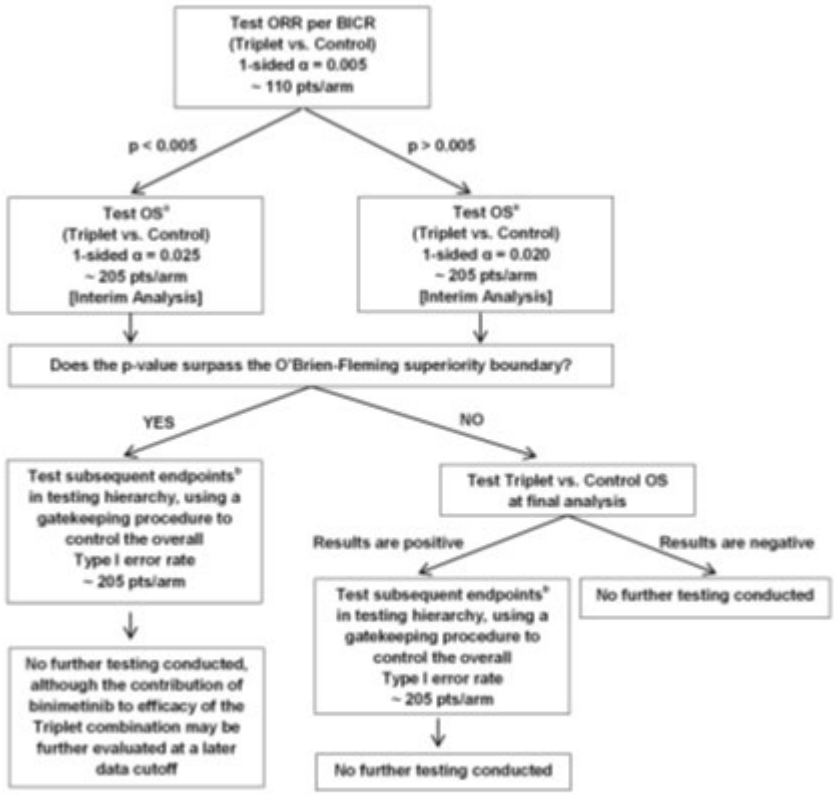
The primary analysis of Triplet arm vs. Control arm ORR by BICR was to occur at this time and was to be based on the first 330 randomized patients. An interim analysis for superiority or (non-binding) futility of the Triplet arm vs. Control arm OS endpoint was also to be performed at the time of the primary ORR analysis based on all available data. The independent DMC reviewed and interpreted the analysis results for both of the primary endpoints, which were conducted by an independent statistician. If the interim analysis for OS of the Triplet arm vs. Control arm exceeded the superiority boundary, patients in the Triplet and Doublet arms will continue to be followed for a more mature comparison.

If the OS interim analysis results did not cross the superiority boundary, the OS final analysis was to occur once at least 268 events were observed in the Triplet arm + Control arm and at least 338 events were observed in the Doublet arm + Control arm.

If the p value for the Triplet arm vs. Control arm OS comparison exceeded the superiority boundary at either the interim or final analysis, the following endpoints were to be tested at that time in the following order: 1) OS of Doublet arm vs. Control arm, 2) ORR (per BICR) of Doublet arm vs. Control arm, 3) PFS (per BICR) of Triplet arm vs. Control arm, and 4) PFS (per BICR) of Doublet arm vs. Control arm.

The overall testing strategy of the study is summarized in Figure 2.

Figure 2: Testing Strategy for Phase 3 Primary and Secondary Endpoints



[a] A Lan-DeMets spending function that approximates O'Brien-Fleming boundaries will be used to account for the multiple (i.e., interim and final) analyses of OS.

[b] Subsequent endpoints would be tested in the following order: Doublet vs. Control OS, Doublet vs. Control ORR per BICR, Triplet vs. Control PFS per BICR, and then Doublet vs. Control PFS per BICR.

The study consisted of the following phases:

BRAF Testing/Molecular Prescreening, Screening and Enrollment (SLI and JSLICohorts)/Randomization (Phase III)

Patients must have had an identified BRAF V600E mutation to be eligible for the study. For patients with unknown BRAF mutation status or BRAF wild-type by local assay, the BRAF V600E mutation status was to be determined by the central laboratory during molecular prescreening from an adequate archival tumor sample or fresh tumor biopsy.

Central laboratory *BRAF* mutation tests with a definitive result (positive or negative) were not permitted to be repeated to resolve a discordant result. If at any time in the study there was lack of *BRAF V600E* confirmation in a total of 37 patients (6% of the total planned total planned randomization of 615 patients) or discordance between the local assay and the central laboratory in 18 patients, all subsequent patients were required to have *BRAF V600E* determined by the central laboratory for enrollment.

The Screening period began once the patient signed the Screening ICF, and all assessments, including screening tumor assessments, were performed within a maximum of 28 days prior to enrollment (SLI and JSLI cohorts)/randomization (Phase III).
Upon completion of all Screening evaluations, patient eligibility for the study was determined. In the SLI and JSLI cohorts, the sponsor or designee handled the enrolment of eligible patients. In Phase III, eligible patients were randomized via the IWRS to one of the treatment arms in a 1:1:1 ratio.

Treatment Phase

Patients in Phase III were to be treated as soon as possible after the randomization number was assigned. The first day of treatment was defined as Cycle 1 Day 1. Study treatments were administered in continuous 28-day cycles.

Safety was evaluated through continuous AE monitoring, clinical laboratory assessments (hematology, clinical chemistry, coagulation profiles, urinalysis and pregnancy), physical examination, vital signs, dermatologic evaluations, ophthalmic assessments, cardiac assessments (ECG, ECHO/MUGA) and assessment of ECOG PS.

Disease status was evaluated locally by the Investigator and retrospectively by BICR according to RECIST version 1.1. Tumor evaluations were performed at Screening, every 6 weeks ($\pm$ 7 days) from the date of randomization (or from first dose for SLI and JSLI cohorts) for the first 24 weeks of treatment. Then it was performed every 12 weeks ($\pm$ 7 days) thereafter until disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, patient was lost to follow-up, death or defined end of study, regardless of whether study treatment was discontinued. Patient-reported outcome assessments were also to be performed using QoL questionnaires at Screening and periodically on study.

Blood and tumor samples were to be collected at Screening and at specified pre- and post-dose time points during the study for PK and/or biomarker analyses.

Patients were to continue study treatment until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy, death or discontinuation from study treatment for any other reason. Continuation of treatment beyond disease progression was allowed in special circumstances in which the Investigator believed that the patient may have clinically benefited from continued treatment beyond progression and provided that other protocol-specified conditions were met.

End of Treatment

An EOT visit was to be performed for all patients, even those who discontinued prematurely, within 14 days after the last dose of study treatment. The EOT visit was not considered as the end of the study. All patients were to enter the follow-up period.

Follow-up Period

Regardless of the reason for study treatment discontinuation, all patients were to have a Safety Follow-up Visit approximately 30 days after the last dose of study treatment, or prior to the initiation of subsequent anticancer therapy, whichever occurred first. Information related to AEs (including concomitant medication taken for ongoing AEs) and ongoing antineoplastic treatments were to be collected for 30 days after the last dose of study treatment. All AEs suspected to be related to study treatment were to be followed until resolution or stabilization of the event.

After the Safety Follow-up visit, patients were to be followed for survival status, and disease progression, if applicable:

- **Survival Follow-up**: patients (including those in the SLI/JSLI cohorts who provided informed consent for survival follow-up) were to be followed every 3 months, or more frequently as needed, for survival status, all subsequent anticancer therapies, any new SAEs that were considered related to study drug and, for Phase III patients, date of disease progression following the initiation of subsequent therapies until withdrawal of consent, patient was lost to follow-up, death or defined end of study.
- **Tumor Assessment Follow-up**: if study treatment was discontinued for reasons other than disease progression or withdrawal of consent to continue study treatment (but not withdrawal of consent for study participation, i.e., continued follow-up), patients were to continue to be followed

with tumor assessments as per the visit schedule, in addition to survival follow-up, until disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, patient was lost to follow-up or death.

End of Study

The end of the study was defined as the point at which all patients have had the opportunity to be followed for at least 1 year after the randomization date of the last patient enrolled and at least 80% of patients have had an OS event (or were lost to follow-up).

Study participants

Approximately 646 to 651 adult patients (31 to 36 patients in the SLI/JSLI cohorts and approximately 615 in the randomized Phase 3 portion of the study), with histologically confirmed BRAF V600E-mutant mCRC whose disease had progressed after 1 or 2 prior regimens in the metastatic setting, were planned to be enrolled in this study.

Patients were permitted to undergo molecular tumour prescreening with the central laboratory BRAF mutation assay at any time prior to Screening as long as they met all the Molecular Prescreening eligibility criteria.

Inclusion Criteria for Molecular Prescreening

Patients who met all of the following criteria at Prescreening were eligible to undergo molecular tumor prescreening:

1. Provide a signed and dated Prescreening informed consent document
2. Age $\geqslant$ 18 years at time of informed consent
3. Histologically- or cytologically-confirmed CRC that is metastatic
4. Eligible to receive cetuximab per locally approved label with regard to tumor RAS status [explicitly described as RAS wild-type tumors for patients in France per Protocol Version 3.1 (FRA)]
5. Able to provide a sufficient amount of representative tumor specimen (primary or metastatic, archival or newly obtained) for central laboratory testing of BRAF and KRAS mutation status (minimum of 6 slides; optimally up to 15 slides) [modified via Protocol Version 3.0]

Exclusion Criteria for Molecular Prescreening

Patients who met any of the following criteria at Prescreening were not eligible to undergo molecular tumor prescreening:

1. Leptomeningeal disease
2. History or current evidence of RVO or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes)
3. Known history of acute or chronic pancreatitis
4. History of chronic inflammatory bowel disease or Crohn’ s disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) $\leqslant$ 12 months prior to randomization
5. Concurrent neuromuscular disorder that is associated with the potential of elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy)
6. Known history of human immunodeficiency virus (HIV) infection
7. Known history of Gilbert's syndrome or is known to have any of the following genotypes: UGT1A1*6/*6, UGT1A1*28/*28, or UGT1A1*6/*28
8. Known contraindication to receive cetuximab or irinotecan at the planned doses; refer to the most

recent cetuximab and irinotecan summary of product characteristics (SPC) or local label as applicable
9. Prior anti-EGFR treatment
10. More than 2 prior regimens in the metastatic setting

Eligibility Criteria for Study Participation

Inclusion Criteria

Patients who met all of the following criteria at Screening were eligible to enter the study:

1. Provide a signed and dated Screening informed consent document
2. Age ⩾ 18 years at time of informed consent
3. Histologically- or cytologically-confirmed CRC that is metastatic
4. Presence of BRAF V600E in tumor tissue as previously determined by a local assay at any time prior to Screening or by the central laboratory
5. Able to provide a sufficient amount of representative tumor specimen (primary or metastatic, archival or newly obtained) for confirmatory central laboratory testing of BRAF and KRAS mutation status (minimum of 6 slides; optimally up to 15 slides)
6. Eligible to receive cetuximab per locally approved label with regard to tumor RAS status [explicitly described as RAS wild-type tumors for patients in France per Protocol Version 3.1 (FRA)]
7. Progression of disease after 1 or 2 prior regimens in the metastatic setting.
8. Evidence of measurable or evaluable non-measurable disease per RECIST, v1.1
9. ECOG PS of 0 or 1
10. Adequate bone marrow function characterized by the following at screening:

    a. Absolute neutrophil count (ANC) ⩾ 1.5 × 109/L;
    b. Platelets ⩾ 100 × 109/L;
    c. Hemoglobin ⩾ 9.0 g/dL.
11. Adequate renal function characterized by serum creatinine ⩽ 1.5 × upper limit of normal (ULN), or calculated by Cockroft-Gault formula, or directly measured creatinine clearance ⩾ 50 mL/min at screening
12. Adequate electrolytes at Baseline, defined as serum potassium and magnesium levels within institutional normal limits (Note: replacement treatment to achieve adequate electrolytes will be allowed).
13. Adequate hepatic function characterized by the following at screening:
    a. Serum total bilirubin ⩽ 1.5 × ULN and < 2 mg/dL
    Note:
    Patients who have a total bilirubin level > 1.5 × ULN will be allowed if their indirect bilirubin level is ⩽ 1.5 × ULN.
    b. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ⩽ 2.5 × ULN, or ⩽ 5 × ULN in presence of liver metastases
14. Adequate cardiac function characterized by the following at screening:
    a. Left ventricular ejection fraction (LVEF) ⩾ 50% as determined by a MUGA scan or ECHO;
    b. Mean triplicate QT interval corrected for heart rate using Fridericia's formula (QTcF) value ⩽480 msec
15. Able to take oral medications
16. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures
17. Female patients are either postmenopausal for at least 1 year, are surgically sterile for at least 6 weeks, or must agree to take appropriate precautions to avoid pregnancy from screening through follow-up if of childbearing potential
18. Males must agree to take appropriate precautions to avoid fathering a child from screening through

90 days following end of therapy.

19. Patients under guardianship or partial guardianship will be eligible unless prohibited by local laws or by local/central ethic committees (e.g., France, Germany). Where allowed, all procedures prescribed by law must be followed

Exclusion Criteria

Patients who met any of the following criteria at Screening were to be excluded from the study:

1. Prior treatment with any RAF inhibitor, MEK inhibitor, cetuximab, panitumumab or other EGFR inhibitors
2. Prior irinotecan hypersensitivity or toxicity that would suggest an inability to tolerate irinotecan 180 mg/m2 every 2 weeks
3. Symptomatic brain metastasis
4. Leptomeningeal disease
5. History or current evidence of RVO or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes)
6. Use of any herbal medications/supplements or any medications or foods that are strong inhibitors or inducers of cytochrome P450 (CYP) 3A4/5 ⩽ 1 week prior to the start of study treatment
7. Known history of acute or chronic pancreatitis
8. History of chronic inflammatory bowel disease or Crohn’ s disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) ⩽ 12 months prior to randomization
9. Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:
   a. History of acute myocardial infarction, acute coronary syndromes (including unstable angina, coronary artery bypass graft [CABG], coronary angioplasty or stenting) ⩽ 6 months prior to start of study treatment;
   b. Symptomatic congestive heart failure (i.e., Grade 2 or higher), history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality ⩽ 6 months prior to start of study treatment, except atrial fibrillation and paroxysmal supraventricular tachycardia.
10. Uncontrolled hypertension defined as persistent elevation of systolic blood pressure⩾ 150 mmHg or diastolic blood pressure ⩾ 100 mmHg despite current therapy
11. Impaired hepatic function, defined as Child-Pugh class B or C
12. Impaired GI function or disease that may significantly alter the absorption of encorafenib or binimetinib (e.g., ulcerative diseases, uncontrolled vomiting, malabsorption syndrome, small bowel resection with decreased intestinal absorption)
13. Concurrent or previous other malignancy within 5 years of study entry, except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix, or other noninvasive or indolent malignancy without Sponsor approval
14. History of thromboembolic or cerebrovascular events ⩽ 6 months prior to starting study treatment, including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis or pulmonary emboli
15. Concurrent neuromuscular disorder that is associated with the potential of elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy)
16. Treatment with any of the following:
    a. Cyclical chemotherapy within a period of time that was shorter than the cycle length used for that treatment (e.g., 6 weeks for nitrosourea, mitomycin-C) prior to starting study treatment
    b. Biologic therapy (e.g., antibodies) except bevacizumab or aflibercept, continuous or intermittent

small molecule therapeutics, or any other investigational agents within a period of time that is ⩽ 5 half-lives (t1/2) or ⩽ 4 weeks (whichever is shorter) prior to starting study treatment
c. Bevacizumab or aflibercept therapy ⩽ 3 weeks prior to starting study treatment
d. Radiation therapy that included > 30% of the bone marrow

17. Residual CTCAE ⩾ Grade 2 toxicity from any prior anticancer therapy, with the exception of Grade 2 alopecia or Grade 2 neuropathy
18. Known history of HIV infection [HIV testing at Screening required for patients in Italy per Protocol Version 3.1 (ITA)]
19. Active hepatitis B or hepatitis C infection
20. Known history of Gilbert's syndrome or is known to have any of the following genotypes: UGT1A1*6/*6, UGT1A1*28/*28, or UGT1A1*6/*28
21. Known contraindication to receive cetuximab or irinotecan at the planned doses; refer to the most recent cetuximab and irinotecan SPC or local label as applicable
22. Current treatment with a non-topical medication known to be a strong inhibitor of CYP3A4. However, patients who either discontinue this treatment or switch to another medication at least 7 days prior to starting study treatment are eligible
23. Concomitant use of St. John’ s Wort (hypericum perforatum)
24. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient an inappropriate candidate for the study
25. Pregnant, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test result, or nursing (lactating)
26. Prior enrollment into this clinical study.

Treatments

Patients were assigned to the Triplet regimen (SLI/JSLI cohorts) or randomized (Phase III; 1:1:1) to one of the following study treatment regimens (details regarding dose and schedule are outlined in Table 6):

Triplet Regimen (SLI/JSLI Cohorts and Triplet Arm):

- Encorafenib (QD) + binimetinib (BID) + cetuximab (QW)

Doublet Regimen (Doublet Arm):

- Encorafenib (QD) + cetuximab (QW)

Irinotecan/Cetuximab OR FOLFIRI/Cetuximab (Control Arm):

- Irinotecan (Q2W) + cetuximab (QW)

OR

- Irinotecan (Q2W) + FA (Q2W) + 5-FU (Q2W) + cetuximab (QW)

Table 6: Dose and Treatment Schedule

Study Treatments	Pharmaceutical Form and Route of Administration	Dose	Frequency
Triplet Regimen (SLI/JSLI Cohorts and Triplet Arm)			
Encorafenib	4 × 75 mg oral capsule	300 mg	QD
Binimetinib	3 × 15 mg oral film-coated tablet	45 mg	BID
Cetuximab	IV infusion	400 mg/m^2 initial dose (120-min infusion on C1D1), then 250 mg/m^2 (60-min infusion) thereafter	QW (Days 1, 8, 15 and 22 [±3 days)] of every 28-day cycle)
Doublet Regimen (Doublet Arm)			
Encorafenib	4 × 75 mg oral capsule	300 mg	QD
Cetuximab	IV infusion	400 mg/m^2 initial dose (120-min infusion on C1D1), then 250 mg/m^2 (60-min infusion) thereafter	QW (Days 1, 8, 15 and 22 [±3 days)] of every 28-day cycle)
Irinotecan/Cetuximab OR FOLFIRI/Cetuximab (Control Arm)			
Irinotecan/Cetuximab			
Irinotecan	IV infusion	180 mg/m^2 (90-min infusion)	Q2W (Days 1 and 15 [±3 days] of every 28-day cycle
Cetuximab	IV infusion	400 mg/m^2 initial dose (120-min infusion on C1D1), then 250 mg/m^2 (60-min infusion) thereafter	QW (Days 1, 8, 15 and 22 [±3 days)] of every 28-day cycle)
FOLFIRI/Cetuximab			
Irinotecan	IV infusion	180 mg/m^2 (90-min infusion)	Q2W (Days 1 and 15 [±3 days] of every 28-day cycle
Folinic acid[a]	IV infusion	400 mg/m^2 (120-min infusion)	Q2W (Days 1 and 15 [±3 days] of every 28-day cycle
5-FU[a]	IV bolus/IV infusion	400 mg/m^2 bolus (not to exceed 15 min), then 1200 mg/m^2/day × 2 days (total 2400 mg/m^2 over 46-48 hours) continuous infusion	Q2W (Days 1 and 15 [±3 days] of every 28-day cycle
Cetuximab	IV infusion	400 mg/m^2 initial dose (120-min infusion on C1D1), then 250 mg/m^2 (60-min infusion) thereafter	QW (Days 1, 8, 15 and 22 [±3 days)] of every 28-day cycle)

Abbreviations: BID = twice daily; C1D1 = Cycle 1 Day 1; 5-FU = 5-fluorouracil; FA = folinic acid; FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = 5-fluorouracil/folinic acid/oxaliplatin; FOLFOXIRI = 5-fluorouracil/folinic acid/oxaliplatin/irinotecan; IV = intravenous; JSLI = Japanese Safety Lead-in; m = meter(s); mg = milligram(s); min = minute(s) QD = once daily; Q2W = once every 2 weeks; QW = once weekly; SLI = Safety Lead-in

[a] Patients who experienced unacceptable toxicities requiring 5-FU and FA dose reductions in prior regimens (e.g., as part of FOLFOX or FOLFOXIRI regimens) may be initiated at the highest doses which were previously tolerated.

Note: The duration of IV infusions for the non-investigational study drugs was to adhere to institutional standards.

Objectives

Following the protocol (version 7 as of January 25, 2019), the BEACON trial discerned objectives of the SLI and the phase III portion of the trial as follows:

A) Safety Lead-In

In patients with BRAFV600E mCRC:

Primary Objective

- Assess the safety/tolerability of the combination of encorafenib + binimetinib + cetuximab

Secondary Objectives

- Assess the activity of encorafenib + binimetinib + cetuximab as measured by blinded independent central review (BICR)-determined and Investigator-determined ORR, DOR, PFS and time to response

- Characterize the PK of encorafenib, cetuximab, binimetinib and the active metabolite of binimetinib (AR00426032)

Exploratory Objective

- Assess the activity of encorafenib + binimetinib + cetuximab as measured by OS

B) Randomized Phase III

In patients with BRAFV600E mCRC:

Primary Objectives

- Compare the activity of encorafenib + binimetinib + cetuximab (Triplet Arm) vs. irinotecan/cetuximab or 5-FU/FA/irinotecan (FOLFIRI)/cetuximab (Control Arm) as measured by OS
- Compare the activity of encorafenib + binimetinib + cetuximab (Triplet Arm) vs. irinotecan/cetuximab or FOLFIRI/cetuximab (Control Arm) as measured by ORR per BICR

Key Secondary Objectives

- Compare the activity of encorafenib + cetuximab (Doublet Arm) vs. irinotecan/cetuximab or FOLFIRI/cetuximab (Control Arm) as measured by OS

Other Secondary Objectives

- Compare the Investigator-determined ORR of encorafenib + binimetinib + cetuximab (Triplet Arm) vs. irinotecan/cetuximab or FOLFIRI/cetuximab (Control Arm)
- Compare the BICR-determined and Investigator-determined ORR of encorafenib + cetuximab (Doublet Arm) vs. irinotecan/cetuximab or FOLFIRI/cetuximab (Control Arm)
- Compare the BICR-determined and Investigator-determined PFS of encorafenib + binimetinib + cetuximab (Triplet Arm) vs. irinotecan/cetuximab or FOLFIRI/cetuximab (Control Arm)
- Compare the BICR-determined and Investigator-determined PFS of encorafenib + cetuximab (Doublet Arm) vs. irinotecan/cetuximab or FOLFIRI/cetuximab (Control Arm)
- Compare the activity of Triplet Arm vs. Doublet Arm as measured by OS
- Compare the BICR-determined and Investigator-determined ORR of Triplet Arm vs. Doublet Arm
- Compare the BICR-determined and Investigator-determined PFS of Triplet Arm vs. Doublet Arm
- Compare BICR-determined and Investigator-determined DOR of Triplet Arm vs. Control Arm, of Doublet Arm vs. Control Arm and of Triplet Arm vs. Doublet Arm
- Compare BICR-determined and Investigator-determined time to response of Triplet Arm vs. Control Arm, of Doublet Arm vs. Control Arm and of Triplet Arm vs. Doublet Arm
- Assess the safety/tolerability of Triplet Arm, of Doublet Arm and of Control Arm
- Compare the effect on QoL of Triplet Arm vs. Control Arm, of Doublet Arm vs. Control Arm and of Triplet Arm vs. Doublet Arm
- Characterize the PK of encorafenib, cetuximab, binimetinib and the active metabolite of binimetinib (AR00426032)
- Assess for drug interactions between encorafenib, cetuximab, binimetinib and the active metabolite of binimetinib (AR00426032) based on PK modeling

Exploratory Objectives

- Assess the relationship between changes in tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA19-9]) and radiographic response to treatment
- Assess blood- and tissue-based predictive biomarkers of activity

Outcomes/endpoints

The endpoints for the SLI and the phase III portion of the BEACON trial differed as follows:

A) Safety Lead-In

Primary Endpoints

- Incidence of DLTs
- Incidence and severity of AEs, graded according to the NCI CTCAE, version 4.03 (v.4.03), and changes in clinical laboratory parameters, vital signs, ECGs, ECHO/MUGA scans and ophthalmic examinations
- Incidence of dose interruptions, dose modifications and discontinuations due to AEs

Secondary Endpoints

- ORR (by BICR and Investigator) per the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (v1.1), defined as the number of patients achieving an overall best response of complete response (CR) or PR divided by the total number of patients
- DOR (by BICR and Investigator), defined as the time from first radiographic evidence of response to the earliest documented disease progression or death due to underlying disease
- PFS (by BICR and Investigator), defined as the time from first dose to the earliest documented disease progression or death due to any cause
- Time to response (by BICR and Investigator), defined as the time from first dose to first radiographic evidence of response
- PK parameters of encorafenib, cetuximab, binimetinib and the active metabolite of binimetinib (AR00426032)

Exploratory Endpoint

- OS, defined as the time from first dose to death due to any cause

B) Randomized Phase III

Primary Endpoints

- OS, defined as the time from randomization to death due to any cause, of Triplet Arm vs. Control Arm
- Confirmed ORR (by BICR) per RECIST, v1.1 of Triplet Arm vs. Control Arm

Key Secondary Endpoint

- OS of Doublet Arm vs. Control Arm

Other Secondary Endpoints

- Confirmed ORR (by Investigator) per RECIST, v1.1 of Triplet Arm vs. Control Arm
- Confirmed ORR (by BICR and Investigator) per RECIST, v1.1 of Doublet Arm vs. Control Arm
- PFS (by BICR and Investigator), defined as the time from randomization to the earliest documented disease progression or death due to any cause, of Triplet Arm vs. Control Arm
- PFS (by BICR and Investigator) of Doublet Arm vs. Control Arm
- OS of Triplet Arm vs. Doublet Arm
- Confirmed ORR (by BICR and Investigator) per RECIST, v1.1 of Triplet Arm vs. Doublet Arm
- PFS (by BICR and Investigator) of Triplet Arm vs. Doublet Arm
- DOR (by BICR and Investigator) of Triplet Arm vs. Control Arm, of Doublet Arm vs. Control Arm and of Triplet Arm vs. Doublet Arm
- Time to response (by BICR and Investigator), defined as the time from randomization to first radiographic evidence of response, of Triplet Arm vs. Control Arm, of Doublet Arm vs. Control Arm and of Triplet Arm vs. Doublet Arm
- Incidence and severity of AEs, graded according to NCI CTCAE, v.4.03, and changes in clinical laboratory parameters, vital signs, ECGs, ECHO/MUGA scans and ophthalmic examinations
- Change from baseline in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Cancer Patients (QLQ-C30), Functional Assessment of Cancer Therapy-Colon Cancer (FACT-C), EuroQol-5D-5L (EQ-5D-5L), and Patient Global Impression of Change (PGIC) of Triplet Arm vs. Control Arm, of Doublet Arm vs. Control Arm and of Triplet Arm vs. Doublet Arm
- Model-based PK parameters of encorafenib, cetuximab, binimetinib and the active metabolite of binimetinib (AR00426032)
- Model-based PK assessment of drug-drug interactions between encorafenib, cetuximab, binimetinib and the active metabolite of binimetinib (AR00426032)

Exploratory Endpoints

- Changes in CEA and CA19-9
- Genomic and proteomic analysis of blood and tissue samples at baseline and at end of treatment (optional for tumor samples at end of treatment).

Sample size

Based on historical evidence, it was assumed that both Control arm options would have an approximate median OS of 5 months. The number of patients required for the randomized Phase 3 portion of the study was driven by the key secondary endpoint of OS of the Doublet arm vs. Control arm. For this comparison, the study was powered to detect an improvement of 2.1 months (7.1 months vs. 5 months; HR = 0.70). With 338 OS events, the study has approximately 90% power to detect this improvement using a group-sequential design and one-sided $\alpha = 0.025$. Assuming accrual to the randomized Phase 3 portion of the study increased over a period of time before reaching a maximum of 25 patients per month (for an accrual duration of approximately 25 months) and 5% loss to follow-up, approximately 615 patients

would be randomized to reach 338 events. The final analysis for OS will occur once at least 268 events are observed in the Triplet arm + Control arm and at least 338 events are observed in the Doublet arm + Control arm.

The Sample size calculation was appropriate.

Randomisation

In Phase III, randomization was used to ensure that treatment assignment was unbiased. Patients were randomized to one of the 3 treatment arms (Triplet arm, Doublet arm or Control arm) in a ratio of 1:1:1. The proportion of third-line patients (i.e., those who had received 2 prior regimens) was limited to 35% of the total randomized population (estimated in the protocol to be 215 patients, assuming a total planned randomization of 615 patients), after which only patients with 1 prior regimen were to be randomized. Patients with 2 prior regimens who entered Screening at the time that the limit was reached were permitted to continue into the study if they were otherwise determined to be eligible. Randomization was stratified by ECOG PS (0 or 1), prior use of irinotecan (yes or no), and cetuximab source (US-licensed vs. EU-approved). Prior to dosing, all patients who fulfilled all inclusion/exclusion criteria were randomized via the interactive web response system (IWRS) to one of the treatment arms.

Blinding (masking)

The study was open-label.

Statistical methods

For patients in the CSLI (incorporating the SLI [patients in the US and EU] and the JSLI [patients in Japan]), the full analysis set (FAS) consisted of all patients who received at least 1 dose of study drug and had at least 1 post-treatment assessment, which may have included death.

For patients in the Phase III portion of the study, FAS consisted of all randomized Phase III patients. Patients were analyzed according to the treatment arm and stratum they were assigned to at randomization.

The dose determining set (DDS) included all CSLI patients from the Safety Set who either completed a minimum exposure requirement and had sufficient safety evaluations or experienced a DLT.

For the Phase III portion of the study, a primary endpoint and the key secondary efficacy endpoint was OS, defined as the time from randomization to death due to any cause. Patients who did not have a death date by the data cut-off date were censored for OS at their last contact date. Overall survival was calculated for all patients in the FAS and summarized by treatment arm using the Kaplan-Meier method. In the SLI portion of the study, OS was an exploratory endpoint, defined as the time from first dose of study drug to death due to any cause, using the SLI Efficacy Set.

For the OS primary endpoint, the null hypothesis of the primary objective was that the OS for the Triplet combination is less than or equal to the OS of the Control Arm. The null hypothesis was tested using a stratified log-rank test against the α assigned to the endpoint based on the fallback approach (see below). The stratification factors used in the test were those used for randomization.

The distribution of OS was described in tabular and graphical format by treatment group using Kaplan-Meier methods, reporting the estimated median (in months) with 95% CI and 25th and 75th percentiles

and Kaplan-Meier estimated probabilities with corresponding 95% CI at several time points. A Cox regression model stratified by randomization stratification factors was used to estimate the HR of OS, along with 95% CI based on the Wald test.

The following sensitivity analyses were conducted for the randomized Phase III portion of the study to support the analyses of OS. The OS analyses were repeated using the PPS. Also, as the Triplet and Control arms were anticipated to have more than 268 combined OS events by the time the required number of OS events were observed in the Doublet arm and Control arm, the OS analysis of the Triplet arm vs. Control arm was repeated using all available OS events. The distribution of OS in the FAS was compared between treatment arms using an unstratified log-rank test and the HR (with associated 95% CI) resulting from an unstratified Cox model was presented. For the randomized Phase 3 portion of the study, the effect of potential prognostic factors was investigated using multivariate stratified Cox regression.

Subgroup analyses were performed for each of the 3 Baseline stratification factors and other relevant Baseline variables provided the number of patients randomized with these particular covariates allowed (i.e., at least 10 events were to be available in the considered subgroup).

The ORR by BICR was tested for the primary endpoint of Triplet arm vs. Control arm based on the Phase 3 Response Efficacy Set and using the Cochran-Mantel-Haenszel test at a one-sided α of 0.005. Both confirmed and unconfirmed ORR were summarized but, for purposes of formal testing, the analysis of the confirmed responses was used. The stratification factors used in the test were those used for randomization. For the primary analysis, ORR was presented by arm, along with 95% and 99% CIs. A similar analysis for ORR (Triplet arm vs. Control arm) was performed on the FAS. The secondary ORR endpoints (including Investigator-assessed ORR) were analyzed in a similar manner based on the Phase 3 Response Efficacy Set and the FAS.

Progression-free survival was calculated for all patients in the FAS and summarized by treatment arm or SLI cohort using the Kaplan-Meier method. Progression-free survival as determined by both BICR and by Investigator was analyzed. For the randomized Phase 3 portion of the study, PFS by BICR was prioritized in the hierarchical testing, followed by PFS by Investigator assessment. Overall treatment arm estimates, as well as treatment arm estimates by stratum, were provided. For the primary PFS analysis, disease progression and death (from any cause) were considered as events. If death or disease progression was not observed, PFS was censored at the date of last adequate tumour assessment (i.e., at the date of last tumor assessment of CR, PR or stable disease) prior to cutoff date or date a subsequent therapy is started (e.g., systemic therapy, surgery, radiotherapy). However, if a PFS event was observed after more than 1 missing or inadequate tumour assessment, PFS was censored at the last adequate tumor assessment. If a PFS event was observed after a single missing or non-adequate tumour assessment, the actual date of event was used. Sensitivity analyses were performed on patients with early censoring because they have the potential to cause bias, as they have incomplete follow-up and their progression status at the data cut-off is unknown.

The Type I error rate for the primary endpoints was controlled using a fallback procedure described by Wiens and Dmitrienko (2005). A one-sided α of 0.005 was assigned to the Triplet arm vs. Control arm ORR endpoint. The remaining 0.020 was assigned to the Triplet arm vs. Control arm OS endpoint. Because the p value of the Triplet arm vs. Control arm comparison of ORR at the primary analysis was < 0.005, then the Triplet vs. Control OS comparison was assigned a total one-sided α of 0.025.

The key secondary endpoint and 3 secondary endpoints were formally tested. To control the overall Type I error rate, a gatekeeping procedure using hierarchical testing was used. Because the OS of the Triplet arm vs. Control arm was found to be significant at the interim analysis the following tests then were conducted sequentially, each at the same total α assigned to the Triplet arm vs. Control arm OS endpoint:

1. OS of Doublet arm vs. Control arm
2. ORR (by BICR) of Doublet arm vs. Control arm
3. PFS (by BICR) of Triplet arm vs. Control arm
4. PFS (by BICR) of Doublet arm vs. Control arm

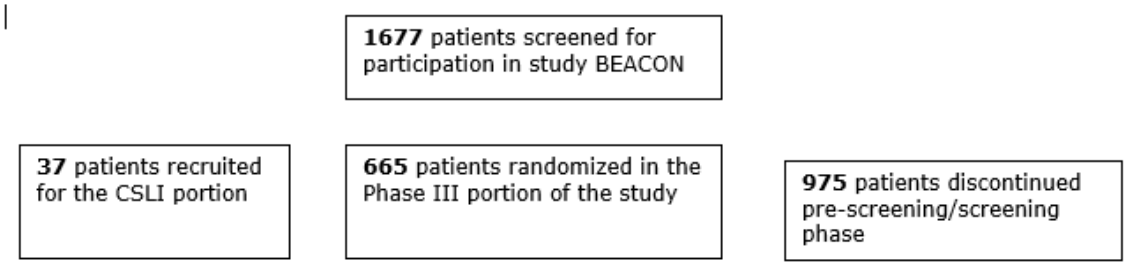
According to the original protocol, OS was the only primary endpoint and the primary analysis was planned to occur once at least 232 events were observed in the Triplet Arm + Control Arm and at least 338 events were observed in the Doublet Arm + Control Arm. The study design included a nonbinding futility interim analysis when approximately 50% of the expected OS events in the Triplet Arm + Control Arm occur (i.e., 167 deaths). With protocol amendment 6, a primary objective and endpoint was added to the randomized portion of the study for confirmed ORR by BICR of encorafenib + binimetinib + cetuximab (Triplet arm) vs. irinotecan/cetuximab or FOLFIRI/cetuximab (Control arm). An initial analysis of the study was to be performed when all of the following criteria were met:

- Approximately 9 months after randomization of the 330th patient (i.e., approximately 110 patients per arm), to allow a majority of responders among the 330 Phase 3 patients to have had the opportunity to be followed for approximately 6 months or longer after their first response
- At least 188 OS events had occurred in the Triplet and Control arms combined (i.e., approximately 70% information)
- At least 169 OS events had occurred in the Doublet and Control arms combined (i.e., approximately 50% information)

The planned interim analysis of OS (Triplet arm vs. Control arm) was modified to include boundaries for both superiority and (non-binding) futility, and the timing of this analysis was modified to occur at the same time as the primary analysis of the newly added ORR endpoint. The interim analysis for superiority or (non-binding) futility of the Triplet arm vs. Control arm OS endpoint was performed based on all available data (i.e., using the FAS). Futility and superiority boundaries for both the OS interim and final analyses were determined using a Lan-DeMets spending function (Lan and DeMets 1983) that approximated O'Brien-Fleming stopping boundaries. Several measures were taken to preserve data blinding at the time of the Protocol amendment 6 decision for the teams involved in the decision to amend the protocol.

Results

Participant flow



For further participant flow in the randomized (and CSLI) portions of the study see table 10 in the next section.

Recruitment

Enrollment/randomization in the study was conducted as follows:

- The SLI cohort was enrolled between 28 October 2016 and 31 March 2017.
- The JSLI cohort was enrolled between 22 February 2018 and 27 March 2018.
- Randomization into the Phase 3 portion of the study was conducted between 04 May 2017 and 31 January 2019.
    - o Note: Screening at sites in the United States was closed on 15 July 2018 due to the relatively high number of consent withdrawals by patients randomized to the Control arm and the off-label availability of BRAF inhibitors and MEK inhibitors including encorafenib and binimetinib, which were approved for the treatment of patients with BRAF-mutant melanoma in June 2018.

A summary of patient disposition by treatment group for the FAS is provided in Table 10 (data cut-off **11 February 2019)**.

Table 10: Patient Disposition (Full Analysis Set)

Category	Randomized Phase 3 + CSLI (Pooled) ENCO + BINI + CETUX N = 261	CSLI ENCO + BINI + CETUX N = 37	Randomized Phase 3 ENCO + BINI + CETUX N = 224	Randomized Phase 3 ENCO + CETUX N = 220	Randomized Phase 3 CONTROL N = 221
Randomized, Not Treated[a]	2 (0.8)	0 (0.0)	2 (0.9)	4 (1.8)	28 (12.7)
Treatment Ongoing	84 (32.2)	6 (16.2)	78 (34.8)	78 (35.5)	37 (16.7)
Treatment Discontinued	175 (67.0)	31 (83.8)	144 (64.3)	138 (62.7)	156 (70.6)
Progressive Disease	127 (48.7)	23 (62.2)	104 (46.4)	101 (45.9)	103 (46.6)
Unacceptable AEs Or Failure To Tolerate Study Drug	13 (5.0)	2 (5.4)	11 (4.9)	11 (5.0)	10 (4.5)
Changes In The Patient's Condition Or Development Of An Intercurrent Illness	12 (4.6)	3 (8.1)	9 (4.0)	9 (4.1)	13 (5.9)
Death	8 (3.1)	1 (2.7)	7 (3.1)	5 (2.3)	11 (5.0)
Withdrawal Of Consent	5 (1.9)	1 (2.7)	4 (1.8)	3 (1.4)	9 (4.1)
Dose Interruption > 28 consecutive days (Encorafenib or Binimetinib) or 2 Missed Consecutive Irinotecan, 5-FU, or FA or >4 Missed Consecutive Cetuximab	3 (1.1)	1 (2.7)	2 (0.9)	2 (0.9)	4 (1.8)
Patient Decision To Discontinue Study Treatment	2 (0.8)	0 (0.0)	2 (0.9)	2 (0.9)	4 (1.8)
Physician Decision	2 (0.8)	0 (0.0)	2 (0.9)	4 (1.8)	2 (0.9)
Other	3 (1.1)	0 (0.0)	3 (1.3)	1 (0.5)	0 (0.0)
Tumor Assessment Follow-up Ongoing	86 (33.0)	7 (18.9)	79 (35.3)	77 (35.0)	37 (16.7)
Tumor Assessment Follow-up Discontinued	175 (67.0)	30 (81.1)	145 (64.7)	143 (65.0)	184 (83.3)
Progressive Disease	137 (52.5)	24 (64.9)	113 (50.4)	111 (50.5)	113 (51.1)
Death	18 (6.9)	4 (10.8)	14 (6.3)	22 (10.0)	27 (12.2)
Withdrawal Of Consent	7 (2.7)	0 (0.0)	7 (3.1)	5 (2.3)	35 (15.8)
Other	6 (2.3)	0 (0.0)	6 (2.7)	2 (0.9)	6 (2.7)
Physician Decision	4 (1.5)	2 (5.4)	2 (0.9)	1 (0.5)	2 (0.9)
Initiation Of Subsequent Therapy	3 (1.1)	0 (0.0)	3 (1.3)	2 (0.9)	1 (0.5)
Survival Follow-up Ongoing	144 (55.2)	13 (35.1)	131 (58.5)	122 (55.5)	90 (40.7)
Study Discontinued	117 (44.8)	24 (64.9)	93 (41.5)	98 (44.5)	131 (59.3)
Death	113 (43.3)	23 (62.2)	90 (40.2)	93 (42.3)	112 (50.7)
Withdrawal Of Consent	3 (1.1)	0 (0.0)	3 (1.3)	3 (1.4)	18 (8.1)
Lost To Follow-Up	1 (0.4)	1 (2.7)	0 (0.0)	2 (0.9)	1 (0.5)

Abbreviations: AE = adverse event; BINI = binimetinib; CETUX = cetuximab; CSLI = Combined Safety Lead-in; ENCO = encorafenib; FA = folinic acid; 5-FU = 5-fluorouracil

[a] CSLI patients are not included.

Source: Table 14.1-1.3.1

Table 1 below provides an update of patient treated in the FAS (randomized part only) (**data cut-off 15 August 2019**):

Table 1: Patient Disposition (Randomized Phase 3, Full Analysis Set)

	Randomized Phase 3		
Category, n (%)	ENCO + BINI + CETUX N = 224	ENCO + CETUX N = 220	CONTROL N = 221
Randomized, Not Treated	2 (0.9)	4 (1.8)	28 (12.7)
Treatment Ongoing	30 (13.4)	30 (13.6)	7 (3.2)
Treatment Discontinued	192 (85.7)	186 (84.5)	186 (84.2)
Progressive Disease	140 (62.5)	145 (65.9)	123 (55.7)
Changes In The Patient's Condition Or Development Of An Intercurrent Illness	14 (6.3)	11 (5.0)	16 (7.2)
Unacceptable AEs Or Failure To Tolerate Study Drug	13 (5.8)	11 (5.0)	10 (4.5)
Death	8 (3.6)	6 (2.7)	11 (5.0)
Withdrawal Of Consent	4 (1.8)	3 (1.4)	11 (5.0)
Dose Interruption Of > 28 Consecutive Days (Encorafenib Or Binimetinib) Or 2 Missed Consecutive Irinotecan, 5-FU, Or FA Or >4 Missed Consecutive Cetuximab Doses	4 (1.8)	2 (0.9)	6 (2.7)
Patient Decision To Discontinue Study Treatment	3 (1.3)	3 (1.4)	5 (2.3)
Physician Decision	2 (0.9)	4 (1.8)	2 (0.9)
Other	3 (1.3)	1 (0.5)	1 (0.5)
Receipt Of Subsequent Anti-Cancer Therapy	1 (0.4)	0 (0.0)	1 (0.5)
Tumor Assessment Follow-up Ongoing	32 (14.3)	29 (13.2)	10 (4.5)
Tumor Assessment Follow-up Discontinued	192 (85.7)	191 (86.8)	211 (95.5)
Progressive Disease	153 (68.3)	155 (70.5)	136 (61.5)
Death	16 (7.1)	25 (11.4)	27 (12.2)
Withdrawal Of Consent	7 (3.1)	6 (2.7)	37 (16.7)
Other	8 (3.6)	2 (0.9)	6 (2.7)
Initiation Of Subsequent Therapy	6 (2.7)	2 (0.9)	3 (1.4)
Physician Decision	2 (0.9)	1 (0.5)	2 (0.9)
Survival Follow-up Ongoing	84 (37.5)	85 (38.6)	49 (22.2)
Study Discontinued	140 (62.5)	135 (61.4)	172 (77.8)
Death	137 (61.2)	128 (58.2)	151 (68.3)
Withdrawal Of Consent	3 (1.3)	5 (2.3)	20 (9.0)
Lost To Follow-Up	0 (0.0)	2 (0.9)	1 (0.5)

Abbreviations: AE = adverse event; BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib; FA = folinic acid; 5-FU = 5-fluorouracil

Source: Addendum Table 14.1-1.3.1

Conduct of the study

The (final) protocol was subject to overall 6 amendments.

The most relevant protocol changes occurred with version 6 changing the following (affecting the primary objectives and endpoints of the randomized/confirmative portion of the trial):

Protocol Version 6.0 (dated 19 September 2018) included the following substantive changes:

- A primary objective and endpoint was added to the randomized portion of the study for confirmed ORR by BIRC of encorafenib + binimetinib + cetuximab (Triplet arm) vs. irinotecan/cetuximab or FOLFIRI/cetuximab (Control arm). This was to be performed when all of the following criteria were met: approximately 9 months after randomization of the 330th patient, when ≥ 188 OS events had occurred in the Triplet and Control arms combined (i.e., approximately 70% information), and when ≥ 169 OS events occurred in the Doublet and Control arms combined (i.e., approximately 50% information). This primary objective and endpoint was added because demonstration of a high rate of durable responses and/or a positive effect on OS could be the basis for marketing approval for the Triplet combination in some regions, resulting in earlier access for patients in this setting of high unmet need.

- The planned interim analysis of OS (Triplet arm vs. Control arm) was modified to include boundaries for both superiority and (non-binding) futility, and the timing of this analysis was modified to occur at the same time as the primary analysis of the newly added ORR endpoint.
- Retrospective BICR was added for patients' tumor imaging data to support the Phase III primary endpoint of confirmed ORR per BICR (Triplet arm vs. Control arm) as well as secondary efficacy analyses of ORR, PFS, DOR and TTR.

A summary of protocol deviations by treatment group is provided.

Table 14.1-1.6: Protocol Deviations by Deviation Type; (Full Analysis Set)

	Randomized and CSLI (Pooled)	CSLI	Randomized Portion			
Protocol Deviation Category Protocol Deviation Subcategory	ENCO+ BINI+ CETUX (N=261) n (%)	ENCO+ BINI+ CETUX (N=37) n (%)	ENCO+ BINI+ CETUX (N=224) n (%)	ENCO+ CETUX (N=220) n (%)	Control (N=221) n (%)	Phase 3 Total (N=665) n (%)
Major Exclude	13 (5.0)	0 (0.0)	13 (5.8)	19 (8.6)	17 (7.7)	49 (7.4)
Selection criteria not met	13 (5.0)	0 (0.0)	13 (5.8)	19 (8.6)	17 (7.7)	49 (7.4)
Major	73 (28.0)	13 (35.1)	60 (26.8)	58 (26.4)	53 (24.0)	171 (25.7)
Assessment performed out of protocol window	19 (7.3)	1 (2.7)	18 (8.0)	16 (7.3)	8 (3.6)	42 (6.3)
ICF discrepancies	2 (0.8)	0 (0.0)	2 (0.9)	2 (0.9)	4 (1.8)	8 (1.2)
ICH/GCP deviation	2 (0.8)	1 (2.7)	1 (0.4)	3 (1.4)	5 (2.3)	9 (1.4)
Imaging assessment not performed per protocol	8 (3.1)	1 (2.7)	7 (3.1)	7 (3.2)	2 (0.9)	16 (2.4)
Missed assessment	8 (3.1)	0 (0.0)	8 (3.6)	6 (2.7)	9 (4.1)	23 (3.5)
Missed visit	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Not discontinued after meeting withdrawal criteria	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.5)	0 (0.0)	2 (0.3)
Selection criteria not met	16 (6.1)	3 (8.1)	13 (5.8)	4 (1.8)	14 (6.3)	31 (4.7)
Study treatment deviation	30 (11.5)	9 (24.3)	21 (9.4)	21 (9.5)	22 (10.0)	64 (9.6)
Use of prohibited conmeds	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)

All major protocol deviation that led to exclusion were in the category of "selection criteria not met", which were "not positive for BRAF V600 mutation per central assessment" and "prior treatment with any RAF inhibitor, MEK inhibitor, cetuximab, panitumumab or other EGFR inhibitors".

Baseline data

A summary of patient demographics at Baseline for the FAS is provided by treatment group in Table 11.

Table 11: Demographics (Full Analysis Set)

Demographic Variable	Randomized Phase 3 + CSLI (Pooled) ENCO + BINI + CETUX N = 261	CSLI ENCO + BINI + CETUX N = 37	Randomized Phase 3 ENCO + BINI + CETUX N = 224	Randomized Phase 3 ENCO + CETUX N = 220	Randomized Phase 3 CONTROL N = 221
Region, n (%)					
North America	35 (13.4)	5 (13.5)	30 (13.4)	28 (12.7)	29 (13.1)
Europe	175 (67.0)	25 (67.6)	150 (67.0)	145 (65.9)	125 (56.6)
Rest of World [a]	51 (19.5)	7 (18.9)	44 (19.6)	47 (21.4)	67 (30.3)
Race, n (%)					
Asian	27 (10.3)	7 (18.9)	20 (8.9)	25 (11.4)	39 (17.6)
White	224 (85.8)	29 (78.4)	195 (87.1)	183 (83.2)	172 (77.8)
Black/African American	3 (1.1)	1 (2.7)	2 (0.9)	0 (0.0)	0 (0.0)
Other [b]	3 (1.1)	0 (0.0)	3 (1.3)	4 (1.8)	3 (1.4)
Not reported due to confidentiality reasons	4 (1.5)	0 (0.0)	4 (1.8)	8 (3.6)	7 (3.2)
Sex, n (%)					
Male	120 (46.0)	15 (40.5)	105 (46.9)	115 (52.3)	94 (42.5)
Female	141 (54.0)	22 (59.5)	119 (53.1)	105 (47.7)	127 (57.5)
Age (years)					
Mean (SD)	59.3 (11.46)	58.3 (10.34)	59.5 (11.65)	60.2 (11.65)	58.4 (12.07)
Median	61	61	62	61	60
Min, Max	26, 85	36, 77	26, 85	30, 91	27, 91
Age category (years), n (%)					
< 65	164 (62.8)	23 (62.2)	141 (62.9)	137 (62.3)	149 (67.4)
65- < 75	80 (30.7)	13 (35.1)	67 (29.9)	63 (28.6)	55 (24.9)
≥ 75	17 (6.5)	1 (2.7)	16 (7.1)	20 (9.1)	17 (7.7)

Abbreviations: BINI = binimetinib; CETUX = cetuximab; CSLI = Combined Safety Lead-in; ENCO = encorafenib; Max = maximum; Min = minimum; SD = standard deviation

[a] Mexico is included in Rest of World rather than North America due to the use of European-approved cetuximab.

[b] "Other" includes categories of American Indian/Alaska Native and Other.

Source: Table 14.1-3.1.1

A summary of patient and disease characteristics by treatment group for the FAS is provided in Table 12.

Table 12: Patient and Disease Characteristics (Full Analysis Set)

Disease Characteristic	Randomized Phase 3 + CSLI (Pooled) ENCO + BINI + CETUX N = 261	CSLI ENCO + BINI + CETUX N = 37	Randomized Phase 3 ENCO + BINI + CETUX N = 224	Randomized Phase 3 ENCO + CETUX N = 220	Randomized Phase 3 CONTROL N = 221
ECOG PS at Baseline [a], n (%)					
0	138 (52.9)	22 (59.5)	116 (51.8)	112 (50.9)	108 (48.9)
1	123 (47.1)	15 (40.5)	108 (48.2)	104 (47.3)	113 (51.1)
2	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.8) [b]	0 (0.0)
Stage at Study Entry, n (%)					
Stage IV	261 (100.0)	37 (100.0)	224 (100.0)	220 (100.0)	221 (100.0)
Primary Tumor Location, n (%)					
Left Colon [c]	90 (34.5)	11 (29.7)	79 (35.3)	83 (37.7)	68 (30.8)
Right Colon	149 (57.1)	23 (62.2)	126 (56.3)	110 (50.0)	119 (53.8)
Left and Right Colon	8 (3.1)	0 (0.0)	8 (3.6)	11 (5.0)	22 (10.0)
Unknown	14 (5.4)	3 (8.1)	11 (4.9)	16 (7.3)	12 (5.4)
Primary Tumor Removed, n (%)					
Completely Resected	153 (58.6)	20 (54.1)	133 (59.4)	123 (55.9)	122 (55.2)
Partially Resected/Unresected	108 (41.4)	17 (45.9)	91 (40.6)	97 (44.1)	99 (44.8)
Number of Organs Involved					
Mean (SD)	3 (1.4)	3 (1.7)	3 (1.3)	3 (1.4)	3 (1.3)
Median	3	3	2	2	2
Min, Max	1, 8	1, 8	1, 7	0, 7	1, 8
Number of Organs Involved, n (%)					
≤ 2	130 (49.8)	16 (43.2)	114 (50.9)	117 (53.2)	123 (55.7)
≥ 3	131 (50.2)	21 (56.8)	110 (49.1)	103 (46.8)	98 (44.3)
Sites of Metastases, n (%)					
Liver	168 (64.4)	24 (64.9)	144 (64.3)	134 (60.9)	128 (57.9)
Lung	96 (36.8)	10 (27.0)	86 (38.4)	83 (37.7)	86 (38.9)
Lymph Node	103 (39.5)	17 (45.9)	86 (38.4)	82 (37.3)	88 (39.8)
Peritoneum/Omentum	94 (36.0)	17 (45.9)	77 (34.4)	97 (44.1)	93 (42.1)
MSI Status (PCR), n (%)					
Abnormal high	22 (8.4)	0 (0.0)	22 (9.8)	19 (8.6)	12 (5.4)
Abnormal low	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)
Normal	187 (71.6)	34 (91.9)	153 (68.3)	157 (71.4)	147 (66.5)
Not evaluable	15 (5.7)	0 (0.0)	15 (6.7)	16 (7.3)	10 (4.5)
Missing	37 (14.2)	3 (8.1)	34 (15.2)	27 (12.3)	51 (23.1)
CEA at Baseline, n (%)					
> 5 µg/L	206 (78.9)	27 (73.0)	179 (79.9)	153 (69.5)	178 (80.5)
≤ 5 µg/L	55 (21.1)	10 (27.0)	45 (20.1)	67 (30.5)	42 (19.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
CRP at Baseline, n (%)					
> 0.01 g/L	115 (44.1)	20 (54.1)	95 (42.4)	79 (35.9)	90 (40.7)
≤ 0.01 g/L	136 (52.1)	15 (40.5)	121 (54.0)	139 (63.2)	126 (57.0)
Missing	10 (3.8)	2 (5.4)	8 (3.6)	2 (0.9)	5 (2.3)

Disease Characteristic	Randomized Phase 3 + CSLI (Pooled) ENCO + BINI + CETUX N = 261	CSLI ENCO + BINI + CETUX N = 37	Randomized Phase 3 ENCO + BINI + CETUX N = 224	Randomized Phase 3 ENCO + CETUX N = 220	Randomized Phase 3 CONTROL N = 221

Abbreviations: BINI = binimetinib; CEA = carcinoembryonic antigen; CETUX = cetuximab; CRP = C-reactive protein; CSLI = Combined Safety Lead-in; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eCRF = electronic case report form; ENCO = encorafenib; IWRS = interactive web response system; Max = maximum; Min = minimum; MSI = microsatellite instability; PCR = polymerase chain reaction; SD = standard deviation

[a] ECOG PS as per eCRF at Baseline and not per IWRS at randomization.

[b] All 4 patients were ECOG PS 1 at randomization per the IWRS (Table 14.1-1.4.1).

[c] "Left colon" includes rectum.

Source: Table 14.1-3.2.1

A summary of BRAF and RAS tumor mutational status by treatment group for the FAS is provided in Table 13.

Table 13: Mutational Status (Full Analysis Set)

	Randomized Phase 3 + CSLI (Pooled)	CSLI	Randomized Phase 3		
	ENCO + BINI + CETUX N = 261	ENCO + BINI + CETUX N = 37	ENCO + BINI + CETUX N = 224	ENCO + CETUX N = 220	CONTROL N = 221
BRAF V600E Mutation Status (Local), n (%)					
Detected	205 (78.5)	36 (97.3)	169 (75.4)	166 (75.5)	173 (78.3)
Not Detected	1 (0.4)	1 (2.7)	0 (0.0)	2 (0.9)	0 (0.0)
Not Available	55 (21.1)	0 (0.0)	55 (24.6)	52 (23.6)	48 (21.7)
BRAF V600E Mutation Status (Central), n (%)					
Mutation Detected	246 (94.3)	33 (89.2)	213 (95.1)	201 (91.4)	201 (91.0)
No Mutation Detected	4 (1.5)	2 (5.4)	2 (0.9)	3 (1.4)	5 (2.3)
No Neoplastic Cell in Tissue	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.5)	3 (1.4)
Indeterminate	10 (3.8)	2 (5.4)	8 (3.6)	11 (5.0)	9 (4.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.8)	3 (1.4)
*RAS*wt Status (Local), n (%)					
Detected	187 (71.6)	35 (94.6)	152 (67.9)	147 (66.8)	159 (71.9)
Not Detected	3 (1.1)	0 (0.0)	3 (1.3)	0 (0.0)	2 (0.9)
Not Available	71 (27.2)	2 (5.4)	69 (30.8)	73 (33.2)	60 (27.1)
KRAS Status (Central), n (%)					
Mutation Detected	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.5)	5 (2.3)
No Mutation Detected	249 (95.4)	37 (100.0)	212 (94.6)	201 (91.4)	200 (90.5)
Indeterminate	7 (2.7)	0 (0.0)	7 (3.1)	7 (3.2)	4 (1.8)
Missing	4 (1.5)	0 (0.0)	4 (1.8)	11 (5.0)	12 (5.4)

Abbreviations: BINI = binimetinib; CETUX = cetuximab; CSLI = Combined Safety Lead-in; ENCO = encorafenib; wt = wild type
Source: Table 14.1-3.3.1

Baseline plasma samples were available for 29 of 39 randomized patients whose central BRAF V600E mutation result did not confirm the local positive result. Analysis of circulating tumor DNA (Idylla™ ctBRAF Mutation Assay, Biocartis, Mechelen, Belgium) detected a BRAF V600E mutation in 25 of these 29 patients (86.2%).

As the study reached its protocol-specified limit of patients whose central BRAF V600E mutation result was either indeterminate or discordant with the local assay result, central laboratory confirmation of BRAF V600E tumour mutation status became mandatory for study eligibility with Administrative Letter dated 21 December 2018.

A summary of prior systemic antineoplastic therapies by treatment group for the FAS is provided in Table 15.

Table 15: Prior Systemic Antineoplastic Therapy (Full Analysis Set)

	Randomized Phase 3 + CSLI (Pooled)	CSLI	Randomized Phase 3		
	ENCO + BINI + CETUX N = 261	ENCO + BINI + CETUX N = 37	ENCO + BINI + CETUX N = 224	ENCO + CETUX N = 220	CONTROL N = 221
Prior Systemic Therapy, n (%)	261 (100.0)	37 (100.0)	224 (100.0)	220 (100.0)	221 (100.0)
Number of Prior Systemic Regimens for Metastatic Disease- n (%) [a]					
1	167 (64.0)	21 (56.8)	146 (65.2)	146 (66.4)	145 (65.6)
2	93 (35.6)	16 (43.2)	77 (34.4)	74 (33.6)	75 (33.9)
> 2	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.5)
Prior Irinotecan, n (%)	134 (51.3)	18 (48.6)	116 (51.8)	114 (51.8)	117 (52.9)
Prior Oxaliplatin, n (%)	235 (90.0)	36 (97.3)	199 (88.8)	210 (95.5)	201 (91.0)

Abbreviations: BINI = binimetinib; CETUX = cetuximab; CSLI = Combined Safety Lead-in; ENCO = encorafenib
[a] Based on a Sponsor assessment (see Section 9.7.1.5.3).
Source: Table 14.1-3.9.1

The overall use of concomitant medications reflected the toxicity profiles of each treatment regimen.

The ATC classes that were most commonly administered (> 30.0% of patients in any Phase III treatment arm) included:

- Pretreatment for cetuximab infusions/chemotherapy, allowed per protocol: glucocorticoids (i.e., steroids) (71.6% Triplet arm, 74.1% Doublet arm, 82.4% Control arm) and substituted alkylamines (i.e., antihistamines) (35.1% Triplet arm, 37.5% Doublet arm, 39.9% Control arm), serotonin antagonist antiemetics (27.0% Triplet arm, 19.4% Doublet arm, 74.6% Control arm) and belladonna alkaloids, semisynthetic, quaternary ammonium compounds, specifically the medication of atropine (0.0% Triplet and Doublet arms, 31.1% Control arm).
- For rash: tetracyclines (54.5% Triplet arm, 32.9% Doublet arm, 49.7% Control arm).
- For pain or preexisting conditions: anilide analgesics (45.5% Triplet arm, 53.2% Doublet arm, 42.0% Control arm) and opium alkaloids (26.1% Triplet arm, 38.4% Doublet arm, 31.6% Control arm).
- For GI toxicities or preexisting GI conditions: proton pump inhibitors (46.4% Triplet arm, 43.5% Doublet arm, 42.5% Control arm), antidiarrheals (41.9% Triplet arm, 20.8% Doublet arm, 38.3% Control arm) and propulsive medications (36.5% Triplet arm, 29.6% Doublet arm, 42.0% Control arm).

Numbers analysed

The SAP pre-specified the following analysis sets:

Full Analysis Set (FAS)

For patients in the CSLI, the FAS consisted of all patients who received at least 1 dose of study drug and had at least 1 post-treatment assessment, which may have included death.

Safety Set

The Safety Set consisted of all patients who received at least 1 dose of study drug and had at least 1 post-treatment assessment, which may have included death.

Dose-determining Set

The DDS included all CSLI patients from the Safety Set who either completed a minimum exposure requirement and had sufficient safety evaluations or experienced a DLT.

Patients who did not experience a DLT during the first cycle were considered to have sufficient safety evaluations if they were observed for ≥ 28 days following the first dose, and were considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

Safety Lead-in Efficacy Set

The SLI Efficacy Set consisted of all CSLI patients in the FAS who were identified at screening as having a BRAF V600E mutation (per local or central testing).

Phase III Response Efficacy Set

The Phase III Response Efficacy Set consisted of the first 330 patients randomized into the Phase III portion of the study and any additional patients randomized on the same day as the 330th randomized patient.

Per-protocol Set

The PPS consisted of all Phase 3 patients from the FAS without any major protocol deviations (or other criteria that could largely impact efficacy results) and who received at least 1 dose of study drug.

The reasons that led to exclusion of patients from the PPS are listed below:

- No histologically or cytologically confirmed CRC that was metastatic;
- Not positive for BRAF V600E mutation per central assessment;
- Prior treatment with any RAF inhibitor, MEK inhibitor, cetuximab, panitumumab or other EGFR inhibitor;
- Baseline ECOG PS greater or equal to 3 (i.e., at least 2 categories worse than the defined inclusion criterion);
- Study treatment received different from treatment assigned by randomization.

Pharmacokinetic Set

The PK set included all patients in the Safety Set who had at least 1 post-dose blood collection for PK with associated bioanalytical results. Patients were analyzed according to the actual treatment and dose received.

A summary of analysis sets by treatment group is provided in Table 17.

Table 17: Analysis Sets

	Randomized and CSLI (Pooled)	CSLI	Randomized Portion			
	ENCO + BINI + CETUX (N = 261)	ENCO + BINI + CETUX (N = 37)	ENCO + BINI + CETUX (N = 224)	ENCO + CETUX (N = 220)	CONTROL (N = 221)	Phase 3 Total (N = 665)
Full Analysis Set[a]	261 (100.0)	37 (100.0)	224 (100.0)	220 (100.0)	221 (100.0)	665 (100.0)
Safety Set[b]	259 (99.2)	37 (100.0)	222 (99.1)	216 (98.2)	193 (87.3)	631 (94.9)
Phase 3 Response Efficacy Set[c, d]	111 (42.5)	0 (0.0)	111 (49.6)	113 (51.4)	107 (48.4)	331 (49.8)
Per Protocol Set[c, e]	209 (80.1)	0 (0.0)	209 (93.3)	199 (90.5)	178 (80.5)	586 (88.1)
Pharmacokinetic Set[f]	95 (36.4)	37 (100.0)	58 (25.9)	73 (33.2)	99 (44.8)	230 (34.6)
Dose-determining Set[g, h]	34 (13.0)	34 (91.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SLI Efficacy Set[g, i]	36 (13.8)	36 (97.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: BINI = binimetinib; CETUX = cetuximab; CSLI = Combined Safety Lead-in; ENCO = encorafenib; FAS = Full Analysis Set; JSLI = Japanese Safety Lead-in; PK = pharmacokinetic(s); SLI = Safety Lead-in

[a] For patients in the SLI and JSLI, the FAS includes all patients who received at least 1 dose of study drug and had at least 1 post-treatment assessment, which may include death. For the randomized Phase 3 portion of the study, the FAS consists of all randomized patients.

[b] The Safety Set includes all patients who received at least 1 dose of study drug and had at least 1 post-treatment assessment, which may include death.

[c] Applies to patients in the Randomized portion only.

[d] The Phase 3 Response Efficacy Set includes the first 330 randomized patients and any additional patients randomized on the same day as the 330th randomized patient.

[e] The Per-protocol Set includes all Phase 3 patients from the FAS without any major protocol deviations (or other criteria that could largely impact efficacy results) and who received at least 1 dose of study drug.

[f] The Pharmacokinetic Set includes all patients in the Safety Set who had at least at least 1 postdose blood collection for PK with associated analytical results.

[g] Applies to patients in CSLI only.

[h] The Dose-determining Set includes all SLI and JSLI patients from the Safety Set who either completed a minimum exposure requirement and have sufficient safety evaluations or experienced a dose-limiting toxicity.

[i] The SLI Efficacy Set includes all SLI and JSLI patients in the FAS who were identified at screening as having a *BRAF* V600E mutation per local or central testing.

Source: Table 14.1-2.1.1

Overall survival, including the randomized Phase III primary endpoint of OS, was analyzed based on the **FAS** population in the randomized Phase III portion of the study, which included **665 patients**.

Overall response rate, including the randomized Phase 3 primary endpoint of ORR, was analysed based on the **Phase III Response Efficacy Set** of **331 patients**.

Efficacy analyses of the CSLI were performed on the **SLI Efficacy Set**, which included **36 patients**.

The **PPS** included **586 patients** from the randomized Phase III FAS.

Patients in the **Safety Set** were analyzed according to the study treatment they actually received. All treated patients in the Triplet and Doublet arms received the study treatment to which they were randomized, and no patients randomized to a treatment arm received a regimen for a different treatment arm. In the Phase III portion of the study, 34 patients were randomized but did not receive study drug (2 patients to the Triplet arm, 4 patients to the Doublet arm, 28 patients to the Control arm). These patients were excluded from the Safety Set and the PPS.

An additional 45 patients were excluded from the PPS based on the reasons summarized in Table 16.

Table 16: Reasons Leading to Exclusion of Patients from Per-protocol Set (Randomized Phase 3, Full Analysis Set)

	Randomized Phase 3		
Reason	ENCO + BINI + CETUX N = 224	ENCO + CETUX N = 220	CONTROL N = 221
Patients Excluded from Per Protocol Set	15 (6.7)	21 (9.5)	43 (19.5)
Reasons for Exclusion from Per Protocol Set			
No histologically or cytologically confirmed CRC that is metastatic	0 (0.0)	0 (0.0)	0 (0.0)
Not positive for *BRAF* V600 mutation per central assessment	11 (4.9)	20 (9.1)	20 (9.0)
Prior treatment with any RAF inhibitor, MEK inhibitor, cetuximab, panitumumab or other EGFR inhibitor	2 (0.9)	0 (0.0)	1 (0.5)
Baseline ECOG PS greater or equal to 3	0 (0.0)	0 (0.0)	0 (0.0)
Study treatment received different from treatment assigned by randomization	2 (0.9)	4 (1.8)	31 (14.0)
Not Treated	2 (0.9)	4 (1.8)	28 (12.7)
Different Treatment [a]	0 (0.0)	0 (0.0)	3 (1.4)

Abbreviations: BINI = binimetinib; CETUX = cetuximab; CSLI = Combined Safety Lead-in; CRC = colorectal cancer; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; ENCO = encorafenib; MEK = mitogen activated protein kinase kinase

Note: Data derived from exclusionary protocol deviations and/or other data collected on the eCRFs.

[a] "Different treatment" means not all components of the assigned Control arm regimen were administered to the patient; all 3 patients received cetuximab only.

Source: Table 14.1-1.7

All analyses by strata were conducted based on IWRS data used for randomization. Per IWRS, approximately equal numbers of patients were ECOG PS 0 and ECOG PS 1, with approximately equal numbers having/not having prior use of irinotecan (Table 18). A majority of patients received EU-approved cetuximab, as US-licensed cetuximab was used at sites in only the United States and Canada.

Table 18: Randomization by Stratification Factors

	Randomized Portion			
	ENCO+ BINI+ CETUX (N=224)	ENCO+ CETUX (N=220)	Control (N=221)	Phase 3 Total (N=665)
ECOG PS				
0	115 (51.3)	113 (51.4)	112 (50.7)	340 (51.1)
1	109 (48.7)	107 (48.6)	109 (49.3)	325 (48.9)
Prior Irinotecan Use				
Yes	114 (50.9)	113 (51.4)	112 (50.7)	339 (51.0)
No	110 (49.1)	107 (48.6)	109 (49.3)	326 (49.0)
Cetuximab Source				
US-licensed	30 (13.4)	28 (12.7)	29 (13.1)	87 (13.1)
EU-approved	194 (86.6)	192 (87.3)	192 (86.9)	578 (86.9)
Cross-classification of Stratification				
ECOG PS 0, Prior Irinotecan, US Cetuximab	7 (3.1)	7 (3.2)	6 (2.7)	20 (3.0)
ECOG PS 0, Prior Irinotecan, EU Cetuximab	54 (24.1)	54 (24.5)	53 (24.0)	161 (24.2)
ECOG PS 0, No Prior Irinotecan, US Cetuximab	8 (3.6)	6 (2.7)	8 (3.6)	22 (3.3)
ECOG PS 0, No Prior Irinotecan, EU Cetuximab	46 (20.5)	46 (20.9)	45 (20.4)	137 (20.6)
ECOG PS 1, Prior Irinotecan, US Cetuximab	6 (2.7)	6 (2.7)	6 (2.7)	18 (2.7)
ECOG PS 1, Prior Irinotecan, EU Cetuximab	47 (21.0)	46 (20.9)	47 (21.3)	140 (21.1)
ECOG PS 1, No Prior Irinotecan, US Cetuximab	9 (4.0)	9 (4.1)	9 (4.1)	27 (4.1)
ECOG PS 1, No Prior Irinotecan, EU Cetuximab	47 (21.0)	46 (20.9)	47 (21.3)	140 (21.1)

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ENCO = encorafenib; EU = European Union; US = United States
Source: Table 14.1-1.5.1

In some cases, stratification per IWRS differed from data subsequently documented at Baseline in the eCRF. Discordance rates of 10.5% and 2.4% were observed for the stratification factors of ECOG PS and prior irinotecan use, respectively.

There was no discordance for cetuximab source.

Outcomes and estimation

After testing the randomized Phase 3 primary endpoint of ORR by BICR (Triplet arm vs. Control arm), the primary endpoint of Triplet arm vs. Control arm OS and 4 secondary efficacy endpoints were tested using a gatekeeping hierarchical procedure to control the Type I error rate in the order presented in Table 20.

Table 20: Hierarchical Testing Summary for Efficacy Endpoints

Primary / Secondary	Endpoint		Criterion for Significance (p value[a])	Actual P Value[a]	Location
	Assessment	Treatment Arms			
Primary	ORR by BICR[b]	Triplet vs. Control	0.005	< 0.0001	Section 11.3.1.1.2
	OS[c]	Triplet vs. Control	0.0102	< 0.0001	Section 11.3.1.1.1
Key Secondary	OS[c]	Doublet vs. Control	0.0042	0.0002	Section 11.3.1.2.1
Secondary	ORR by BICR[b]	Doublet vs. Control	0.025	< 0.0001	Section 11.3.1.2.2
	PFS by BICR[c]	Triplet vs. Control	0.0112	< 0.0001	Section 11.3.1.1.6
	PFS by BICR[c]	Doublet vs. Control	0.0117	< 0.0001	Section 11.3.1.2.5

Abbreviations: BICR = blinded independent central review; FAS= Full Analysis Set; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; vs. = versus

[a] All p values provided here are one-sided.

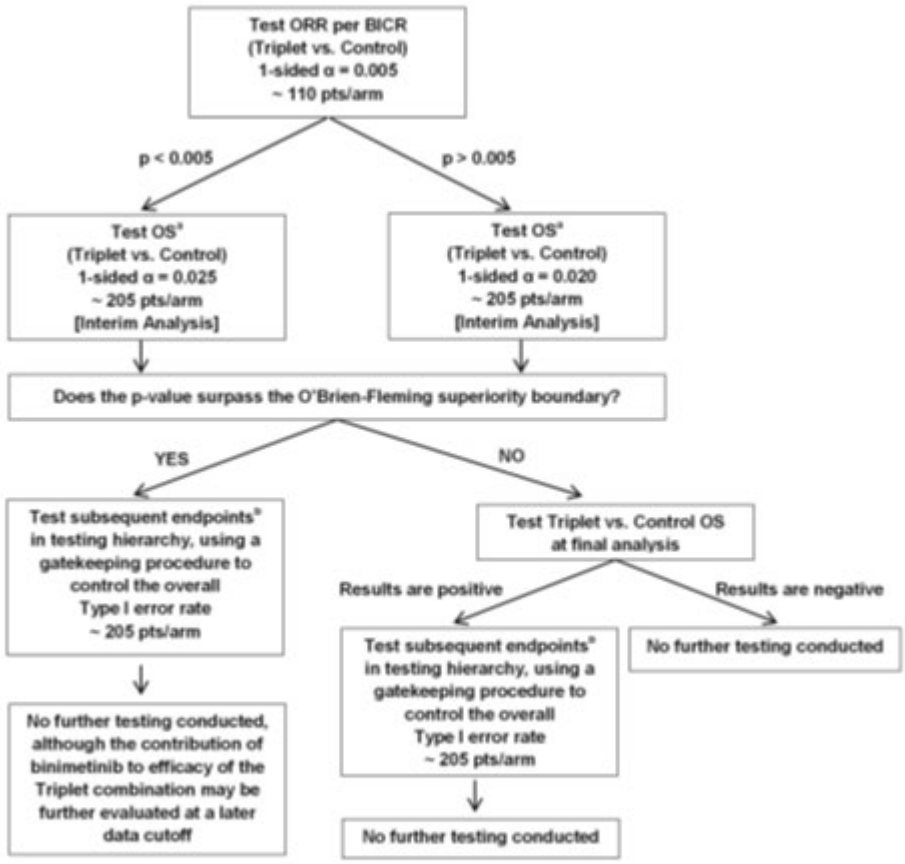
[b] Analysis of ORR was based on the Phase 3 Response Efficacy Set.

[c] Analyses of OS and PFS were based on the FAS; critical p values with O'Brien-Fleming stopping boundaries calculated using Lan-DeMets spending functions.

If any of these tests had been found to not be statistically significant, subsequent comparisons were to be summarized using descriptive statistics, including nominal p values.

Additional secondary efficacy analyses of randomized Phase III data and all efficacy analyses of CSLI data were performed independently of the outcome of the testing described in Figure 2.

Figure 2: Testing Strategy for Phase 3 Primary and Secondary Endpoints



[a] A Lan-DeMets spending function that approximates O'Brien-Fleming boundaries will be used to account for the multiple (i.e., interim and final) analyses of OS.

[b] Subsequent endpoints would be tested in the following order: Doublet vs. Control OS, Doublet vs. Control ORR per BICR, Triplet vs. Control PFS per BICR, and then Doublet vs. Control PFS per BICR.

Results from the study showed that BRAF V600E-mutant patients with mCRC in the Triplet arm demonstrated statistically significant improvements in both primary efficacy endpoints (ORR by BICR and OS) over the Control arm (Table 20). These results, in turn, permitted the formal testing of the key secondary efficacy endpoint of OS for the Doublet arm vs. Control arm, which also achieved statistical significance. Each of 3 remaining secondary efficacy endpoints included in the testing hierarchy achieved a statistically significant improvement over the Control arm in formal testing. All comparisons of the Triplet and Doublet arms are descriptive and were conducted outside of the formal testing hierarchy.

For all randomized Phase 3 patients, the median duration of potential follow-up was 7.79 months for OS and 5.39 months for PFS by BICR.

Primary Efficacy Endpoint: OS, Triplet Arm vs. Control Arm

The following table and figure present the results of the primary endpoint at the cut-off date: 11 February 2019.

Table 21: Kaplan-Meier Summary of OS, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

	ENCO + BINI + CETUX (N = 224)	CONTROL (N = 221)
Patients with events/Patients included in analysis (%)	90/224 (40.2)	114/221 (51.6)
Percentiles (95% CI), months		
25th	5.59 (4.67, 6.41)	3.19 (2.60, 3.84)
Median (50th)	9.03 (8.02, 11.43)	5.42 (4.76, 6.57)
75th	NR (13.40, NR)	12.35 (9.13, 17.12)
Stratified hazard ratio (95% CI)[a,b]	0.52 (0.39, 0.70)	
Stratified log-rank (one-sided) p value[a,b]	< 0.0001	
Survival probability estimates, % (95% CI)[c]		
2 months	94.3 (90.3, 96.8)	86.1 (80.4, 90.2)
4 months	85.5 (79.6, 89.8)	66.2 (58.6, 72.7)
6 months	70.8 (63.2, 77.2)	46.7 (38.6, 54.4)
8 months	59.3 (50.9, 66.7)	36.3 (28.3, 44.3)
10 months	44.2 (35.3, 52.7)	27.4 (19.4, 36.0)
12 months	37.3 (28.2, 46.5)	27.4 (19.4, 36.0)
14 months	31.3 (21.7, 41.4)	18.5 (10.4, 28.5)

Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ENCO = encorafenib; NR = not reached; OS = overall survival; vs. = versus

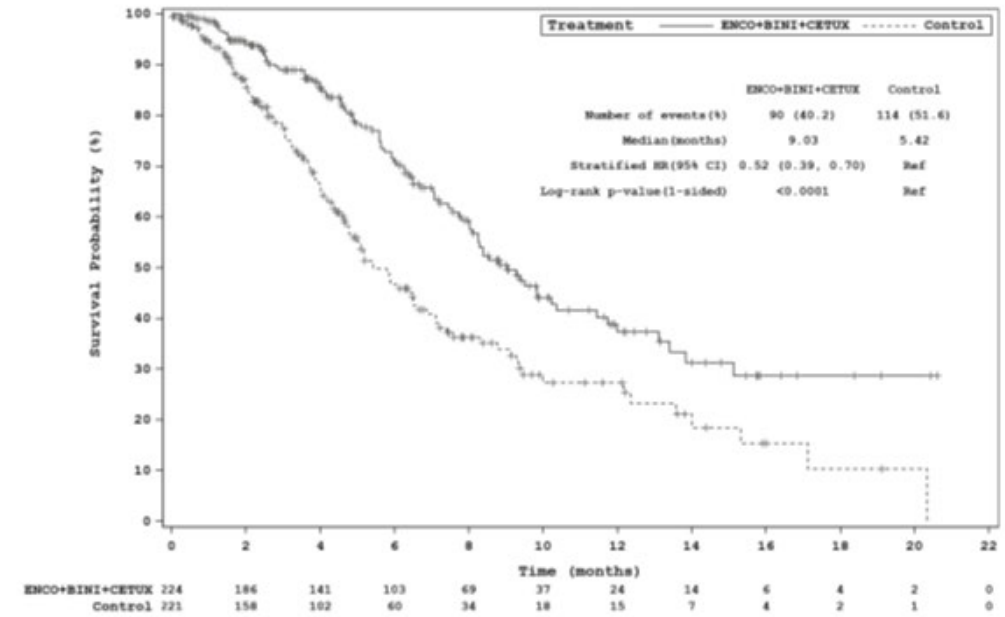
[a] Reference group for comparisons is 'Control'.

[b] Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomization.

[c] Probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates were obtained from Kaplan-Meier survival estimates. Greenwood formula was used for CIs of Kaplan-Meier estimates.

Source: Table 14.2-2.1.1

Figure 3: Kaplan-Meier Plot of OS, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO= encorafenib; HR= hazard ratio; OS = overall survival; Ref = reference; vs. = versus
+ indicates censoring.
Source: Figure 14.2-2.1.1

Update

Results from the data cut-off date of 15 August 2019 are presented below.

Table 5: Kaplan-Meier Summary of OS, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

	ENCO + BINI + CETUX (N = 224)	CONTROL (N = 221)
Patients with events/Patients included in analysis (%)	137/224 (61.2)	157/221 (71.0)
Percentiles (95% CI), months		
25th	5.62 (4.93, 6.51)	3.25 (2.73, 3.94)
Median (50th)	9.26 (8.25, 10.81)	5.88 (5.09, 7.10)
75th	17.77 (15.11, NR)	11.60 (9.56, 15.31)
Stratified hazard ratio (95% CI)[a,b]	0.60 (0.47, 0.75)	
Stratified log-rank (one-sided) p value[a,b]	<0.0001	
Survival probability estimates, % (95% CI)[c]		
2 months	94.6 (90.8, 96.9)	86.9 (81.6, 90.8)
4 months	86.1 (80.8, 90.0)	67.8 (61.1, 73.7)
6 months	72.0 (65.6, 77.4)	49.9 (42.9, 56.4)
8 months	59.6 (52.7, 65.9)	39.9 (33.1, 46.6)
10 months	44.5 (37.4, 51.4)	29.2 (22.7, 35.9)
12 months	39.8 (32.6, 46.8)	24.8 (18.5, 31.5)
14 months	35.6 (28.4, 42.8)	19.4 (13.4, 26.1)

Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ENCO = encorafenib; NR = not reached; OS = overall survival; vs. = versus

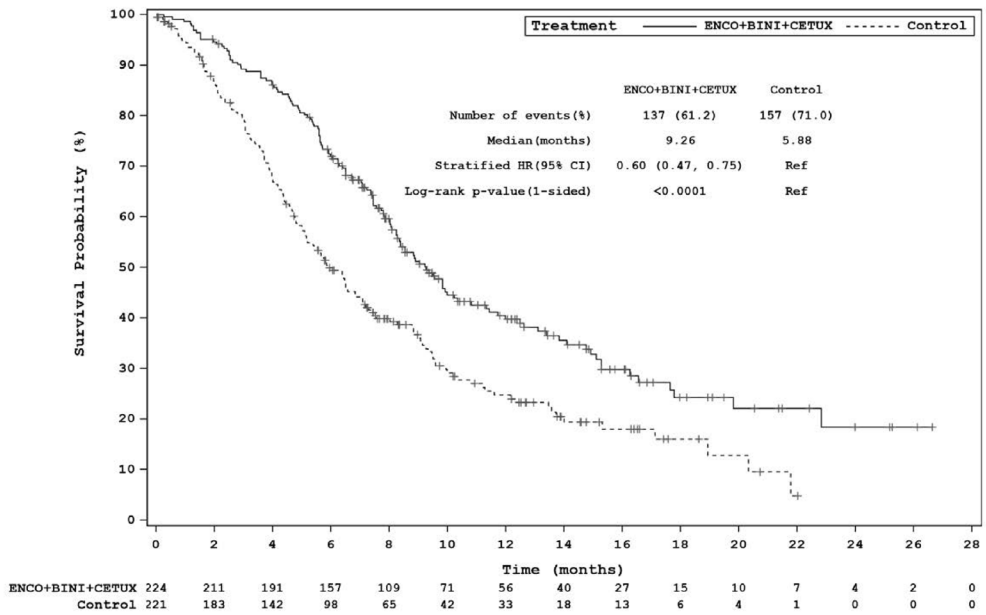
[a] Reference group for comparisons is Control.

[b] Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomization.

[c] Probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates were obtained from Kaplan-Meier survival estimates. Greenwood formula was used for CIs of Kaplan-Meier estimates.

Source: Addendum Table 14.2-2.1.1

Figure 1: Kaplan-Meier Plot of OS, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; HR = hazard ratio; OS = overall survival; Ref = reference; vs. = versus
+ indicates censoring.
Source: Addendum Figure 14.2-2.1.1

Sensitivity Analyses of OS, Triplet Arm vs. Control Arm

To assess the robustness of this OS analysis, the following sensitivity analyses were performed:

- OS, stratified test (PPS)
- OS, unstratified test (FAS)

In a post hoc analysis, OS was analyzed in the Phase III Response Efficacy Set (i.e., the first

331 patients randomized). As shown in Figure 4, an estimated 47% reduction in risk of death was observed for the Triplet arm compared to the Control arm (HR 0.53, 95% CI: 0.38, 0.74). The median OS in the Triplet arm was 4.33 months longer than in the Control arm, with median OS estimates using Kaplan-Meier methodology of 9.49 months (95% CI: 8.08, 11.99) in the Triplet arm and 5.16 months (95% CI: 4.44, 6.57) in the Control arm ($p < 0.0001$, stratified log-rank test).

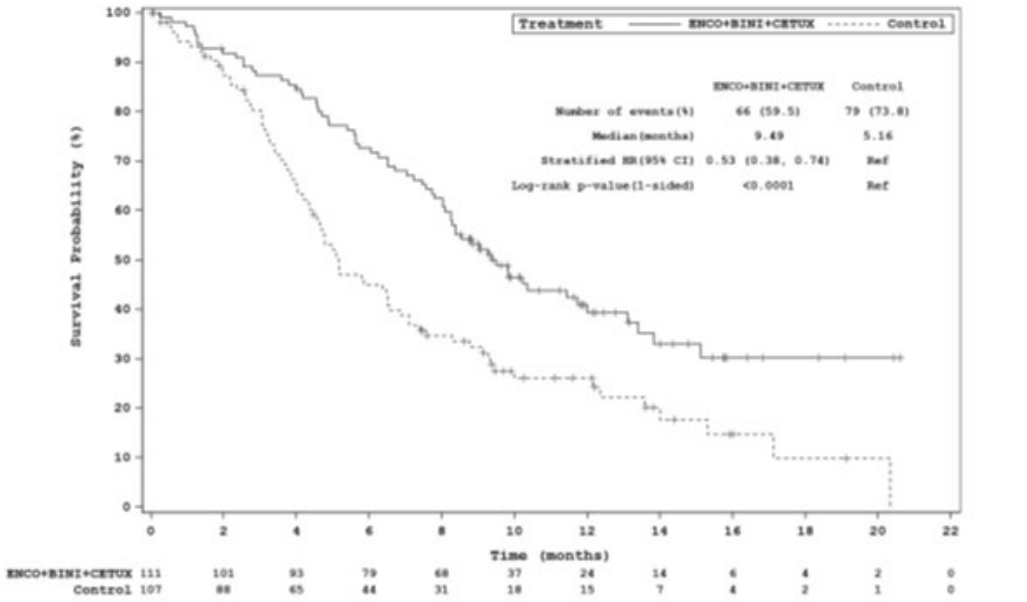
Using a reverse Kaplan-Meier analysis (i.e., OS events were presented as censored events and vice versa), the estimated median duration of potential follow-up for OS was 12.45 months (95% CI: 11.24, 14.36) for the Triplet arm and 12.19 months (95% CI: 9.89, 14.39) for the Control arm. Therefore, data in patients with more mature follow-up support the conclusions reached in the primary analysis of OS and in prespecified sensitivity analyses.

Table 23: OS Sensitivity Analyses, Triplet Arm vs. Control Arm (Randomized Phase 3)

	Median (95% CI)[a]	HR (95% CI)	P value	Source
Primary OS analysis (FAS), Stratified				**Table 14.2-2.1.1 Figure 14.2-2.1.1**
Triplet arm	**9.03 months (8.02, 11.43)**	**0.52 (0.39, 0.70)**	**< 0.0001**	
Control arm	**5.42 months (4.76, 6.57)**			
OS, Stratified (PPS)				Table 14.2-2.2 Figure 14.2-2.2.1
Triplet arm	9.49 months (8.25, 11.99)	0.48 (0.35, 0.65)	< 0.0001	
Control arm	5.39 months (4.63, 6.51)			
OS, Unstratified (FAS)				Table 14.2-2.1.1
Triplet arm	9.03 months (8.02, 11.43)	0.54 (0.41, 0.71)	< 0.0001	
Control arm	5.42 months (4.76, 6.57)			
OS, Stratified (Phase 3 Response Efficacy Set)				Table 14.2-2.14
Triplet arm	9.49 months (8.08, 11.99)	0.53 (0.38, 0.74)	< 0.0001	
Control arm	5.16 months (4.44, 6.57)			

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; HR = hazard ratio; OS = overall survival; PPS = Per-protocol Set; vs. = versus
Note: Reference group for comparisons is 'Control'.
[a] Greenwood formula was used for confidence intervals of Kaplan-Meier estimates.
Source: Figure 14.2-2.1.1; Figure 14.2-2.2.1; Table 14.2-2.1.1; Table 14.2-2.2; Table 14.2-2.14

Figure 4: Kaplan-Meier Plot of OS, Triplet Arm vs. Control Arm (Randomized Phase 3, Phase 3 Response Efficacy Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; HR = hazard ratio; OS = overall survival; Ref = reference; vs. = versus
+ indicates censoring.
Source: Figure 14.2-2.14.1

Supportive Analysis: Multivariate Cox Regression of OS, Triplet Arm vs. Control Arm

The effect of Baseline covariates and potential prognostic factors on OS was investigated using a multivariate Cox regression model stratified by the study stratification factors (ECOG PS, prior irinotecan use and cetuximab source). The objective of this analysis was to explore the consistency of treatment effect on OS after adjusting for these Baseline covariates.

This multivariate Cox regression model demonstrated that, after adjusting for pre-specified Baseline covariates, the outcome of the comparison of Triplet arm vs. Control arm was consistent with the primary

OS analysis (55% reduction in the risk of death in the Triplet arm), which was nominally significant (HR 0.45, 95% CI: 0.33, 0.61; 2-sided p value < 0.0001).

Two pre-specified covariates also reached nominal significance: the presence of liver metastases at Baseline was associated with a 2.68-fold increase in the risk of death (HR 2.68, 95% CI: 1.88, 3.81; 2-sided p value < 0.0001) and Baseline CRP > ULN was associated with a 2.70-fold increase in the risk of death (expressed as the inverse of HR 0.37, 95% CI: 0.27, 0.51; 2-sided p value < 0.0001).

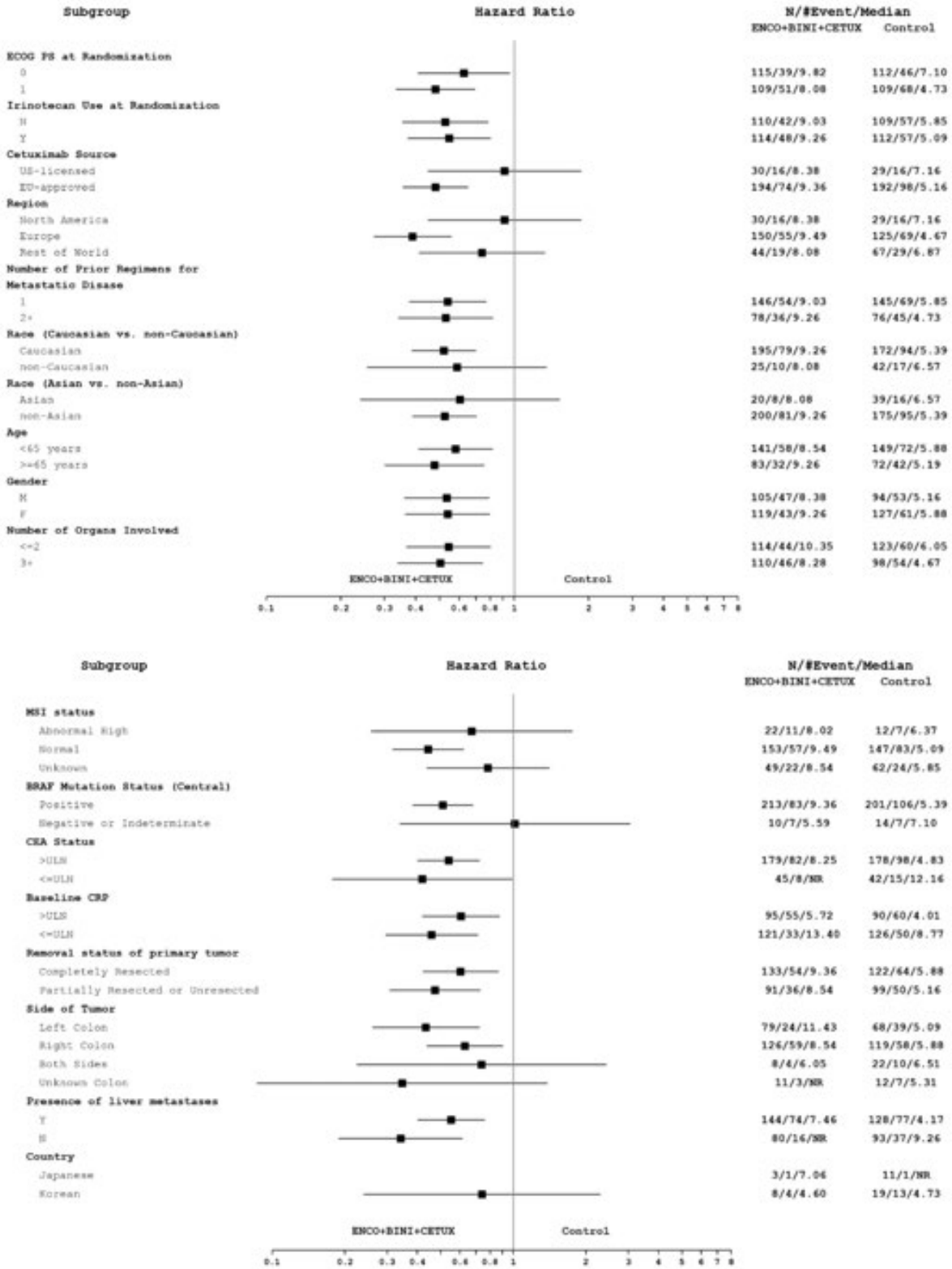
In addition, post hoc un-stratified univariate Cox regression analyses, for all Phase III patients in the FAS combined (i.e., all 3 arms combined), were conducted to investigate the relationship between OS and the study stratification factors (ECOG PS, prior irinotecan use and cetuximab source) and Baseline covariates, without including treatment effect in the model. Of the stratification factors, a Baseline ECOG PS score of 1 was associated with a 1.78-fold increase in the risk of death (HR 1.78, 95% CI: 1.41, 2.24; 2-sided p value < 0.0001) and prior irinotecan use was associated with a 1.35-fold increase in the risk of death (HR 1.35, 95% CI: 1.07, 1.69; 2-sided p value = 0.0103).

Several Baseline covariates were strongly associated (2-sided p < 0.0001) with an increase in the risk of death. Baseline CRP > ULN was associated with a 3.13-fold increase in the risk of death. The presence of liver metastases at Baseline was associated with a 2.60-fold increase in the risk of death. Baseline CEA > ULN was associated with a 2.56-fold increase in the risk of death. Also, Baseline CA19-9 > ULN was associated with a 1.96-fold increase in the risk of death and having > 2 organs involved at Baseline was associated with a 1.61-fold increase in risk of death.

Subgroup Analyses of OS, Triplet Arm vs. Control Arm

Subgroup analyses were performed for each Baseline stratification factor and other relevant Baseline variables. Only analyses for which at least 10 events were available in each subgroup are discussed here. With the exception of the small subgroup ("BRAF mutation status [central] negative or indeterminate" [total n = 24; total number of events = 14], HR 1.01[95% CI: 0.34, 3.05]), all analyses demonstrated OS HRs in favor of the Triplet arm. The greatest difference in favor of the Triplet arm was observed in the subgroup with no liver metastases at Baseline (HR 0.34, 95% CI: 0.19, 0.62). The smallest differences in favor of the Triplet arm were observed in the overlapping subgroups of patients who were randomized to receive US-licensed cetuximab and patients who were randomized at sites in North America (excluding Mexico) (HR 0.91 [95% CI: 0.45, 1.86] for both subgroups).

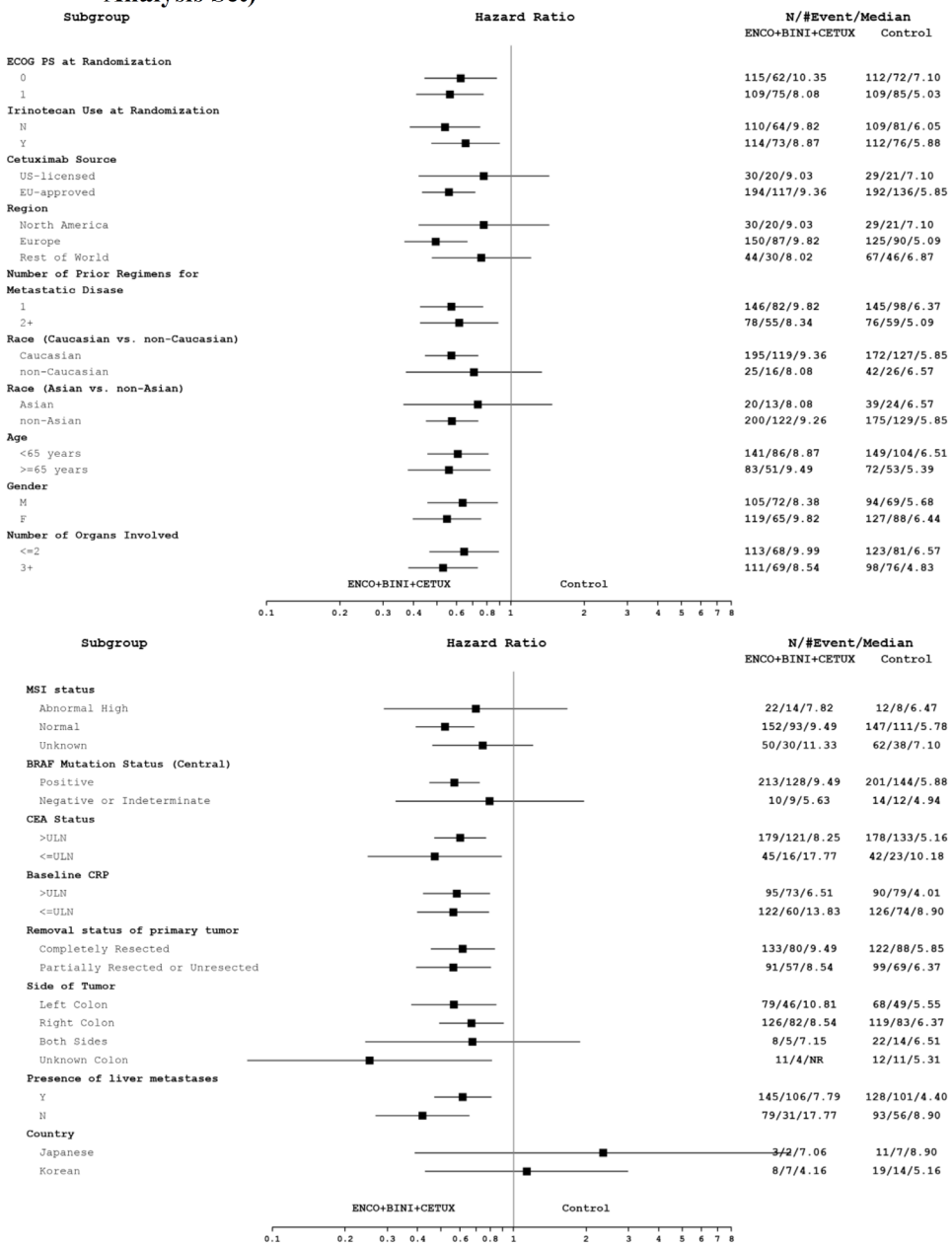
Figure 5: Forest Plot of OS, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CEA = carcinoembryonic antigen; CETUX = cetuximab; CI = confidence interval; CRP = C-reactive protein; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ENCO = encorafenib; EU = European Union; F = female; HR = hazard

The updated version of this subgroup analysis with a cut-off date **15 August 2019** is presented in figure 2 below:

Figure 2: Forest Plot of OS, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CEA = carcinoembryonic antigen; CETUX = cetuximab; CI = confidence interval; CRP = C-reactive protein; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ENCO = encorafenib; EU = European Union; F = female; HR = hazard ratio; M = male; MSI = microsatellite instability; N/Y = no/yes; NR = not reached; OS = overall survival; ULN = upper limit of normal; US = United States; vs. = versus
Note: The HR is obtained from an unstratified Cox model. The error bars represent 95% CI.
Source: Addendum Figure 14.2-2.9

As already mentioned, 2 patients in the Triplet arm and 28 patients in the Control arm were randomized but not treated. In both patients in the Triplet arm, the documented reason for not receiving study treatment was because of changes in the patient's condition or development of an intercurrent illness. In the Control arm, the documented reason for not receiving study treatment was withdrawal of consent (21 patients), patient decision (4 patients) and changes in patient's condition/development of intercurrent illness (3 patients). Due to the small number of patients not treated in the Triplet arm, a formal comparison of OS between these subgroups was not performed. In the Triplet arm, the patients who were

randomized but not treated had an OS of 0.26 months and 9.26 months. The median OS for patients randomized but not treated in the Control arm was 7.56 months (95% CI: 4.57, 20.34).

The CSR contains a brief description of subsequent systemic anti-cancer therapy. Accordingly, 49.3% and 44.6% of patients in the Triplet and Control arms, respectively, used subsequent systemic anticancer therapy. The actual difference in use of (subsequent/post progression) anticancer therapy was slightly different, but the differences are actually minor. E.g., no patients in the Triplet arm and 9.2% of patients in the Control arm received a BRAF inhibitor plus a MEK inhibitor plus an EGFR inhibitor.

Of the patients who were randomized but not treated, 1 of 2 patients (50%) in the Triplet arm received subsequent systemic anticancer therapy after study withdrawal (cetuximab, irinotecan, fluorouracil and a second line of systemic therapy with TAS 102).

In the Control arm, 11 of 28 patients (39.3%) received subsequent systemic anticancer therapy; therapies used at the highest incidence (> 10%) were irinotecan (21.4%); fluorouracil (21.4%); bevacizumab (14.3%); panitumumab (14.3%); folinic acid (10.7%); oxaliplatin (10.7%) and investigational antineoplastic drugs (10.7%) (2 patients received PLX8394 [a BRAF inhibitor] and 1 patient received RO6958688 [anti-CEA/CD3 bi-specific antibody])

Primary Efficacy Endpoint: ORR by BICR, Triplet Arm vs. Control Arm-Cut off February 2019 data:

Table 24: Best Overall Response by BICR, Triplet Arm vs. Control Arm (Randomized Phase 3, Response Efficacy Set)

	ENCO + BINI + CETUX (N = 111)	CONTROL (N = 107)
Best Confirmed Overall Response[a], n (%)		
Complete Response	4 (3.6)	0 (0.0)
Partial Response	25 (22.5)	2 (1.9)
Stable Disease	41 (36.9)	26 (24.3)
Progressive Disease	11 (9.9)	36 (33.6)
Non-CR/Non-PD[b]	6 (5.4)	5 (4.7)
Not Evaluable	24 (21.6)	38 (35.5)
Evidence of disease progression or AE	15 (13.5)	17 (15.9)
Insufficient information to assess response	9 (8.1)	21 (19.6)
Confirmed Overall Response Rate (ORR: CR+PR), n (%)	29 (26.1)	2 (1.9)
95% CI[c]	(18.2, 35.3)	(0.2, 6.6)
99% CI[c]	(16.2, 38.2)	(0.1, 8.4)
Confirmed Disease Control Rate (DCR: CR+PR+stable disease+Non-PD/Non-CR), n (%)	76 (68.5)	33 (30.8)
95% CI[c]	(59.0, 77.0)	(22.3, 40.5)

Abbreviations: AE= adverse event; BICR = blinded independent central review; BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; CR = complete response; DCR = disease control rate; ENCO = encorafenib; ORR = overall response rate; PD = progressive disease; PR = partial response; vs. = versus

[a] CR and PR were confirmed by repeat assessments performed not less than 4 weeks after criteria for response were met.

[b] Patients with only non-measurable disease, whose best non-target lesion response was Non-CR/non-PD and did not have any new lesions.

[c] The CIs were computed using Clopper-Pearson's method.

Source: Table 14.2-1.1.1; Table 14.2-1.7.4

The updated version of this response analysis with a cut-off date **15 August 2019** is presented in table 7 below:

Table 7: Best Overall Response by BICR, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

	ENCO + BINI + CETUX (N = 224)	CONTROL (N = 221)
Best Confirmed Overall Response[a], n (%)		
Complete Response	8 (3.6)	0 (0.0)
Partial Response	52 (23.2)	4 (1.8)
Stable Disease	98 (43.8)	59 (26.7)
Progressive Disease	24 (10.7)	82 (37.1)
Non-CR/Non-PD[b]	10 (4.5)	6 (2.7)
Not Evaluable	32 (14.3)	70 (31.7)
Evidence of disease progression or AE	19 (8.5)	30 (13.6)
Insufficient information to assess response	13 (5.8)	40 (18.1)
Confirmed Overall Response Rate (ORR: CR+PR), n (%)	60 (26.8)	4 (1.8)
95% CI[c]	(21.1, 33.1)	(0.5, 4.6)
99% CI[c]	(19.5, 35.1)	(0.3, 5.6)
Confirmed Disease Control Rate (DCR: CR+PR+stable disease+Non-PD/Non-CR), n (%)	168 (75.0)	69 (31.2)
95% CI[c]	(68.8, 80.5)	(25.2, 37.8)

Abbreviations: AE= adverse event; BICR = blinded independent central review; BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; CR = complete response; DCR = disease control rate; ENCO = encorafenib; ORR = overall response rate; PD = progressive disease; PR = partial response; vs. = versus

[a] CR and PR were confirmed by repeat assessments performed not less than 4 weeks after criteria for response were met.

[b] Patients with only non-measurable disease, whose best non-target lesion response was Non-CR/non-PD and did not have any new lesions.

[c] The CIs were computed using Clopper-Pearson's method.

Source: Addendum Table 14.2-1.2.1; Addendum Table 14.2-1.7.4

Updated ORR analysis as of January 20, 2020 (cut-off 15 August 2019)

	Triplet N=224	Control N=221
Objective Response Rate	**26.8%**	**1.8%**
95% CI	(21.1%, 33.1%)	(0.5%, 4.6%)
Duration of Response		
DOR, Kaplan-Meier median (95% CI), months	4.4 (3.8, 7.3)	NR*
DOR ≥ 6 months, n (%)	19/60 (31.7)	1/4 (25.0)
DOR < 6 months, response ongoing, n (%)	4/60 (6.7)	0

* Not reported due to only 2 events in 4 responders

Sensitivity Analyses of ORR by BICR, Triplet Arm vs. Control Arm

To assess the robustness of the ORR primary analysis the following sensitivity analyses were performed:

- ORR unstratified test in Phase III Response Efficacy Set
- ORR stratified test in FAS
- ORR unstratified test in FAS
- ORR stratified test, for patients in Phase 3 Response Efficacy Set with measurable disease at Baseline

These sensitivity analyses of ORR support the conclusions reached in the primary analysis, yielding similar ORRs and p values (Table 25). In the Triplet and Control arms, 36 of 224 patients and 35 of 221 patients, respectively, had not been on study long enough to experience a confirmed response (i.e., a response at their first tumor assessment, confirmed at the scan 6 weeks later). An additional 18 patients

in each of the Triplet and Control arms had not been on study long enough to experience a response at their second tumor assessment, confirmed 6 weeks later.

Table 25: ORR by BICR Sensitivity Analyses, Triplet Arm vs. Control Arm (Randomized Phase 3)

	ORR (95% CI)	P value	Source
Primary ORR analysis (Phase 3 Response Efficacy Set), Stratified			Table 14.2-1.1.1
Triplet arm	**26.1% (18.2, 35.3)**	**< 0.0001**	
Control arm	**1.9% (0.2, 6.6)**		
ORR, Unstratified (Phase 3 Response Efficacy Set)			Table 14.2-1.1.1
Triplet arm	26.1% (18.2, 35.3)	< 0.0001	
Control arm	1.9% (0.2, 6.6)		
ORR, Stratified (FAS)			Table 14.2-1.2.1
Triplet arm	22.3% (17.0, 28.3)	< 0.0001	
Control arm	1.4% (0.3, 3.9)		
ORR, Unstratified (FAS)			Table 14.2-1.2.1
Triplet arm	22.3% (17.0, 28.3)	< 0.0001	
Control arm	1.4% (0.3, 3.9)		
ORR (Phase 3 Response Efficacy Set with measurable disease at Baseline), Stratified			Table 14.2-1.4
Triplet arm	28.3% (19.7, 38.2)	< 0.0001	
Control arm	2.0% (0.2, 7.0)		

Abbreviations: BICR = blinded independent central review; CI = confidence interval; FAS = Full Analysis Set; ORR = overall response rate; vs. = versus
Source: Table 14.2-1.1.1; Table 14.2-1.2.1; Table 14.2-1.4

Supportive Analysis: Multivariate Logistic Regression of ORR by BICR, Triplet Arm vs. Control Arm

The effect of Baseline characteristics and potential prognostic factors on ORR by BICR in the Phase III Response Efficacy Set was investigated using a multivariate logistic regression model stratified by the study stratification factors (ECOG PS, prior irinotecan use and cetuximab source). The objective of this analysis was to explore the consistency of treatment effect on ORR by BICR after adjusting for main prognostic factors.

To provide a comparison to this stratified multivariate logistic regression model, a separate stratified univariate model looking only at treatment group (Triplet arm vs. Control arm) was also assessed. The stratified univariate model showed that patients in the Triplet arm had a 19.10-fold increased odds (95% CI: 4.41, 82.80) of responding compared to patients in the Control arm.

The stratified multivariate logistic regression model demonstrated that, after adjusting for pre-specified Baseline covariates, the outcome of the Triplet arm vs. Control arm comparison was consistent with the stratified univariate model (odds ratio 25.26 [95% CI: 5.38, 118.7; 2-sided p value < 0.0001],). Of all the pre-specified covariates that reached nominal significance in the multivariate model, treatment group had the largest effect.

Patients with liver metastases at Baseline had decreased odds of responding compared to patients without liver metastases (odds ratio 0.22 [95% CI: 0.07, 0.69; 2-sided p value = 0.0087]), and patients with 1 metastatic site had increased odds of responding compared to patients with ≥ 2 metastatic sites (odds ratio 3.89 [95% CI: 1.13, 13.39; 2-sided p value = 0.0314]).

In addition, post hoc un-stratified univariate logistic regression analyses were conducted to investigate the effect of study stratification factors (ECOG PS, prior irinotecan use and cetuximab source) and

Baseline characteristics and potential prognostic factors in the Phase 3 Response Efficacy Set, without including treatment effect in the model. None of the stratification factors were found to have a significant effect on ORR. Two pre-specified Baseline covariates were associated with decreased odds of responding to treatment: Baseline CRP and the number of prior regimens for metastatic disease. Patients with Baseline CRP > ULN had decreased odds of responding (odds ratio 0.44 [95% CI: 0.23, 0.83; 2-sided p value = 0.0120]), as did patients with ≥ 2 prior regimens for metastatic disease (odds ratio 0.47 [95% CI: 0.24, 0.91; 2-sided p value = 0.0256]).

Subgroup Analyses of ORR by BICR, Triplet Arm vs. Control Arm

Subgroup analyses were performed for each Baseline stratification factor and other relevant Baseline variables. Because there were 2 patients in the Control arm with confirmed responses by BICR in the Phase 3 Response Efficacy Set, this discussion focuses on 5 clinically relevant subgroups in the Triplet arm:

- In the Triplet arm, patients who had progressed after 1 prior regimen for metastatic disease had a confirmed ORR of 34.3% (23 of 67 patients, 95% CI: 23.2, 46.9), compared to 13.6% (6 of 44 patients, 95% CI: 5.2, 27.4) in patients who had progressed after ≥ 2 prior regimens for metastatic disease.
- In the Triplet arm, patients with ≤ 2 organs involved at Baseline had a confirmed ORR of 24.1% (14 of 58 patients, 95% CI: 13.9, 37.2), compared to 28.3% (15 of 53 patients, 95% CI: 16.8, 42.3) in patients with ≥ 3 organs involved at Baseline.
- In the Triplet arm, patients with a Baseline CEA ≤ ULN had a confirmed ORR of 38.1% (8 of 21 patients, 95% CI: 18.1, 61.6), compared to 23.3% (21 of 90 patients, 95% CI: 15.1, 33.4) in patients with a Baseline CEA > ULN.
- In the Triplet arm, patients with a Baseline CRP ≤ ULN had a confirmed ORR of 33.3% (19 of 57 patients, 95% CI: 21.4, 47.1), compared to 18.4% (9 of 49 patients, 95% CI: 8.8, 32.0) in patients with a Baseline CRP > ULN.
- • In the Triplet arm, patients with no liver metastases at Baseline had a confirmed ORR of 41.5% (17 of 41 patients, 95% CI: 26.3, 57.9), compared to 17.1% (12 of 70 patients, 95% CI: 9.2, 28.0) in patients with liver metastases at Baseline.

Secondary endpoints

ORR by Investigator, Triplet Arm vs. Control Arm

Table 14.2-1.13.1: Summary of Best Overall Response per RECIST 1.1 by Investigator (Phase III FAS)

	Randomized Portion		
	ENCO+ BINI+ CETUX (N=224)	ENCO+ CETUX (N=220)	Control (N=221)
Best Confirmed Overall Response[a], n (%)			
Complete Response	2 (0.9)	2 (0.9)	0 (0.0)
Partial Response	47 (21.0)	29 (13.2)	7 (3.2)
Stable Disease	106 (47.3)	112 (50.9)	55 (24.9)
Progressive Disease	23 (10.3)	24 (10.9)	74 (33.5)
Non-CR/Non-PD[b]	4 (1.8)	6 (2.7)	7 (3.2)
Not Evaluable	42 (18.8)	47 (21.4)	78 (35.3)
Confirmed Objective Response Rate (ORR: CR+PR), n (%)	49 (21.9)	31 (14.1)	7 (3.2)
95% CI[c]	(16.6, 27.9)	(9.8, 19.4)	(1.3, 6.4)
99% CI[c]	(15.2, 29.8)	(8.7, 21.1)	(0.9, 7.6)

Source: Listing 14.2-1.2 Data Cutoff Date: 11Feb2019
[a]CR and PR are confirmed by repeat assessments performed not less than 4 weeks after criteria for response is met.
[b]Patients with only non-measurable disease, whose best non-target lesion response was Non-CR/non-PD and did not have any new lesions
[c]Reference group for comparisons is 'Control'.
[d]Reference group for comparisons is 'ENCO+CETUX'.
[e]Cochran-Mantel-Haenszel test, stratified by ECOG Performance Status, source of cetuximab, and prior irinotecan use at randomization. The p-values are 1-sided.
[f]P-value calculated using Chi-squared test. The p-values are 1-sided.
[g]Confidence intervals were calculated using the Clopper-Pearson method.
[h]Stratified by ECOG Performance Status, source of cetuximab, and prior irinotecan use at randomization.
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	Randomized Portion		
	ENCO+ BINI+ CETUX (N=224)	ENCO+ CETUX (N=220)	Control (N=221)
P-value (stratified)[c,e]	<0.0001	<0.0001	
P-value (stratified)[d,e]	0.0145		
P-value (unstratified)[c,f]	<0.0001	<0.0001	
P-value (unstratified)[d,f]	0.0164		
Stratified Odds Ratio for Confirmed ORR(95% CI)[c,h]	8.52 (3.76, 19.30)	5.05 (2.16, 11.81)	
Stratified Odds Ratio for Confirmed ORR(95% CI)[d,h]	1.73 (1.05, 2.85)		
Confirmed Disease Control Rate (DCR: CR+PR+SD+Non-PD/Non-CR), n (%)	159 (71.0)	149 (67.7)	69 (31.2)
95% CI[g]	(64.6, 76.8)	(61.1, 73.9)	(25.2, 37.8)
99% CI[g]	(62.6, 78.5)	(59.1, 75.6)	(23.4, 39.8)

Source: Listing 14.2-1.2 Data Cutoff Date: 11Feb2019
[a]CR and PR are confirmed by repeat assessments performed not less than 4 weeks after criteria for response is met.
[b]Patients with only non-measurable disease, whose best non-target lesion response was Non-CR/non-PD and did not have any new lesions
[c]Reference group for comparisons is 'Control'.
[d]Reference group for comparisons is 'ENCO+CETUX'.
[e]Cochran-Mantel-Haenszel test, stratified by ECOG Performance Status, source of cetuximab, and prior irinotecan use at randomization. The p-values are 1-sided.
[f]P-value calculated using Chi-squared test. The p-values are 1-sided.
[g]Confidence intervals were calculated using the Clopper-Pearson method.
[h]Stratified by ECOG Performance Status, source of cetuximab, and prior irinotecan use at randomization.
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DOR, Triplet Arm vs. Control Arm

The Kaplan-Meier estimate of median DOR by BICR in the Phase 3 Response Efficacy Set, calculated for confirmed responses in the Triplet arm, was 4.80 months (95% CI: 2.96, 9.69). For an updated analysis see preceeding table updated ORR analysis. Of the 2 patients in the Control arm with confirmed responses, 1 patient had a DOR of 2.56 months; the other patient's DOR was 6.93 months. In the Triplet arm, individual DORs ranged from 1.41 months to 15.01 months, with 24.1% of confirmed responders (7

of 29) having a DOR by BICR of ≥ 6 months. At the data cut-off date, 13.8% of confirmed responders (4 of 29) in the Triplet arm had a DOR of < 6 months with responses ongoing (5.55 months, 3.19 months, 1.41 months and 5.59 months), compared to 0% of confirmed responders in the Control arm.

The Kaplan-Meier estimate of median DOR by Investigator in the Phase 3 Response Efficacy Set, calculated for confirmed responses, was similar to the by BICR result in the Triplet arm:

4.80 months (95% CI: 3.29, 6.57). Of the 4 patients in the Control arm with confirmed responses, patients had DORs of 2.56 months, 5.75 months, 8.48 months and 5.55 months.

Similarly, Kaplan-Meier estimates of median DOR by BICR and Investigator in the FAS were calculated for confirmed responses. The results are consistent with results observed using the Phase 3 Response Efficacy Set.

TTR, Triplet Arm vs. Control Arm

The Kaplan-Meier estimate of median TTR by BICR in the Phase 3 Response Efficacy Set, calculated for patients with confirmed responses, was 1.48 months in the Triplet arm (95% CI: 1.41, 2.00). For patients in the Triplet arm with confirmed CRs, the TTRs were 1.41, 1.58, 16.56 and 1.41 months. Of the 2 patients in the Control arm with confirmed responses, 1 patient had a TTR of 1.41 months; the other patient's TTR was 1.45 months.

The time to most responses by BICR in the Phase 3 Response Efficacy Set corresponded with the first post-Baseline response assessment at 6 weeks (± 7 days) after randomization. In the Triplet arm, 69.0% of confirmed responses (20/29) were based on the first tumor assessment, 24.1% (7/29) were based on the second tumor assessment and 6.9% (2/29) were based on the third or subsequent tumor assessment. In the Control arm, 100.0% of confirmed responses (2/2) were based on the first tumor assessment.

PFS, Triplet Arm vs. Control Arm

Estimates of median PFS by Investigator assessment in the FAS were comparable to the PFS by BICR results (HR 0.37, 95% CI: 0.28, 0.48). The Triplet arm had a median PFS that was 2.89 months longer than that in the Control arm (Triplet arm 4.47 months [95% CI: 4.24, 5.36] and Control arm 1.58 months [95% CI: 1.51, 2.07], stratified log-rank test p < 0.0001).

Table 27: Kaplan-Meier Summary of PFS by BICR, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

	ENCO + BINI + CETUX (N = 224)	CONTROL (N = 221)
Patients with events/Patients included in analysis (%)	118/224 (52.7)	128/221 (57.9)
Death	15/224 (6.7)	27/221 (12.2)
Disease Progression	103/224 (46.0)	101/221 (45.7)
Percentiles (95% CI), months		
25[b]	2.79 (2.50, 3.29)	1.31 (1.22, 1.41)
Median (50[b])	4.30 (4.14, 5.19)	1.51 (1.45, 1.71)
75[b]	8.18 (5.82, 11.04)	3.38 (2.76, 4.30)
Stratified hazard ratio (95% CI)[a,b]	0.38 (0.29, 0.49)	
Stratified log-rank (one-sided) p value[a,b]	< 0.0001	
Patients event-free probability estimates, % (95% CI)[c]		
2 months	84.7 (78.6, 89.2)	39.2 (31.3, 47.0)
4 months	62.9 (54.9, 69.8)	23.0 (16.3, 30.5)
6 months	31.3 (23.5, 39.4)	12.4 (6.9, 19.5)
8 months	26.0 (18.5, 34.1)	12.4 (6.9, 19.5)
10 months	20.0 (12.7, 28.5)	6.9 (2.0, 16.0)
12 months	12.7 (6.3, 21.4)	0.0 (0.0, 0.0)
14 months	7.6 (2.5, 16.7)	0.0 (0.0, 0.0)

Abbreviations: BICR = blinded independent central review; BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ENCO = encorafenib; PFS = progression-free survival; vs. = versus

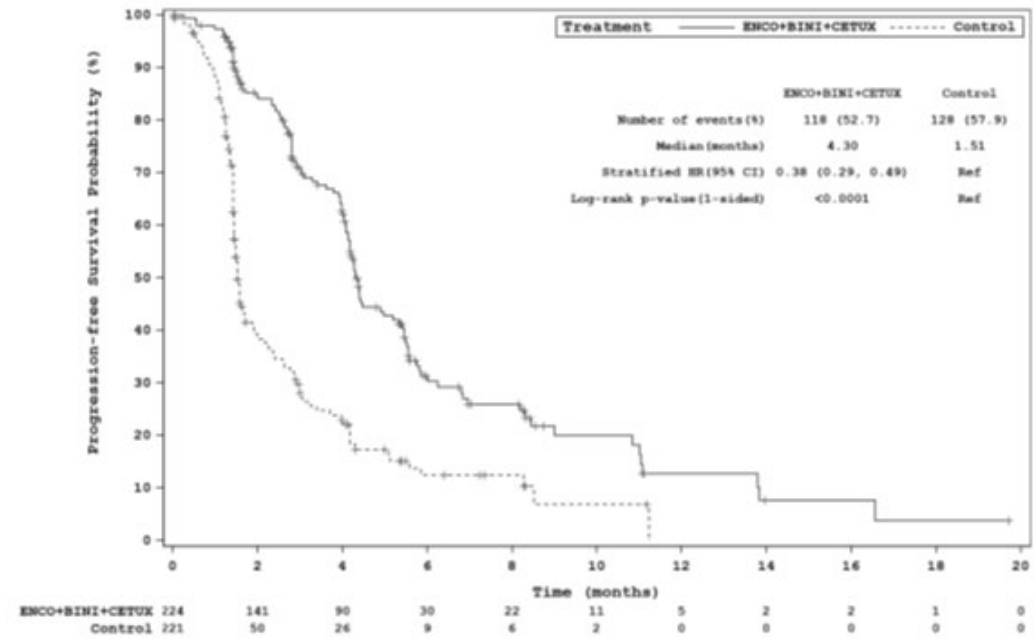
[a] Reference group for comparisons is 'Control'.

[b] Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomization.

[c] Probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates were obtained from Kaplan-Meier survival estimates. Greenwood formula was used for CIs of Kaplan-Meier estimates.

Source: Table 14.2-3.1.1

Figure 8: Kaplan-Meier Plot of PFS by BICR, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

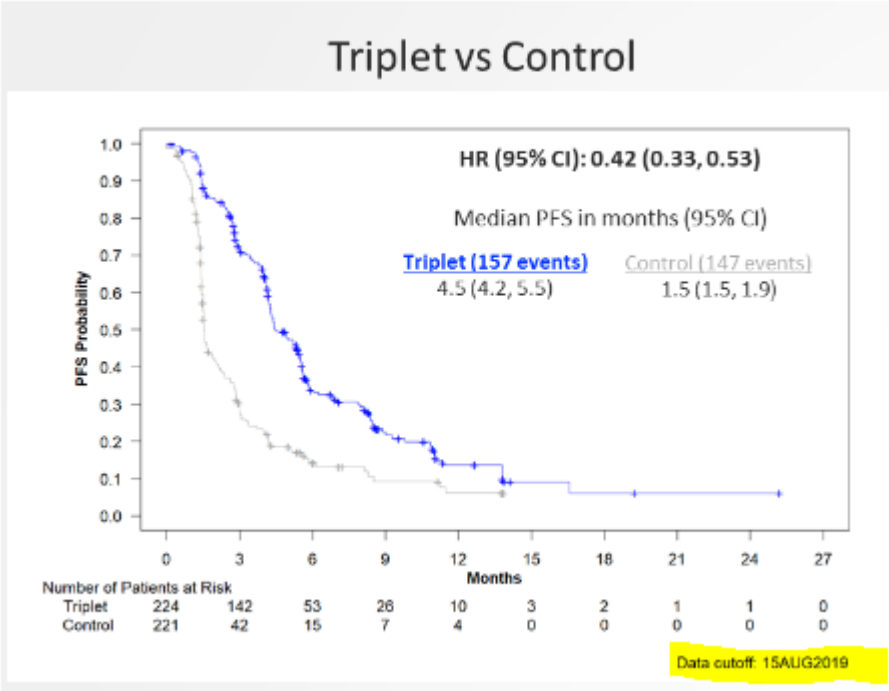


Abbreviations: BICR = blinded independent central review; BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; HR = hazard ratio; PFS = progression-free survival; Ref = reference; vs. = versus

+ indicates censoring.

Source: Figure 14.2-3.1.1

Preliminary, updated PFS results from the 15 August 2019 data cut-off are summarized below:



To assess the robustness of the PFS analysis, the following sensitivity analyses of PFS by BICR were performed:

- PFS (PPS)
- The distribution of PFS in FAS was compared between the treatment arms using unstratified analyses.
- The analyses for PFS were repeated to assess time evaluation bias, whereby event and censoring dates that did not occur within the protocol-specified schedule window were moved to either the previous or the next scheduled assessment.
- "Actual event" analysis for PFS with a censoring rule that included a PFS event even if the event was recorded after 2 or more missing tumor assessments.
- "Backdating" analysis for PFS with a censoring rule that backdated events occurring after 1 or more missing tumor assessments.
- "Further anticancer therapy" analysis for PFS including tumor assessments after initiation of subsequent anticancer therapy.
- The analyses for PFS were repeated to assess early censoring (i.e., censoring > 2 months prior to the data cutoff date) and the impact of any imbalances in censoring distribution.

Results of these sensitivity analyses for PFS by BICR are consistent with the primary PFS analysis of Triplet arm vs. Control arm, yielding similar HRs (0.36 to 0.42), median PFS values and p values. sensitivity analyses for PFS by BICR in patients with early censoring also yielded HRs (0.37 to 0.41) and p values similar to those in the primary analysis.

Supportive Analysis: Multivariate Cox Regression of PFS, Triplet Arm vs. Control Arm

The effect of Baseline covariates and potential prognostic factors on PFS by BICR in the FAS was investigated using a multivariate Cox regression model stratified by the study stratification factors (ECOG

PS, prior irinotecan use and cetuximab source). The objective of this analysis was to explore the consistency of treatment effect on PFS after adjusting for these Baseline covariates.

This multivariate Cox regression model demonstrated that, after adjusting for pre-specified Baseline covariates, the outcome of the comparison of Triplet arm vs. Control arm was consistent with the primary PFS analysis (71% reduction in the risk of disease progression or death in the Triplet arm). The difference was nominally significant (HR 0.29, 95% CI: 0.21, 0.38; 2-sided p value < 0.0001).

Two pre-specified covariates reached nominal significance:

the presence of liver metastases at Baseline and Baseline CRP. The presence of liver metastases at Baseline was associated with a 4.17-fold increase in the risk of disease progression or death (HR 4.17, 95% CI: 2.92, 5.95; 2-sided p value < 0.0001). Baseline CRP > ULN was associated with a 1.47-fold increase in the risk of disease progression or death (expressed as the inverse of HR 0.68, 95% CI: 0.51, 0.91; 2-sided p value = 0.0095).

In addition, post hoc unstratified univariate Cox regression analyses, for all Phase 3 patients in the FAS combined (i.e., all 3 arms combined), were conducted to investigate the relationship between PFS and the study stratification factors (ECOG PS, prior irinotecan use and cetuximab source) and Baseline covariates, without including treatment effect in the model. Of the stratification factors, a Baseline ECOG PS score of 1 was associated with a 1.37-fold increase in the risk of disease progression or death (HR 1.37, 95% CI: 1.12, 1.68; 2-sided p value = 0.0024). Prior irinotecan use was associated with a 1.25-fold increase in the risk of disease progression or death (HR 1.25, 95% CI: 1.02, 1.53; 2-sided p value = 0.0319).

Several Baseline covariates were strongly associated (2-sided p < 0.0001) with an increase in the risk of disease progression or death. The presence of liver metastases at Baseline was associated with a 2.46-fold increase in the risk of disease progression or death (HR 2.46, 95% CI: 1.95, 3.09). Baseline CRP > ULN was associated with a 2.00-fold increase in the risk of disease progression or death (expressed as the inverse of HR 0.50, 95% CI: 0.41, 0.62). Baseline CEA > ULN was associated with a 1.85-fold increase in the risk of disease progression or death (expressed as the inverse of HR 0.54, 95% CI: 0.42, 0.71). Also, Baseline CA19-9 > ULN was associated with a 1.64-fold increase in the risk of disease progression or death (expressed as the inverse of HR 0.61, 95% CI: 0.48, 0.77).

Subgroup Analyses of PFS, Triplet Arm vs. Control Arm

Subgroup analyses were performed for each Baseline stratification factor and other relevant Baseline variables (Table 14.2-3.10). Only analyses for which at least 10 events were available in each subgroup are discussed here. All analyses demonstrated PFS HRs in favor of the Triplet arm. The greatest differences in favor of the Triplet arm were observed in subgroups with liver metastases at Baseline (HR 0.28, 95% CI: 0.21, 0.38), tumor partly resected or unresected (HR 0.29, 95% CI: 0.19, 0.43), and prior irinotecan use (HR 0.29, 95% CI: 0.20, 0.42). The smallest difference in favor of the Triplet arm was observed in the subgroup of Asian patients (HR 0.51, 95% CI: 0.25, 1.03).

Randomized Phase 3: <u>Doublet Arm vs. Control Arm</u>

OS, Doublet Arm vs. Control Arm (Key Secondary Endpoint)

Because the OS primary endpoint of Triplet arm vs. Control arm was found to be significant, the key secondary efficacy endpoint of OS, Doublet arm vs. Control arm was formally tested in the FAS, as pre-specified in the SAP. As of the data cut-off date, 93 deaths were observed in the 220 (42.3%) patients randomized to the Doublet arm and 114 deaths were observed in the 221 (51.6%) patients randomized

to the Control arm (Table 29). Using a Lan-DeMets α spending function that approximates O'Brien-Fleming stopping boundaries, the critical p value with 61% information (i.e., 207 patient deaths out of the planned 338 for the final analysis) was p = 0.0042.

Table 29: Kaplan-Meier Summary of OS, Doublet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

	ENCO + CETUX (N = 220)	CONTROL (N = 221)
Patients with events/Patients included in analysis (%)	93/220 (42.3)	114/221 (51.6)
Percentiles (95% CI), months		
25th	4.50 (4.07, 5.36)	3.19 (2.60, 3.84)
Median (50th)	8.41 (7.46, 11.04)	5.42 (4.76, 6.57)
75th	14.82 (12.32, NR)	12.35 (9.13, 17.12)
Stratified hazard ratio (95% CI)[a,b]	0.60 (0.45, 0.79)	
Stratified log-rank (one-sided) p value[a,b]	0.0002	
Survival probability estimates, % (95% CI)[c]		
2 months	94.2 (90.0, 96.7)	86.1 (80.4, 90.2)
4 months	83.2 (77.0, 87.9)	66.2 (58.6, 72.7)
6 months	65.1 (57.2, 72.0)	46.7 (38.6, 54.4)
8 months	54.3 (45.7, 62.1)	36.3 (28.3, 44.3)
10 months	42.9 (33.9, 51.5)	27.4 (19.4, 36.0)
12 months	35.7 (26.5, 45.0)	27.4 (19.4, 36.0)
14 months	29.7 (20.1, 39.9)	18.5 (10.4, 28.5)

Abbreviations: CETUX = cetuximab; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ENCO = encorafenib; NR = not reached; OS = overall survival; vs. = versus.

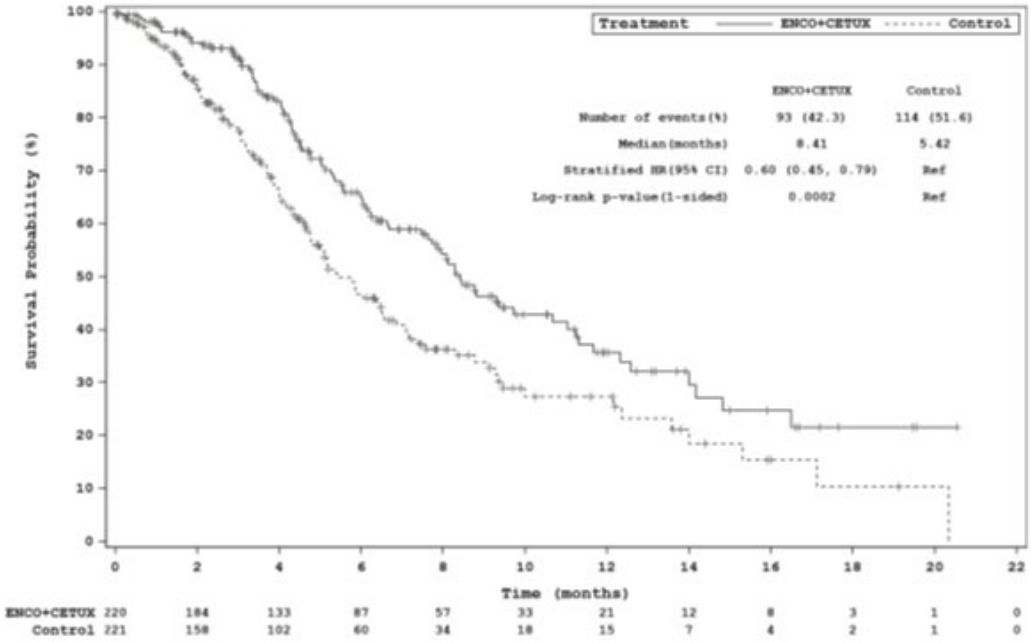
[a] Reference group for comparisons is 'Control'.

[b] Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomization.

[c] Probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates were obtained from Kaplan-Meier survival estimates. Greenwood formula was used for CIs of Kaplan-Meier estimates.

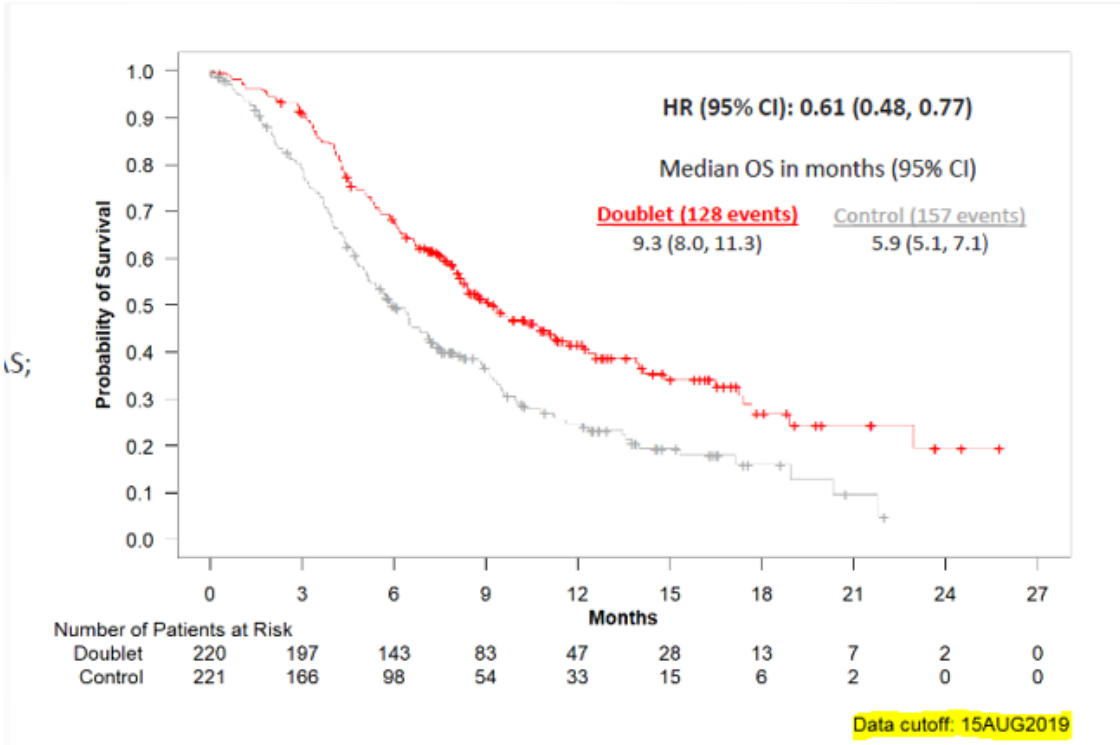
Source: Table 14.2-2.1.1

Figure 9: Kaplan-Meier Plot of OS, Doublet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; HR = hazard ratio; OS = overall survival; Ref = reference; vs. = versus
+ indicates censoring.
Source: Figure 14.2-2.3.1

Updated OS analysis as of January 20, 2020 (cut-off 15 August 2019)



Sensitivity Analyses of OS, Doublet Arm vs. Control Arm

To assess the robustness of this OS analysis, the following sensitivity analyses were performed:

- OS, stratified test (PPS)

- OS, unstratified test (FAS)

These pre-specified sensitivity analyses of OS support the conclusions reached in the primary analysis, yielding similar HRs (0.58 to 0.61), median OS values and p values (Table 31).

In a post hoc analysis, OS was analyzed in the Phase 3 Response Efficacy Set (i.e., the first 331 patients randomized). As shown Figure 10, an estimated 34% reduction in risk of death was observed for the Doublet arm compared to the Control arm (HR 0.66, 95% CI: 0.48, 0.92). The median OS in the Doublet arm was 3.12 months longer than in the Control arm, with median OS estimates using Kaplan-Meier methodology of 8.28 months (95% CI: 6.24, 10.68) in the Doublet arm and 5.16 months (95% CI: 4.44, 6.57) in the Control arm (p = 0.0074, stratified log-rank test).

Therefore, data in patients with more mature follow-up support the conclusions reached in the primary analysis of OS and in prespecified sensitivityanalyses

Table 31: OS Sensitivity Analyses, Doublet Arm vs. Control Arm (Randomized Phase 3)

	Median (95% CI)[a]	HR (95% CI)	P value	Source
Primary OS analysis, Stratified (FAS)				**Table 14.2-2.1.1 Figure 14.2-2.3.1**
Doublet arm	**8.41 months (7.46, 11.04)**	**0.60 (0.45, 0.79)**	**0.0002**	
Control arm	**5.42 months (4.76, 6.57)**			
OS, Stratified (PPS)				Table 14.2-2.2 Figure 14.2-2.4
Doublet arm	8.77 months (7.62, 11.24)	0.58 (0.43, 0.78)	0.0002	
Control arm	5.39 months (4.63, 6.51)			
OS, Unstratified (FAS)				Table 14.2-2.1.1
Doublet arm	8.41 months (7.46, 11.04)	0.61 (0.46, 0.80)	0.0002	
Control arm	5.42 months (4.76, 6.57)			
OS, Stratified (Phase 3 Response Efficacy Set)				Table 14.2-2.14
Doublet arm	8.28 months (6.24, 10.68)	0.66 (0.48, 0.92)	0.0074	
Control arm	5.16 months (4.44, 6.57)			

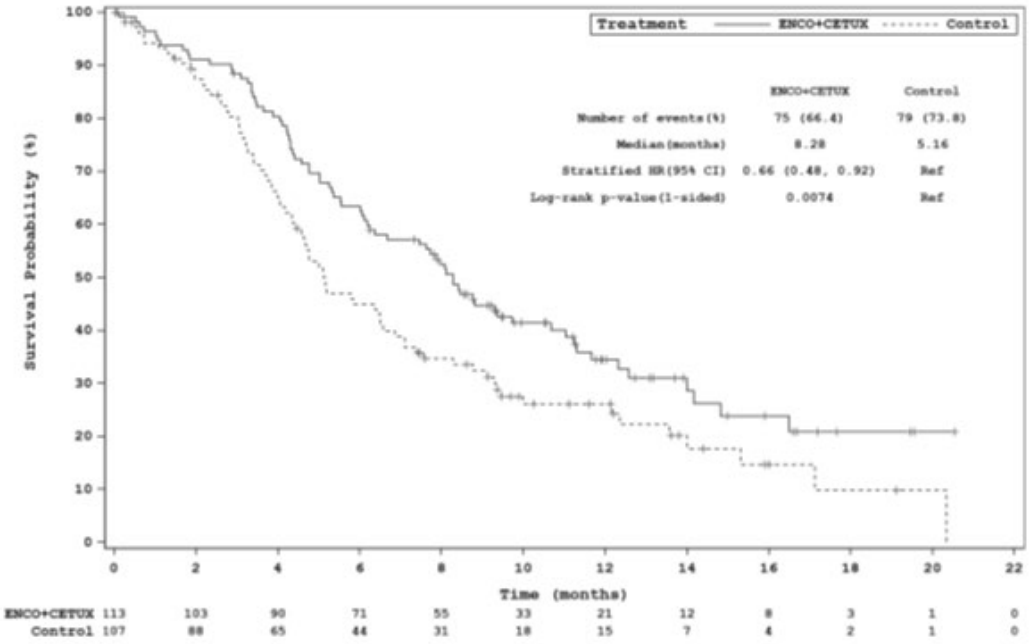
Abbreviations: CI = confidence interval; FAS = Full Analysis Set; HR = hazard ratio; OS = overall survival; PPS= Per-protocol Set; vs. = versus

Note: Reference group for comparisons is 'Control'.

[a] Greenwood formula was used for confidence intervals of Kaplan-Meier estimates.

Source: Figure 14.2-2.3.1; Figure 14.2-2.4; Table 14.2-2.1.1; Table 14.2-2.2; Table 14.2-2.14

Figure 10: Kaplan-Meier Plot of OS, Doublet Arm vs. Control Arm (Randomized Phase 3, Phase 3 Randomized Efficacy Set)



Abbreviations: CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; HR = hazard ratio; OS = overall survival; Ref = reference; vs. = versus
+ indicates censoring.
Source: Figure 14.2-2.14.2

Supportive Analysis: Multivariate Cox Regression of OS, Doublet Arm vs. Control Arm

The effect of Baseline covariates and potential prognostic factors on OS was investigated using a multivariate Cox regression model stratified by the study stratification factors (ECOG PS, prior irinotecan use and cetuximab source). The objective of this analysis was to explore the consistency of treatment effect on OS after adjusting for these Baseline covariates.

This multivariate Cox regression model demonstrated that, after adjusting for pre-specified Baseline covariates, the outcome of the comparison of Doublet arm vs. Control arm was consistent with the primary OS analysis (51% reduction in the risk of death in the Doublet arm), which was nominally significant (HR 0.49, 95% CI: 0.36, 0.67; 2-sided p value < 0.0001).

Subgroup Analyses of OS, Doublet Arm vs. Control Arm

Subgroup analyses were performed for each Baseline stratification factor and other relevant Baseline variables.

Only analyses for which at least 10 events were available in each subgroup are discussed here.

With the exception of the overlapping subgroups of patients randomized to receive US-licensed cetuximab source and patients randomized at sites in North America (excluding Mexico) (HR 1.15 [95% CI: 0.57, 2.32] for both subgroups) and unknown MSI status (HR 1.18, 95% CI: 0.64, 2.14), all analyses demonstrated OS HRs in favor of the Doublet arm.

The greatest differences in favor of the Doublet arm were observed in the subgroup of patients with ≤ 2 organs involved at Baseline (HR 0.43, 95% CI: 0.28, 0.65), patients with MSI normal status (HR 0.45, 95% CI: 0.32, 0.63), and patients at sites in Europe (HR 0.45, 95% CI: 0.32, 0.64).

Subsequent Systemic Anticancer Therapy, Doublet Arm vs. Control Arm

Of the patients who were discontinued from treatment or were not treated (142 Doublet, 184 Control; Table 10 above), 43.0% and 44.6% of patients in the Doublet and Control arms, respectively, used subsequent systemic anticancer therapy.

In the Doublet arm, subsequent systemic therapies used at the highest incidence (> 10%) were irinotecan (25.4%), flourouracil (22.5%) and folinic acid (12.7%).

In the Control arm, subsequent systemic therapies used at the highest incidence (> 10%) were fluorouracil (18.5%), irinotecan (16.8%), cetuximab (13.6%), oxaliplatin (10.3%) and vemurafenib (10.3%).

Notably, a lower percentage of patients in the Doublet arm than in the Control arm received subsequent therapy with a protein kinase inhibitor (7.0% and 17.9%, respectively).

Subsequent Systemic Anticancer Therapy in Patients Randomized but not Treated, Doublet Arm vs. Control Arm

Of the patients who were randomized but not treated, no patient in the Doublet arm and 11 of 28 patients (39.3%) in the Control arm used subsequent systemic anticancer therapy after study withdrawal.

In the Control arm, therapies used at the highest incidence (> 10%) were irinotecan (21.4%); fluorouracil (21.4%); bevacizumab (14.3%); panitumumab (14.3%); folinic acid (10.7%); oxaliplatin (10.7%) and investigational antineoplastic drugs (10.7%) (2 patients received PLX8394 [a BRAF inhibitor] and 1 patient received RO6958688 [anti-CEA/CD3]). Subsequent use of a PD-1/PD-L1 inhibitor was reported in 3.6% of patients in the Control arm. Notably, some patients in the Control arm who were not treated received subsequent combination treatment with a BRAF inhibitor plus a MEK inhibitor plus an EGFR inhibitor.

ORR, Doublet Arm vs. Control Arm

The secondary efficacy endpoint of Doublet arm vs. Control arm ORR by BICR was also formally tested, as all previous endpoints in the hierarchy were statistically significant.

Table 32: Best Overall Response by BICR, Doublet Arm vs. Control Arm (Randomized Phase 3, Response Efficacy Set)

	ENCO + CETUX (N = 113)	CONTROL (N = 107)
Best Confirmed Overall Response[a], n (%)		
Complete Response	6 (5.3)	0 (0.0)
Partial Response	17 (15.0)	2 (1.9)
Stable Disease	57 (50.4)	26 (24.3)
Progressive Disease	8 (7.1)	36 (33.6)
Non-CR/Non-PD[b]	4 (3.5)	5 (4.7)
Not Evaluable	21 (18.6)	38 (35.5)
Evidence of disease progression or AE	19 (16.8)	17 (15.9)
Insufficient information to assess response	2 (1.8)	21 (19.6)
Confirmed Overall Response Rate (ORR: CR+PR), n (%)	23 (20.4)	2 (1.9)
95% CI[c]	(13.4, 29.0)	(0.2, 6.6)
Confirmed Disease Control Rate (DCR: CR+PR+stable disease+Non-PD/Non-CR), n (%)	84 (74.3)	33 (30.8)
95% CI[c]	(65.3, 82.1)	(22.3, 40.5)

Abbreviations: BICR = blinded independent central review; CETUX = cetuximab; CI = confidence interval; CR = complete response; DCR = disease control rate; ENCO = encorafenib; ORR = overall response rate; PD = progressive disease; PR = partial response; vs. = versus

[a] CR and PR were confirmed by repeat assessments performed not less than 4 weeks after criteria for response were met.

[b] Patients with only non-measurable disease, whose best non-target lesion response was Non-CR/non-PD and did not have any new lesions.

[c] The CIs for the frequency distribution of each variable were computed using Clopper-Pearson's method.

Source: Table 14.2-1.1.1; Table 14.2-1.7.4

The pattern of confirmed ORR by Investigator assessment in the Phase III Efficacy Response Set is similar to results observed when evaluated by BICR, though the confirmed ORR in the Doublet arm was slightly lower (Doublet: 15.9% [95% CI: 9.7, 24.0]; Control: 3.7% [95% CI: 1.0, 9.3]; stratified odds ratio 5.04 [95% CI: 1.63, 15.56; p = 0.0011], Cochran-Mantel-Haenszel test). Confirmed CR by Investigator assessment was observed in 1.8% and 0% of patients in the Doublet and Control arms, respectively.

Nine patients (8.0%) in the Doublet arm were classified as confirmed objective responses by BICR and as no confirmed objective responses by Investigator assessment. The Investigator assessments in all 9 patients reported tumor regressions that did not reach criteria for response. Four patients (3.5%) in the Doublet arm were classified as confirmed objective responses by Investigator assessment and as no confirmed objective responses by BICR. Two of these 4 patients had an unconfirmed PR (classified as stable disease) by BICR. No patients in the Doublet arm were considered to be unevaluable by BICR assessment. In the Control arm, 2 patients (1.9%) were classified as confirmed objective responses by Investigator and as no confirmed objective responses by BICR. All other assessments of confirmed objective response by BICR in the Phase 3 Efficacy Set were concordant.

The concordance between Investigator and BICR assessments of overall response in the FAS is similar to that observed in the Phase III Response Efficacy Set.

For reasons of completeness, updated analysis of ORR (and DOR) are added here as follows:

	Doublet N=220	Control N=221
Objective Response Rate	**19.5%**	**1.8%**
95% CI	(14.5%, 25.4%)	(0.5%, 4.6%)
Duration of Response		
DOR, Kaplan-Meier median (95% CI), months	5.6 (4.1, 8.3)	NR*
DOR ≥ 6 months, n (%)	16/43 (37.2)	1/4 (25.0)
DOR < 6 months, response ongoing, n (%)	4/43 (9.3)	0

* Not reported due to only 2 events in 4 responders

Sensitivity Analyses of ORR by BICR, Doublet Arm vs. Control Arm

To assess the robustness of the ORR Doublet arm vs. Control arm analysis the following sensitivity analyses were performed:

- ORR unstratified test in Phase 3 Response Efficacy Set
- ORR stratified test in FAS
- ORR unstratified test in FAS
- ORR stratified test, for patients in Phase 3 Response Efficacy Set with measurable disease at Baseline

These sensitivity analyses of ORR support the conclusions reached in the primary analysis, yielding similar ORRs and p values (Table 33).

Table 33: ORR by BICR Sensitivity Analyses, Doublet Arm vs. Control Arm (Randomized Phase 3)

	ORR (95% CI)	P value	Source
ORR analysis (Phase 3 Response Efficacy Set), Stratified			**Table 14.2-1.1.1**
Doublet arm	**20.4% (13.4, 29.0)**	**< 0.0001**	
Control arm	**1.9% (0.2, 6.6)**		
ORR, Unstratified (Phase 3 Response Efficacy Set)			Table 14.2-1.1.1
Doublet arm	20.4% (13.4, 29.0)	< 0.0001	
Control arm	1.9% (0.2, 6.6)		
ORR, Stratified (FAS)			Table 14.2-1.2.1
Doublet arm	16.4% (11.7, 21.9)	< 0.0001	
Control arm	1.4% (0.3, 3.9)		
ORR, Unstratified (FAS)			Table 14.2-1.2.1
Doublet arm	16.4% (11.7, 21.9)	< 0.0001	
Control arm	1.4% (0.3, 3.9)		
ORR (Phase 3 Response Efficacy Set with measurable disease at Baseline)			Table 14.2-1.4
Doublet arm	21.0% (13.6, 30.0)	< 0.0001	
Control arm	2.0% (0.2, 7.0)		

Abbreviations: BICR = blinded independent central review; CI = confidence interval; FAS = Full Analysis Set; ORR = overall response rate; vs. = versus
Source: Table 14.2-1.1.1; Table 14.2-1.2.1; Table 14.2-1.4

Supportive Analysis: Multivariate Logistic Regression of ORR by BICR, Doublet Arm vs. Control Arm

The effect of Baseline characteristics and potential prognostic factors on ORR by BICR in the Phase III Response Efficacy Set was investigated using a multivariate logistic regression model stratified by the study stratification factors (ECOG PS, prior irinotecan use and cetuximab source). The objective of this analysis was to explore the consistency of treatment effect on ORR by BICR after adjusting for main prognostic factors.

To provide a comparison to this stratified multivariate logistic regression model, a separate stratified univariate model looking only at treatment group (Doublet arm vs. Control arm) was also assessed. The stratified univariate model showed that patients in the Doublet arm had a 13.72-fold increased odds (95% CI: 3.15, 59.80) of responding compared to patients in the Control arm.

The stratified multivariate logistic regression model demonstrated that, after adjusting for pre-specified Baseline covariates, the outcome of the Doublet arm vs. Control arm comparison was consistent with the stratified univariate model (odds ratio 15.74 [95% CI: 3.44, 72.06; 2-sided p value = 0.0004],). No other prespecified covariates were found to have a significant effect on ORR by BICR.

Subgroup Analyses of ORR by BICR, Doublet Arm vs. Control Arm

Subgroup analyses were performed for each Baseline stratification factor and other relevant Baseline variables. Because there were 2 patients in the Control arm with confirmed responses by BICR in the Phase III Response Efficacy Set, this discussion focuses on 5 clinically relevant subgroups in the Doublet arm:

- In the Doublet arm, patients who had progressed after 1 prior regimen for metastatic disease had a confirmed ORR of 22.4% (17 of 76 patients, 95% CI: 13.6, 33.4), compared to 16.2% (6 of 37 patients, 95% CI: 6.2, 32.0) in patients who had progressed after ≥ 2 prior regimens for metastatic disease.
- In the Doublet arm, patients with ≤ 2 organs involved at Baseline had a confirmed ORRof 29.3% (17 of 58 patients, 95% CI: 18.1, 42.7), compared to 10.9% (6 of 55 patients, 95% CI: 4.1, 22.2) in patients with ≥ 3 organs involved at Baseline.
- In the Doublet arm, patients with a Baseline CEA ≤ ULN had a confirmed ORR of 26.5% (9 of 34 patients, 95% CI: 12.9, 44.4), compared to 17.7% (14 of 79 patients, 95% CI: 10.0, 27.9) in patients with a Baseline CEA > ULN.
- In the Doublet arm, patients with a Baseline CRP ≤ ULN had a confirmed ORR of 27.7% (18 of 65 patients, 95% CI: 17.3, 40.2), compared to 10.9% (5 of 46 patients, 95% CI: 3.6, 23.6) in patients with a Baseline CRP > ULN.
- In the Doublet arm, patients with no liver metastases at Baseline had a confirmed ORR of 20.0% (8 of 40 patients, 95% CI: 9.1, 35.6), compared to 20.5% (15 of 73 patients, 95% CI: 12.0, 31.6) in patients with liver metastases at Baseline.

DOR, Doublet Arm vs. Control Arm

The Kaplan-Meier estimate of median DOR by BICR in the Phase 3 Response Efficacy Set, calculated for confirmed responses in the Doublet arm, was 6.06 months (95% CI: 4.07, 8.28). Of the 2 patients in the Control arm with confirmed responses, 1 patient had a DOR of 2.56 months; the other patient's DOR was 6.93 months.

TTR, Doublet Arm vs. Control Arm

The median TTR by BICR in the Phase 3 Response Efficacy Set, calculated for patients with confirmed responses, was 1.54 months in the Doublet arm (95% CI: 1.41, 1.64). For patients in the Doublet arm with confirmed CRs, the TTRs were 1.31, 1.58, 1.71, 1.48, 1.48 and 4.17 months. Of the 2 patients in the Control arm with confirmed responses, 1 patient had a TTR of 1.41 months; the other patient's TTR was 1.45 months.

The time to most responses by BICR in the Phase 3 Response Efficacy Set corresponded with the first post-Baseline response assessment at 6 weeks (± 7 days) after randomization.

PFS, Doublet Arm vs. Control Arm

Table 34: Kaplan-Meier Summary of PFS by BICR, Doublet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

	ENCO + CETUX (N = 220)	CONTROL (N = 221)
Patients with events/Patients included in analysis (%)	133/220 (60.5)	128/221 (57.9)
Death	23/220 (10.5)	27/221 (12.2)
Disease Progression	110/220 (50.0)	101/221 (45.7)
Percentiles (95% CI), months		
25th	2.73 (2.53, 2.83)	1.31 (1.22, 1.41)
Median (50th)	4.21 (3.71, 5.36)	1.51 (1.45, 1.71)
75th	8.08 (6.01, 8.34)	3.38 (2.76, 4.30)
Stratified hazard ratio (95% CI)[a,b]	0.40 (0.31, 0.52)	
Stratified log-rank (one-sided) p value[a,b]	< 0.0001	
Patients event-free probability estimates, % (95% CI)[c]		
2 months	83.8 (77.7, 88.4)	39.2 (31.3, 47.0)
4 months	57.6 (49.6, 64.8)	23.0 (16.3, 30.5)
6 months	32.8 (25.0, 40.8)	12.4 (6.9, 19.5)
8 months	25.5 (18.3, 33.4)	12.4 (6.9, 19.5)
10 months	11.9 (6.7, 18.7)	6.9 (2.0, 16.0)
12 months	4.5 (1.5, 9.9)	0.0 (0.0, 0.0)
14 months	2.2 (0.4, 6.9)	0.0 (0.0, 0.0)

Abbreviations: BICR = blinded independent central review; CETUX = cetuximab; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ENCO = encorafenib; PFS = progression-free survival; vs. = versus

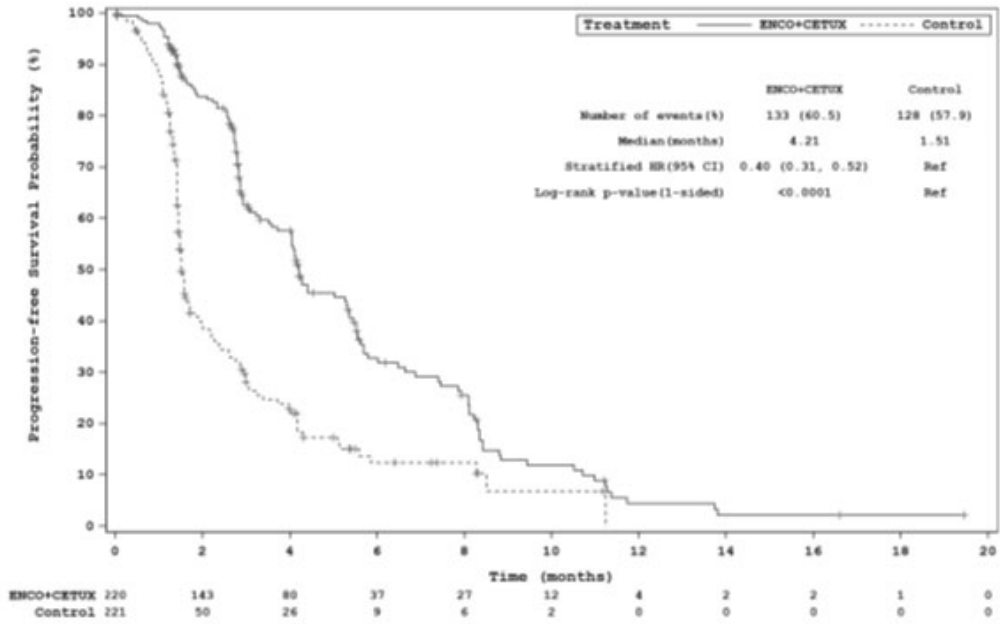
[a] Reference group for comparisons is 'Control'.

[b] Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomization.

[c] Probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates were obtained from Kaplan-Meier survival estimates. Greenwood formula was used for CIs of Kaplan-Meier estimates.

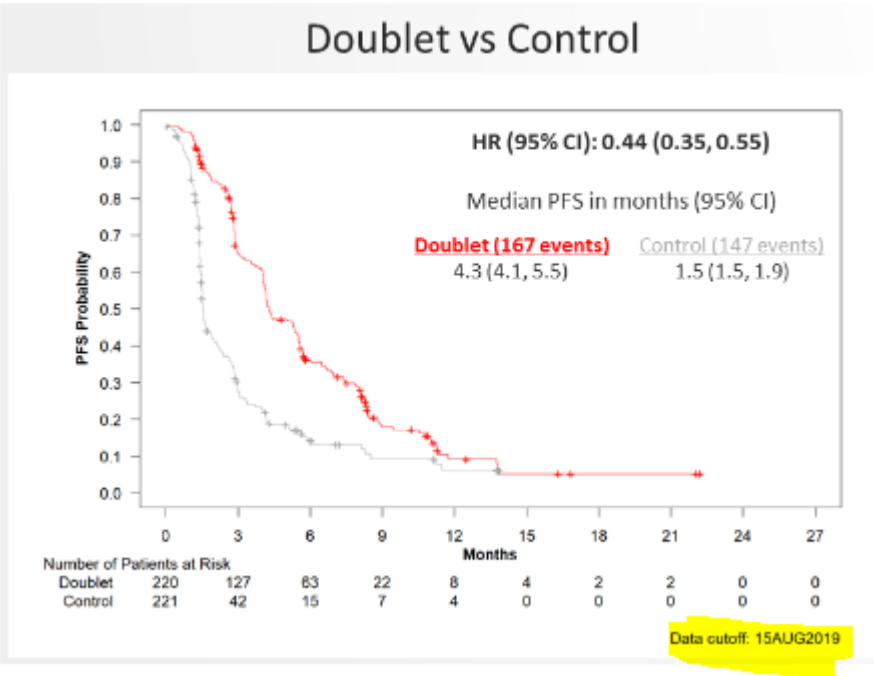
Source: Table 14.2-3.1.1

Figure 13: Kaplan-Meier Plot of PFS by BICR, Doublet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BICR = blinded independent central review; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; HR = hazard ratio; PFS = progression-free survival; Ref = reference; vs. = versus
+ indicates censoring.
Source: Figure 14.2-3.2.1

The updated PFS (Doublet vs. Control) is summarized in the following figure:



Sensitivity Analyses of PFS, Doublet Arm vs. Control Arm

To assess the robustness of the PFS analysis, the following sensitivity analyses of PFS by BICR were performed:

- PFS (PPS)

- The distribution of PFS in FAS was compared between the treatment arms using unstratified analyses.
- The analyses for PFS were repeated to assess time evaluation bias, whereby event and censoring dates that did not occur within the protocol-specified schedule window were moved to either the previous or the next scheduled assessed, as outlined in the SAP.
- "Actual event" analysis for PFS with a censoring rule that included a PFS event even if the event was recorded after 2 or more missing tumour assessments.
- "Backdating" analysis for PFS with a censoring rule that backdated events occurring after 1 or more missing tumour assessments.
- "Further anticancer therapy" analysis for PFS including tumour assessments after initiation of subsequent anticancer therapy.
- The analyses for PFS were repeated to assess early censoring (i.e., censoring > 2 months prior to the data cut-off date) and the impact of any imbalances in censoring distribution.

Results of these sensitivity analyses for PFS by BICR are consistent with the primary PFS analysis of Doublet arm vs. Control arm, yielding similar HRs (0.40 to 0.46), median PFS values and p values. Sensitivity analyses for PFS by BICR in patients with early censoring also yielded HRs (0.38 to 0.41) and p values similar to those in the primary analysis.

Supportive Analysis: Multivariate Cox Regression of PFS, Doublet Arm vs. Control Arm

The effect of Baseline covariates and potential prognostic factors on PFS by BICR in the FAS was investigated using a multivariate Cox regression model stratified by the study stratification factors (ECOG PS, prior irinotecan use and cetuximab source). The objective of this analysis was to explore the consistency of treatment effect on PFS after adjusting for these Baseline covariates.

This multivariate Cox regression model demonstrated that, after adjusting for pre-specified Baseline covariates, the outcome of the comparison of Doublet arm vs. Control arm was consistent with the primary PFS analysis (67% reduction in the risk of disease progression or death in the Doublet arm), which was nominally significant (HR 0.33, 95% CI: 0.25, 0.44; 2-sided p value < 0.0001). Two pre-specified covariates reached nominal significance: the presence of liver metastases at Baseline and Baseline CRP.

The presence of liver metastases at Baseline was associated with a 2.58-fold increase in the risk of disease progression or death.

Baseline CRP > ULN was associated with a 1.61-fold increase in the risk of disease progression or death.

Subgroup Analyses of PFS, Doublet Arm vs. Control Arm

Subgroup analyses were performed for each Baseline stratification factor and other relevant Baseline variables. Only analyses for which at least 10 events were available in each subgroup are discussed here. All analyses demonstrated PFS HRs in favor of the Doublet arm.

The greatest differences in favour of the Doublet arm were observed in subgroups with liver metastases at Baseline (HR 0.28, 95% CI: 0.20, 0.38) and a Baseline ECOG PS of 0 (HR 0.32, 95% CI: 0.22, 0.48). The smallest differences in favor of the Doublet arm was observed in subgroups with a Baseline ECOG PS of 1 (HR 0.51, 95% CI: 0.37, 0.72) and patients at sites in rest of world (i.e., outside of the US, Canada and the EU) (HR 0.51, 95% CI: 0.30, 0.85).

Randomized Phase 3: <u>Triplet Arm vs. Doublet Arm</u>

OS, Triplet Arm vs. Doublet Arm

Table 36: Kaplan-Meier Summary of OS, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Full Analysis Set)

	ENCO + BINI + CETUX (N = 224)	ENCO + CETUX (N = 220)
Patients with events/Patients included in analysis (%)	90/224 (40.2)	93/220 (42.3)
Percentiles (95% CI), months		
25th	5.59 (4.67, 6.41)	4.50 (4.07, 5.36)
Median (50th)	9.03 (8.02, 11.43)	8.41 (7.46, 11.04)
75th	NR (13.40, NR)	14.82 (12.32, NR)
Stratified hazard ratio (95% CI)[a,b]	0.79 (0.59, 1.06)	
Stratified log-rank (one-sided) p value[a,b]	0.0582	
Survival probability estimates, % (95% CI)[c]		
2 months	94.3 (90.3, 96.8)	94.2 (90.0, 96.7)
4 months	85.5 (79.6, 89.8)	83.2 (77.0, 87.9)
6 months	70.8 (63.2, 77.2)	65.1 (57.2, 72.0)
8 months	59.3 (50.9, 66.7)	54.3 (45.7, 62.1)
10 months	44.2 (35.3, 52.7)	42.9 (33.9, 51.5)
12 months	37.3 (28.2, 46.5)	35.7 (26.5, 45.0)
14 months	31.3 (21.7, 41.4)	29.7 (20.1, 39.9)

Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ENCO = encorafenib; NR = not reached; OS= overall survival; vs. = versus

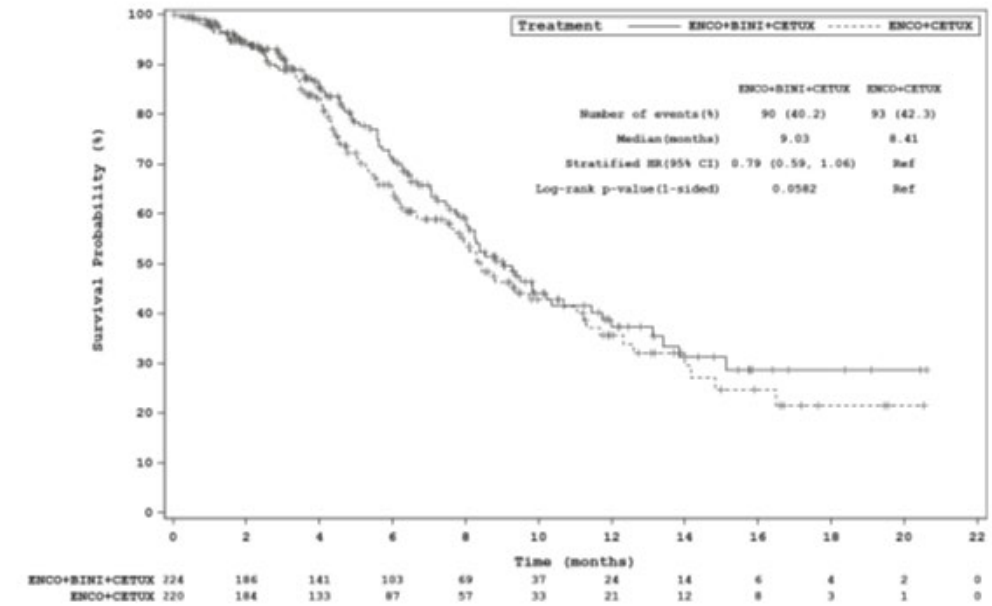
[a] Reference group for comparisons is 'ENCO + CETUX'.

[b] Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomization.

[c] Probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates were obtained from Kaplan-Meier survival estimates. Greenwood formula was used for CIs of Kaplan-Meier estimates.

Source: Table 14.2-2.1.1

Figure 14: Kaplan-Meier Plot of OS, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; HR = hazard ratio; OS = overall survival; Ref = reference; vs. = versus
+ indicates censoring.
Source: Figure 14.2-2.5.1

<u>Update</u>

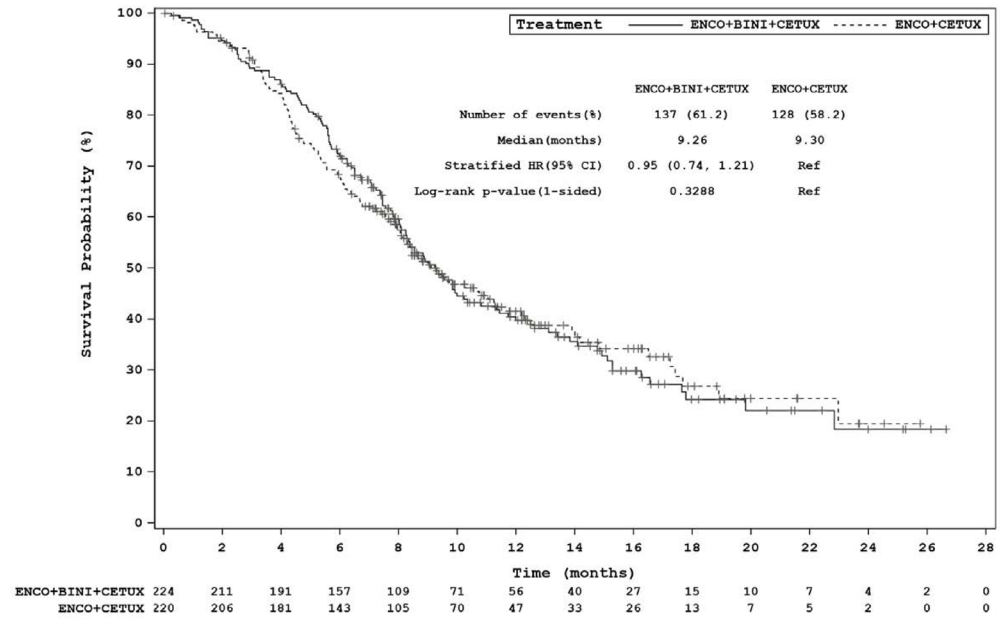
The updated results from the data cut-off date of 15 August 2019 are presented below.

Table 13: Kaplan-Meier Summary of OS, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Full Analysis Set)

	ENCO + BINI + CETUX (N = 224)	ENCO + CETUX (N = 220)
Patients with events/Patients included in analysis (%)	137/224 (61.2)	128/220 (58.2)
Percentiles (95% CI), months		
25th	5.62 (4.93, 6.51)	4.76 (4.24, 5.85)
Median (50th)	9.26 (8.25, 10.81)	9.30 (8.05, 11.30)
75th	17.77 (15.11, NR)	18.89 (16.49, NR)
Stratified hazard ratio (95% CI)[a,b]	0.95 (0.74, 1.21)	
Stratified log-rank (one-sided) p value[a,b]	0.3288	
Survival probability estimates, % (95% CI)[c]		
2 months	94.6 (90.8, 96.9)	94.5 (90.5, 96.8)
4 months	86.1 (80.8, 90.0)	84.3 (78.7, 88.5)
6 months	72.0 (65.6, 77.4)	67.9 (61.2, 73.7)
8 months	59.6 (52.7, 65.9)	57.5 (50.5, 63.9)
10 months	44.5 (37.4, 51.4)	46.8 (39.6, 53.7)
12 months	39.8 (32.6, 46.8)	41.5 (34.2, 48.7)
14 months	35.6 (28.4, 42.8)	36.5 (29.0, 44.1)

Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ENCO = encorafenib; NR = not reached; OS = overall survival; vs. = versus
[a] Reference group for comparisons is ENCO + CETUX.
[b] Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomization.
[c] Probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates were obtained from Kaplan-Meier survival estimates. Greenwood formula was used for CIs of Kaplan-Meier estimates.
Source: Addendum Table 14.2-2.1.1

Figure 9: Kaplan-Meier Plot of OS, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; HR = hazard ratio; OS = overall survival; Ref = reference; vs. = versus
+ indicates censoring.
Source: Addendum Figure 14.2-2.5.1

Sensitivity Analyses of OS, Triplet Arm vs. Doublet Arm

To assess the robustness of this OS analysis, the following sensitivity analyses were performed:

- OS, stratified test (PPS)
- OS, unstratified test (FAS)

These pre-specified sensitivity analyses of OS support the conclusions reached in the primary analysis, yielding similar HRs (0.75 to 0.87), median OS values and p values (Table 38).

Table 38: OS Sensitivity Analyses, Triplet Arm vs. Doublet Arm (Randomized Phase 3)

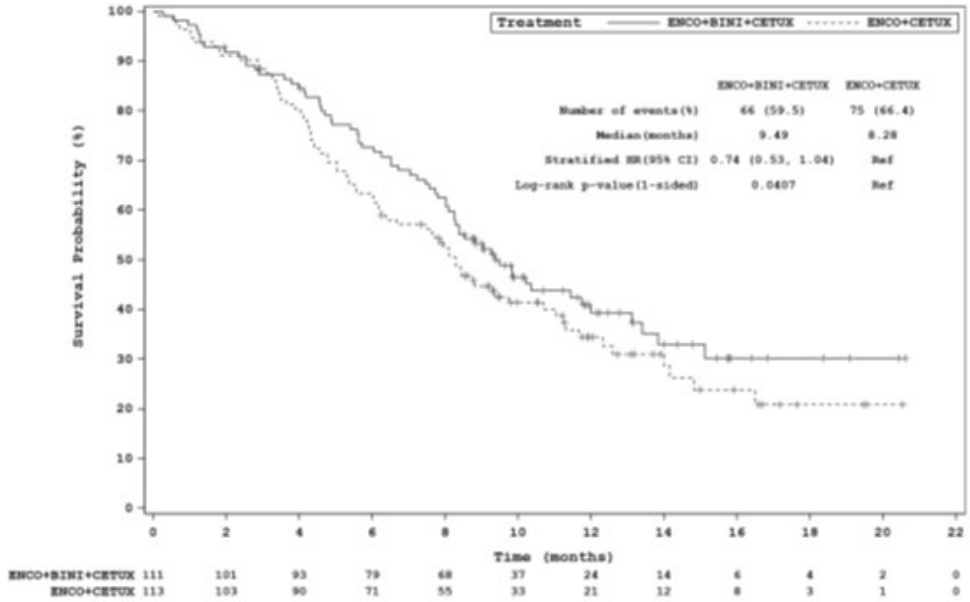
	Median (95% CI)[a]	HR (95% CI)	P value	Source
Primary OS analysis (FAS), Stratified				**Table 14.2-2.1.1 Figure 14.2-2.5.1**
Triplet arm	**9.03 months (8.02, 11.43)**	**0.79 (0.59, 1.06)**	**0.0582**	
Doublet arm	**8.41 months (7.46, 11.04)**			
OS, Stratified (PPS)				Table 14.2-2.2 Figure 14.2-2.5.4
Triplet arm	9.49 months (8.25, 11.99)	0.75 (0.55, 1.03)	0.0368	
Doublet arm	8.77 months (7.62, 11.24)			
OS, Unstratified (FAS)				Table 14.2-2.1.1
Triplet arm	9.03 months (8.02, 11.43)	0.87 (0.65, 1.16)	0.1672	
Doublet arm	8.41 months (7.46, 11.04)			
OS, Stratified (Phase 3 Response Efficacy Set)				Table 14.2-2.14
Triplet arm	9.49 months (8.08, 11.99)	0.74 (0.53, 1.04)	0.0407	
Doublet arm	8.28 months (6.24, 10.68)			

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; HR = hazard ratio; OS = overall survival; PPS = Per-protocol Set; vs. = versus
Note: Reference group for comparisons is 'Doublet'.
[a] Greenwood formula was used for confidence intervals of Kaplan-Meier estimates.
Source: Figure 14.2-2.5.1; Figure 14.2-2.5.4; Table 14.2-2.1.1; Table 14.2-2.2; Table 14.2-2.14

In a post hoc analysis, OS was analyzed in the Phase 3 Response Efficacy Set (i.e., the first 331 patients randomized). As shown in Figure 15, an estimated 26% reduction in risk of death was observed for the Triplet arm compared to the Doublet arm (HR 0.74, 95% CI: 0.53, 1.04). The median OS estimates using Kaplan-Meier methodology were 9.49 months (95% CI: 8.08, 11.99) in the Triplet arm compared to 8.28 months (95% CI: 6.24, 10.68) in the Doublet arm (p = 0.0407, stratified log-rank test).

Using a reverse Kaplan-Meier analysis (i.e., OS events were presented as censored events and vice versa), the estimated median duration of potential follow-up was 12.45 months (95% CI: 11.24, 14.36) in the Triplet arm and 12.71 months (95% CI: 11.20, 14.98) for the Doublet arm. These results support what was found in the primary analysis of OS, as well as in prespecified sensitivity analyses.

Figure 15: Kaplan-Meier Plot of OS, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Phase 3 Response Efficacy Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; HR = hazard ratio; OS = overall survival; Ref = reference; vs. = versus
+ indicates censoring.
Source: Figure 14.2-2.14.3

Supportive Analysis: Multivariate Cox Regression of OS, Triplet Arm vs. Doublet Arm

The effect of Baseline covariates and potential prognostic factors on OS was investigated using a multivariate Cox regression model stratified by the study stratification factors (ECOG PS, prior irinotecan use and cetuximab source). The objective of this analysis was to explore the consistency of treatment effect on OS after adjusting for these Baseline covariates.

After adjusting for pre-specified Baseline covariates, the multivariate Cox regression model found a 25% reduction in risk of death in the Triplet arm compared to the Doublet arm (HR 0.75, 95% CI: 0.55, 1.03; 2-sided p value = 0.0754).

The pre-specified covariate with the largest effect on OS was Baseline CRP > ULN, which was associated with a 3.13-fold increase in the risk of death (HR 0.32, 95% CI: 0.23, 0.44; 2-sided p value < 0.0001). The presence of liver metastases at Baseline was associated with a 2.35-fold increase in the risk of death (HR 2.35, 95% CI: 1.60, 3.46; 2-sided p value < 0.0001). In addition, right-sided tumors were associated with a 1.92-fold increase in the risk of death compared to left-sided tumors (HR 0.52, 95% CI: 0.36, 0.74; 2-sided p value = 0.0004).

Subgroup Analyses of OS, Triplet Arm vs. Doublet Arm

Subgroup analyses were performed for each Baseline stratification factor and other relevant Baseline variables. Only analyses for which at least 10 events were available in each subgroup are discussed here.

Twenty-seven of the 31 subgroup analyses with at least 10 events in each subgroup demonstrated OS HRs that favored the Triplet arm. The greatest difference in favor of the Triplet arm was observed in the subgroup with ≥ 3 organs involved at Baseline (HR 0.58, 95% CI: 0.39, 0.86).

Four of the 31 subgroup analyses with at least 10 events in each subgroup did not demonstrate OS HRs in favor of the Triplet arm (i.e., HR ≥ 1.0) (ECOG PS at Baseline of 0, no prior irinotecan, rest of world location, and ≤ 2 organs involved at Baseline). However, the CIs for all HRs > 1.0 also included lower bounds < 1.0.

ORR, Triplet Arm vs. Doublet Arm

Table 39: Best Overall Response by BICR, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Response Efficacy Set)

	ENCO + BINI + CETUX (N = 111)	ENCO + CETUX (N = 113)
Best Confirmed Overall Response[a], n (%)		
Complete Response	4 (3.6)	6 (5.3)
Partial Response	25 (22.5)	17 (15.0)
Stable Disease	41 (36.9)	57 (50.4)
Progressive Disease	11 (9.9)	8 (7.1)
Non-CR/Non-PD[b]	6 (5.4)	4 (3.5)
Not Evaluable	24 (21.6)	21 (18.6)
Evidence of disease progression or AE	15 (13.5)	19 (16.8)
Insufficient information to assess response	9 (8.1)	2 (1.8)
Confirmed Overall Response Rate (ORR: CR+PR), n (%)	29 (26.1)	23 (20.4)
95% CI[c]	(18.2, 35.3)	(13.4, 29.0)
Confirmed Disease Control Rate (DCR: CR+PR+stable disease+Non-PD/Non-CR), n (%)	76 (68.5)	84 (74.3)
95% CI[c]	(59.0, 77.0)	(65.3, 82.1)

Abbreviations: BICR = blinded independent central review; BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; CR = complete response; DCR = disease control rate; ENCO = encorafenib; ORR = overall response rate; PD = progressive disease; PR = partial response; vs. = versus

[a] CR and PR were confirmed by repeat assessments performed not less than 4 weeks after criteria for response were met.

[b] Patients with only non-measurable disease, whose best non-target lesion response was Non-CR/non-PD and did not have any new lesions.

[c] The CIs for the frequency distribution of each variable were computed using Clopper-Pearson's method.

Source: Table 14.2-1.1.1; Table 14.2-1.7.4

For reasons of completeness, updated analysis of ORR (and DOR) are added here as follows:

Updated analysis: ORR* (Triplet vs Doublet)

*Per BIRC and RECIST 1.1

	Triplet (N=224)	Doublet (N=220)
Best Confirmed Overall Response, n (%)		
Complete Response	8 (3.6)	7 (3.2)
Partial Response	52 (23.2)	36 (16.4)
Stable Disease	98 (43.8)	117 (53.2)
Progressive Disease	24 (10.7)	21 (9.5)
Non-CR/Non-PD	10 (4.5)	7 (3.2)
Not Evaluable	32 (14.3)	32 (14.5)
Confirmed Objective Response Rate, %	**26.8%**	**19.5%**
95% CI	(21.1%, 33.1%)	(14.5%, 25.4%)
Duration of Response		
Kaplan-Meier median (95% CI), months	4.4 (3.8, 7.3)	5.6 (4.1, 8.3)
DOR ≥ 6 months, n (%)	19/60 (31.7)	16/43 (37.2)
DOR < 6 months, response ongoing, n (%)	4/60 (6.7)	4/43 (9.3)

Sensitivity Analyses of ORR by BICR, Triplet Arm vs. Doublet Arm

To assess the robustness of the ORR Triplet arm vs. Doublet arm analysis the following sensitivity analyses were performed:

- ORR un-stratified test in Phase 3 Response Efficacy Set
- ORR stratified test in FAS
- ORR un-stratified test in FAS
- ORR stratified test, for patients in Phase 3 Response Efficacy Set with measurable disease at Baseline

These sensitivity analyses yielded ORR values similar to what was found in the primary analysis. The largest differences in ORR between the Triplet and Doublet arms were observed in the FAS (stratified and un-stratified) (Table 40).

Table 40: ORR by BICR Sensitivity Analyses, Triplet Arm vs. Doublet Arm (Randomized Phase 3)

	ORR (95% CI)	P value	Source
ORR analysis (Phase 3 Response Efficacy Set), Stratified			Table 14.2-1.1.1
Triplet arm	**26.1% (18.2, 35.3)**	**0.1928**	
Doublet arm	**20.4% (13.4, 29.0)**		
ORR, Unstratified (Phase 3 Response Efficacy Set)			Table 14.2-1.1.1
Triplet arm	26.1% (18.2, 35.3)	0.1531	
Doublet arm	20.4% (13.4, 29.0)		
ORR, Stratified (FAS)			Table 14.2-1.2.1
Triplet arm	22.3% (17.0, 28.3)	0.0513	
Doublet arm	16.4% (11.7, 21.9)		
ORR, Unstratified (FAS)			Table 14.2-1.2.1
Triplet arm	22.3% (17.0, 28.3)	0.0561	
Doublet arm	16.4% (11.7, 21.9)		
ORR (Phase 3 Response Efficacy Set with measurable disease at Baseline)			Table 14.2-1.4
Triplet arm	28.3% (19.7, 38.2)	0.1608	
Doublet arm	21.0% (13.6, 30.0)		

Abbreviations: BICR = blinded independent central review; CI = confidence interval; FAS = Full Analysis Set; ORR = overall response rate; vs. = versus
Source: Table 14.2-1.1.1; Table 14.2-1.2.1; Table 14.2-1.4

Supportive Analysis: Multivariate Logistic Regression of ORR by BICR, Triplet Arm vs. Doublet Arm

The effect of Baseline characteristics and potential prognostic factors on ORR by BICR in the Phase III Response Efficacy Set was investigated using a multivariate logistic regression model stratified by the study stratification factors (ECOG PS, prior irinotecan use and cetuximab source). The objective of this analysis was to explore the consistency of treatment effect on ORR by BICR after adjusting for main prognostic factors.

To provide a comparison to this stratified multivariate logistic regression model, a separate stratified univariate model looking only at treatment group (Triplet arm vs. Doublet arm) was also assessed. The stratified univariate model showed that patients in the Triplet arm had a 1.32-fold increased odds (95% CI: 0.70, 2.50) of responding compared to patients in the Doublet arm.

The stratified multivariate logistic regression model demonstrated that, after adjusting for pre-specified Baseline covariates, the outcome of the Triplet arm vs. Doublet arm comparison was consistent with the stratified univariate model (odds ratio 1.53 [95% CI: 0.76, 3.08; 2-sided p value = 0.2308]).

Patients with a Baseline CRP ≤ ULN had increased odds of responding compared to patients with a Baseline CRP > ULN (odds ratio 2.49 [95% CI: 1.11, 5.57; 2-sided p value = 0.0262]).

Subgroup Analyses of ORR by BICR, Triplet Arm vs. Doublet Arm

Subgroup analyses were performed for each Baseline stratification factor and other relevant Baseline variables.

Of the 29 subgroup analyses with at least 5 responders in each subgroup, 23 point estimates for confirmed ORR favored the Triplet arm and 4 point estimates for confirmed ORR favored the Doublet arm.

The greatest differences in **favor** of the **Triplet** arm (≥ 10% higher ORR than in the Doublet arm) were observed in the following subgroups:

- Baseline ECOG PS of 1,
- patients who had progressed after 1 prior regimen for metastatic disease,
- patients aged ≥ 65 years,
- patients with ≥ 3 organs involved at Baseline,
- Baseline CEA ≤ ULN,and
- no liver metastases at Baseline.

The subgroups with differences in **favor** of the **Doublet** arm (all ≤ 5% higher than the estimates in the Triplet arm) were

- ECOG PS of 0,
- patients who had progressed after ≥ 2 prior regimens for metastatic disease,
- patients with ≤ 2 organs involved at Baseline, and
- patients with liver metastases at Baseline.

Of the 29 subgroup analyses with at least 5 responders in each subgroup,

2 point estimates for confirmed ORR differed by < 1%: patients aged < 65 years and patients

with left-sided tumors.

Comparisons of ORR in 5 clinically relevant subgroups are provided here for the Triplet and Doublet arms. In patients who had progressed after 1 prior regimen for metastatic disease, the ORR was 34.3% (23 of 67 patients, 95% CI: 23.2, 46.9) in the Triplet arm and 22.4% (17 of 76 patients, 95% CI: 13.6, 33.4) in the Doublet arm. In patients who had progressed after ≥ 2 prior regimens for metastatic disease, the ORR was 13.6% (6 of 44 patients, 95% CI: 5.2, 27.4) in the Triplet arm and 16.2% (6 of 37 patients, 95% CI: 6.2, 32.0) in the Doublet arm. In patients with ≤ 2 organs involved at Baseline, the ORR was 24.1% (14 of 58 patients, 95% CI:13.9, 37.2) in the Triplet arm and 29.3% (17 of 58 patients, 95% CI: 18.1, 42.7) in the Doublet arm. In patients with ≥ 3 organs involved at Baseline, the ORR was 28.3% (15 of 53 patients, 95% CI: 16.8, 42.3) in the Triplet arm and 10.9% (6 of 55 patients, 95% CI: 4.1, 22.2) in the Doublet arm.

In patients with a Baseline CEA ≤ ULN, the ORR was 38.1% (8 of 21 patients, 95% CI: 18.1,61.6) in the Triplet arm and 26.5% (9 of 34 patients, 95% CI: 12.9, 44.4) in the Doublet arm. In patients with a Baseline CEA > ULN, the ORR was 23.3% (21 of 90 patients, 95% CI: 15.1, 33.4) in the Triplet arm and 17.7% (14 of 79 patients, 95% CI: 10.0, 27.9) in the Doublet arm. In patients with a Baseline CRP ≤ ULN, the ORR was 33.3% (19 of 57 patients, 95% CI: 21.4, 47.1) in the Triplet arm and 27.7% (18 of 65 patients, 95% CI: 17.3, 40.2) in the Doublet arm. In patients with a Baseline CRP > ULN, the ORR was

18.4% (9 of 49 patients, 95% CI: 8.8, 32.0) in the Triplet arm and 10.9% (5 of 46 patients, 95% CI: 3.6, 23.6) in the Doublet arm.

In patients with no liver metastases at Baseline, the ORR was 41.5% (17 of 41 patients, 95% CI: 26.3, 57.9) in the Triplet arm and 20.0% (8 of 40 patients, 95% CI: 9.1, 35.6) in the Doublet arm. In patients with liver metastases at Baseline, the ORR was 17.1% (12 of 70 patients, 95% CI: 9.2, 28.0) in the Triplet arm and 20.5% (15 of 73 patients, 95% CI: 12.0, 31.6) in the Doublet arm.

DOR, Triplet Arm vs. Doublet Arm

Kaplan-Meier estimates of median DOR by BICR in the Phase 3 Response Efficacy Set, calculated for confirmed responses, were 4.80 months in the Triplet arm (95% CI: 2.96, 9.69) and 6.06 months in the Doublet arm (95% CI: 4.07, 8.28). In the Triplet arm, individual DORs ranged from 1.41 months to 15.01 months. In the Doublet arm, individual DORs ranged from 1.54 months to 15.31 months.

TTR, Triplet Arm vs. Doublet Arm

Kaplan-Meier estimates of median TTR by BICR in the Phase III Response Efficacy Set, calculated for patients with confirmed responses, was 1.48 months in the Triplet arm (95% CI: 1.41, 2.00) and 1.54 months in the Doublet arm (95% CI: 1.41, 1.64) (Table 14.2-5.1.1). For patients in the Triplet arm with confirmed CRs, the TTRs were 1.41, 1.58, 16.56 and 1.41 months. In the Doublet arm, patients with confirmed CRs had TTRs of 1.31, 1.58, 1.71, 1.48, 1.48 and 4.17 months.

The time to most responses by BICR in the Phase 3 Response Efficacy Set corresponded with the first post-Baseline response assessment at 6 weeks (± 7 days) after randomization.

PFS, Triplet Arm vs. Doublet Arm

Table 41: Kaplan-Meier Summary of PFS by BICR, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Full Analysis Set)

	ENCO + BINI + CETUX (N = 224)	ENCO + CETUX (N = 220)
Patients with events/Patients included in analysis (%)	118/224 (52.7)	133/220 (60.5)
Death	15/224 (6.7)	23/220 (10.5)
Disease Progression	103/224 (46.0)	110/220 (50.0)
Percentiles (95% CI), months		
25th	2.79 (2.50, 3.29)	2.73 (2.53, 2.83)
Median (50th)	4.30 (4.14, 5.19)	4.21 (3.71, 5.36)
75th	8.18 (5.82, 11.04)	8.08 (6.01, 8.34)
Stratified hazard ratio (95% CI)[a,b]	0.84 (0.65, 1.09)	
Stratified log-rank (one-sided) p value[a,b]	0.1004	
Patients event-free probability estimates, % (95% CI)[c]		
2 months	84.7 (78.6, 89.2)	83.8 (77.7, 88.4)
4 months	62.9 (54.9, 69.8)	57.6 (49.6, 64.8)
6 months	31.3 (23.5, 39.4)	32.8 (25.0, 40.8)
8 months	26.0 (18.5, 34.1)	25.5 (18.3, 33.4)
10 months	20.0 (12.7, 28.5)	11.9 (6.7, 18.7)
12 months	12.7 (6.3, 21.4)	4.5 (1.5, 9.9)
14 months	7.6 (2.5, 16.7)	2.2 (0.4, 6.9)

Abbreviations: BICR = blinded independent central review; BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ENCO = encorafenib; PFS = progression-free survival; vs. = versus

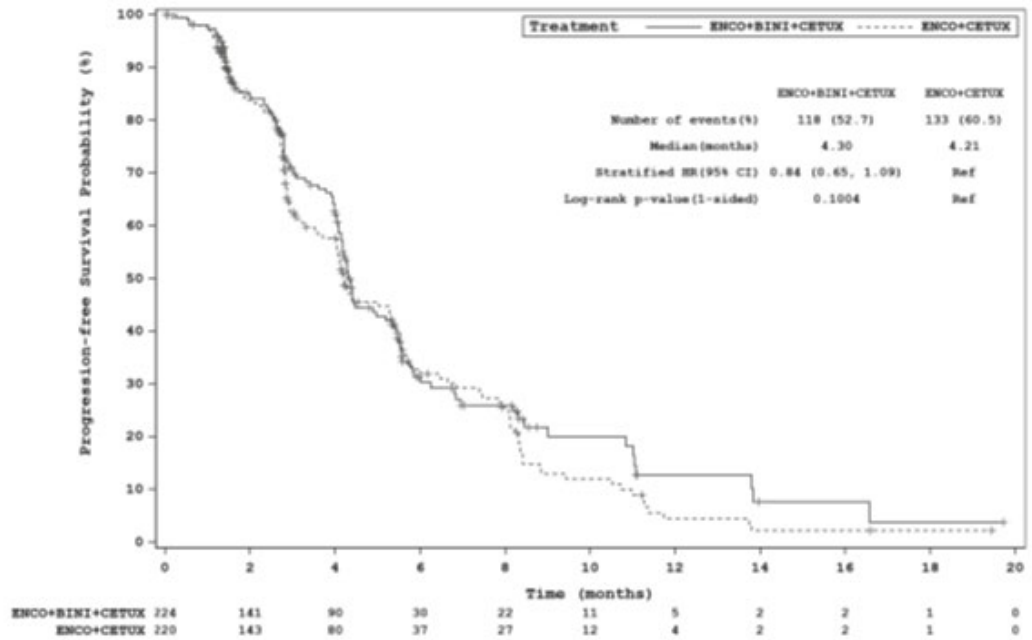
[a] Reference group for comparisons is 'ENCO+CETUX'.

[b] Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomization.

[c] Probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates were obtained from Kaplan-Meier survival estimates. Greenwood formula was used for CIs of Kaplan-Meier estimates.

Source: Table 14.2-3.1.1

Figure 17: Kaplan-Meier Plot of PFS by BICR, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Full Analysis Set)

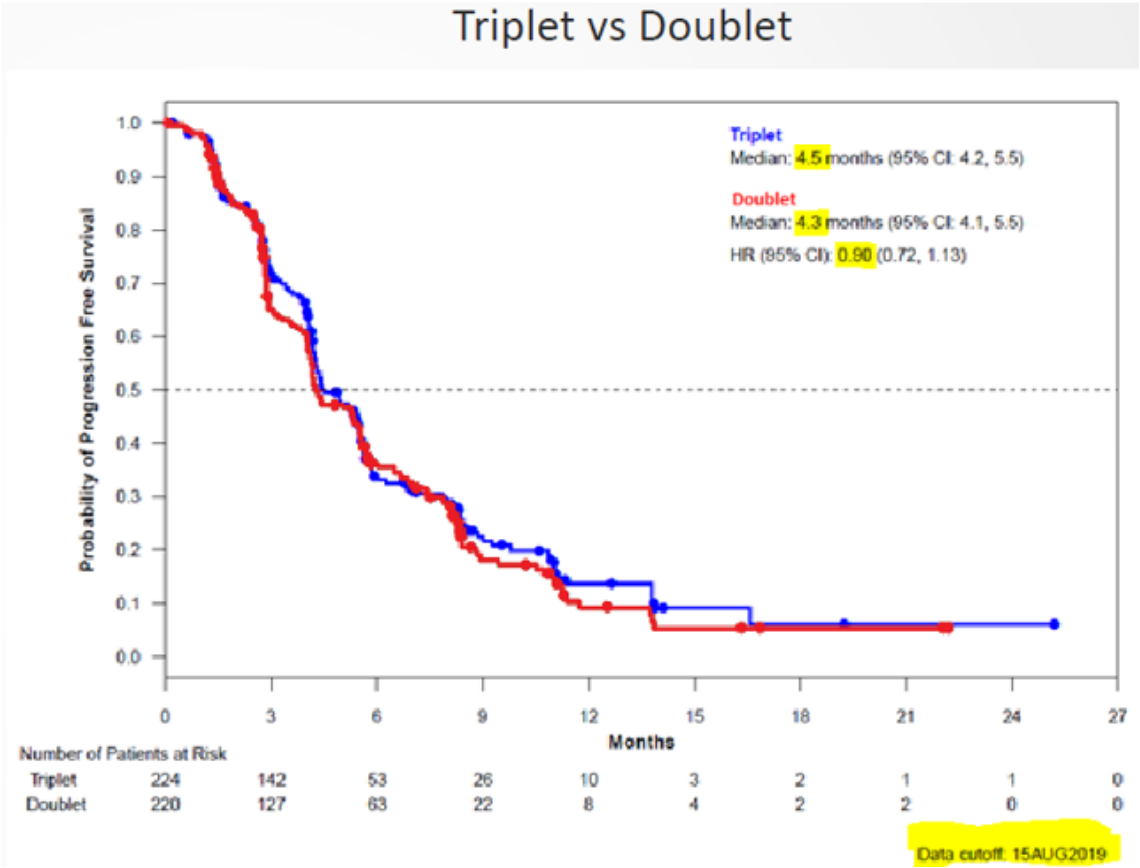


Abbreviations: BICR = blinded independent central review; BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; HR = hazard ratio; PFS = progression-free survival; Ref = reference; vs. = versus

+ indicates censoring.

Source: Figure 14.2-3.3.1

Updated PFS analysis as of January 20, 2020 (cut-off 15 August 2019)



Comparison of PFS by BICR and Investigator Review, Triplet Arm vs. Doublet Arm

Investigator and BICR assessments of PFS events (death or progression) in the FAS were reviewed.

"Type" discordance (i.e., disagreement that patient had an event or did not have an event) was observed in 39 patients (17.4%) in the Triplet arm and 28 patients (12.7%) in the Doublet arm.

"Timing" discordance (i.e., agreed that the patient had an event but disagreed on the timing) was observed in 29 patients (12.9%) in the Triplet arm and 32 patients (14.5%) in the Doublet arm. The most common type of timing discordance in both treatment arms was that PFS events were identified by BICR prior to their identification by Investigator assessment.

Sensitivity Analyses of PFS, Triplet Arm vs. Doublet Arm

To assess the robustness of the PFS analysis, the following sensitivity analyses of PFS by BICR were performed:

- PFS (PPS)
- The distribution of PFS in FAS was compared between the treatment arms using unstratified analyses.
- The analyses for PFS were repeated to assess time evaluation bias, whereby event and censoring dates that did not occur within the protocol-specified schedule window were moved to either the previous or the next scheduled assessment, as outlined in the SAP.

- "Actual event" analysis for PFS with a censoring rule that included a PFS event even if the event was recorded after 2 or more missing tumor assessments.
- "Backdating" analysis for PFS with a censoring rule that backdated events occurring after 1 or more missing tumor assessments (Appendix 16.1.9, SAP Table 7-1 lines C1 and C2).
- "Further anticancer therapy" analysis for PFS including tumor assessments after initiation of subsequent anticancer therapy.
- The analyses for PFS were repeated to assess early censoring (i.e., censoring > 2 months prior to the data cutoff date) and the impact of any imbalances in censoring distribution.

Results of these sensitivity analyses for PFS by BICR are consistent with the primary PFS analysis of Triplet arm vs. Doublet arm, yielding similar HRs (0.81 to 0.87), median PFS values and p values. Sensitivity analyses for PFS by BICR in patients with early censoring also yielded HRs (0.85 to 0.92) and p values similar to those in the primary analysis.

Supportive Analysis: Multivariate Cox Regression of PFS, Triplet Arm vs. Doublet Arm

The effect of Baseline covariates and potential prognostic factors on PFS by BICR in the FAS was investigated using a multivariate Cox regression model stratified by the study stratification factors (ECOG PS, prior irinotecan use and cetuximab source). The objective of this analysis was to explore the consistency of treatment effect on PFS after adjusting for these Baseline covariates.

This multivariate Cox regression model demonstrated that, after adjusting for pre-specified Baseline covariates, the outcome of the comparison of Triplet arm vs. Doublet arm was consistent with the primary PFS analysis, with a 16% reduction in the risk of disease progression or death in the Triplet arm (HR 0.84, 95% CI: 0.64, 1.10; 2-sided p value = 0.2106).

Right-handed tumor sidedness was associated with a 1.35-fold increase in the risk of disease progression or death vs. left-handed tumor sidedness. The presence of liver metastases at Baseline was associated with a 2.22-fold increase in the risk of disease progression or death. Also, Baseline CRP > ULN was associated with a 1.96-fold increase in the risk of disease progression or death.

Subgroup Analyses of PFS, Triplet Arm vs. Doublet Arm

Subgroup analyses were performed for each Baseline stratification factor and other relevant Baseline variables. Only analyses for which at least 10 events were available in each subgroup are discussed here.

Twenty-seven of the 34 subgroup analyses with at least 10 events in both subgroups demonstrated PFS HRs that favored the Triplet arm. Seven of the 34 subgroup analyses with at least 10 events in each subgroup did not demonstrate PFS HRs in favor of the Triplet arm. The greatest difference in favor of the Triplet arm was observed in the subgroup of patients with left-sided tumors (HR 0.64, 95% CI: 0.42, 0.99).

Subgroups that did not favor the Triplet arm were: ECOG PS at Baseline of 0, no prior irinotecan, non-Caucasian race, Asian race, normal tumor MSI status, patients with completely resected tumors, and patients with liver metastases at Baseline. However, the CIs for all HRs ≥ 1.0 also included lower bounds < 1.0.

Progression After Next Line of Therapy (PFS2) and Time to Second

Subsequent Therapy (PFS2 and TSST), Triplet Arm vs. Doublet Arm

Median PFS2 estimates using Kaplan-Meier methodology were **8.38** months (95% CI: 7.75, 10.45) in the Triplet arm and **8.08** months (95% CI: 7.06, 9.30) in the Doublet arm (HR 0.81, 95% CI: 0.60, 1.09; stratified log-rank test p = 0.0814). Thus, an estimated 19% reduction in risk of disease progression or

death (increase in PFS2) was observed for the Triplet arm compared to the Doublet arm. There were 90 PFS2 events (40.2% of patients) in the Triplet arm and 94 events (42.7% of patients) in the Doublet arm.

The TSSTs in the Triplet and Doublet arms were similar, with median TSST estimates using Kaplan-Meier methodology of **8.31** months (95% CI: 7.56, 10.35) and **8.41** months (95% CI: (7.62, 9.79), respectively.

Randomized Phase 3: Patient-reported Outcomes

The EORTC QLQ-C30, FACT-C, EQ-5D-5L and PGIC were used to assess QoL.

For EORTC QLQ-C30, the global health status/QoL score was identified as the primary PRO variable of interest; physical functioning, emotional functioning and social functioning scores were considered as secondary.

For FACT-C, the functional well-being score was the primary PRO variable of interest; the physical well-being, social/family well-being and emotional well-being scores were considered as secondary.

The EQ-5D-5L contains 1 item for each of 5 dimensions of health-related QoL (i.e., mobility, self-care, usual activities, pain or discomfort and anxiety or depression). Response options for each item varied from having no problems to moderate problems or extreme problems.

Triplet Arm vs. Control

EORTC QLQ-C30

Compliance with the EORTC QLQ-C30 assessment was slightly higher in the Triplet arm (88% to 94%) than in the Control arm (85% to 90%) from Baseline through Cycle 4 (Table 43).

Table 43: EORTC QLQ-C30 Compliance Summary by Time Window and Treatment, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

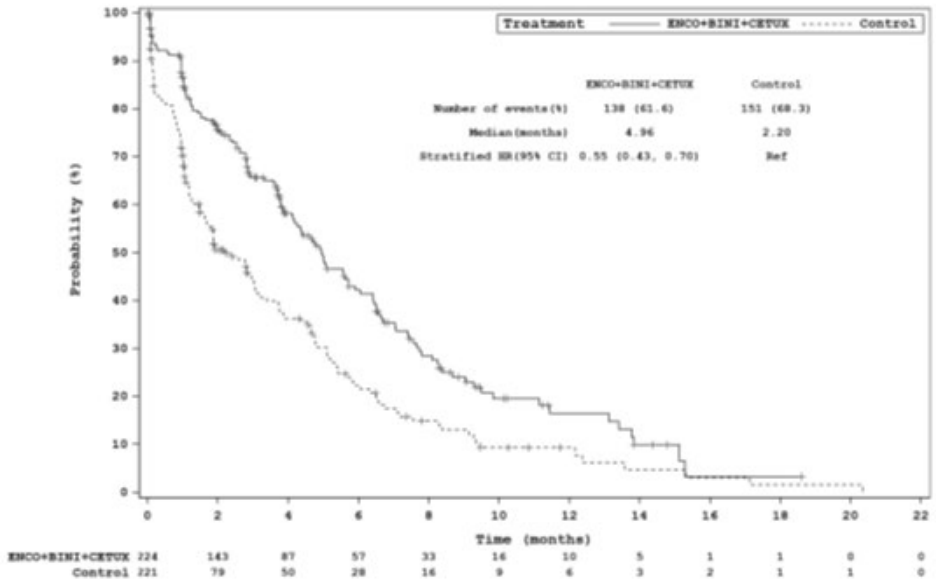
	ENCO+BINI+CETUX (N = 224)		Control (N = 221)	
Visit	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]
Baseline	224	210 (93.8)	221	200 (90.5)
CYCLE 2 DAY 1	205	193 (94.1)	154	134 (87.0)
CYCLE 4 DAY 1	142	125 (88.0)	46	39 (84.8)
CYCLE 6 DAY 1	80	71 (88.8)	18	15 (83.3)
CYCLE 8 DAY 1	49	42 (85.7)	11	8 (72.7)
CYCLE 10 DAY 1	26	24 (92.3)	6	4 (66.7)
CYCLE 12 DAY 1	14	14 (100.0)	3	2 (66.7)
CYCLE 14 DAY 1	7	7 (100.0)	1	0
CYCLE 16 DAY 1	6	5 (83.3)	0	0
CYCLE 18 DAY 1	4	1 (25.0)	0	0
CYCLE 20 DAY 1	2	1 (50.0)	0	0
CYCLE 22 DAY 1	1	0	0	0
END OF TREATMENT	146	81 (55.5)	184	87 (47.3)
30 DAY FOLLOW UP		24		22

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer's core quality of life questionnaire

[a] Includes instruments fully or partially completed.

Source: Table 14.2-8.1

Figure 18: Kaplan-Meier Plot of Time to Definitive 10% Deterioration in EORTC QLQ-C30 Global Health Status, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer's core quality of life questionnaire; HR = hazard ratio; Ref = reference
Note: Definitive 10% deterioration is defined as at least 10% relative to Baseline worsening of the corresponding scale score with no later improvement above this threshold observed while on treatment or death due to any cause.
Source: Figure 14.2-6.1

FACT-C

Compliance with the FACT-C assessment was slightly higher in the Triplet arm (88% to 94%) than in the Control arm (85% to 91%) from Baseline through Cycle 4 (Table 44).

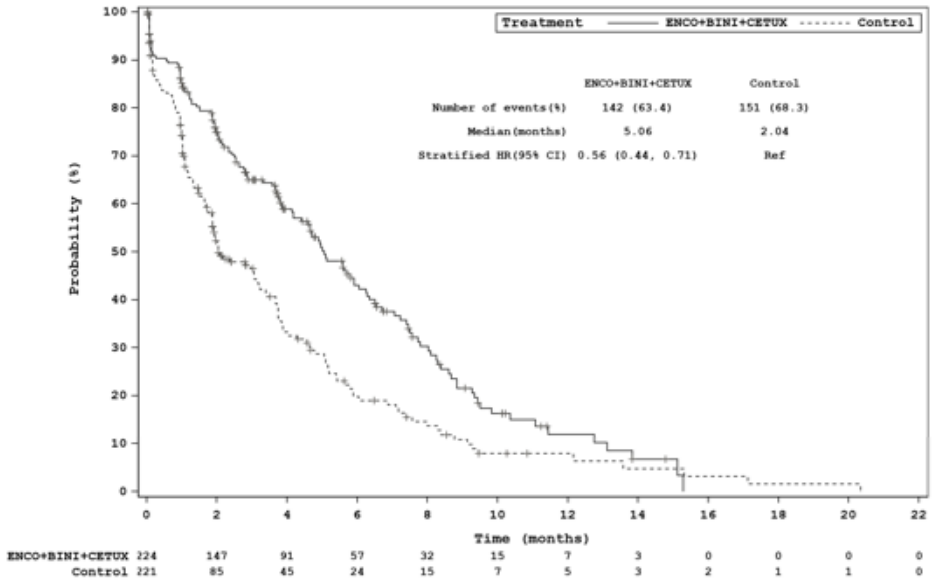
Median FACT-C functional well-being scores at Baseline were similar in the Triplet and Control arms (Triplet = 16 and Control = 17). Through Cycle 4, median scores remained at or near Baseline levels in both treatment arms. At Cycle 4, the median functional well-being score was slightly higher in the Triplet arm than the Control arm.

Table 44: FACT-C Compliance Summary by Time Window and Treatment, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

	ENCO+BINI+CETUX (N = 224)		Control (N = 221)	
Visit	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]
Baseline	224	211 (94.2)	221	200 (90.5)
CYCLE 2 DAY 1	205	192 (93.7)	154	134 (87.0)
CYCLE 4 DAY 1	142	125 (88.0)	46	39 (84.8)
CYCLE 6 DAY 1	80	71 (88.8)	18	15 (83.3)
CYCLE 8 DAY 1	49	43 (87.8)	11	9 (81.8)
CYCLE 10 DAY 1	26	24 (92.3)	6	4 (66.7)
CYCLE 12 DAY 1	14	14 (100.0)	3	2 (66.7)
CYCLE 14 DAY 1	7	7 (100.0)	1	0
CYCLE 16 DAY 1	6	5 (83.3)	0	0
CYCLE 18 DAY 1	4	1 (25.0)	0	0
CYCLE 20 DAY 1	2	1 (50.0)	0	0
CYCLE 22 DAY 1	1	0	0	0
END OF TREATMENT	146	81 (55.5)	184	88 (47.8)
30 DAY FOLLOW UP		24		22

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib; FACT-C = Functional Assessment of Cancer Therapy – Colorectal Cancer
[a] Includes instruments fully or partially completed.
Source: Table 14.2-8.1

Figure 19: Kaplan-Meier Plot of Time to Definitive 10% Deterioration in FACT-C Functional Well-being Subscale, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; FACT-C = Functional Assessment of Cancer Therapy – Colon Cancer; HR = hazard ratio; Ref = reference
Note: Definitive 10% deterioration is defined as at least 10% relative to Baseline worsening of the corresponding scale score with no later improvement above this threshold observed while on treatment or death due to any cause.
Source: Figure 14.2-6.5

EQ-5D-5L

Compliance with the EQ-5D-5L assessment was slightly higher in the Triplet arm (87% to 94%) than in the Control arm (85% to 90%) from Baseline through Cycle 4 (Table 45).

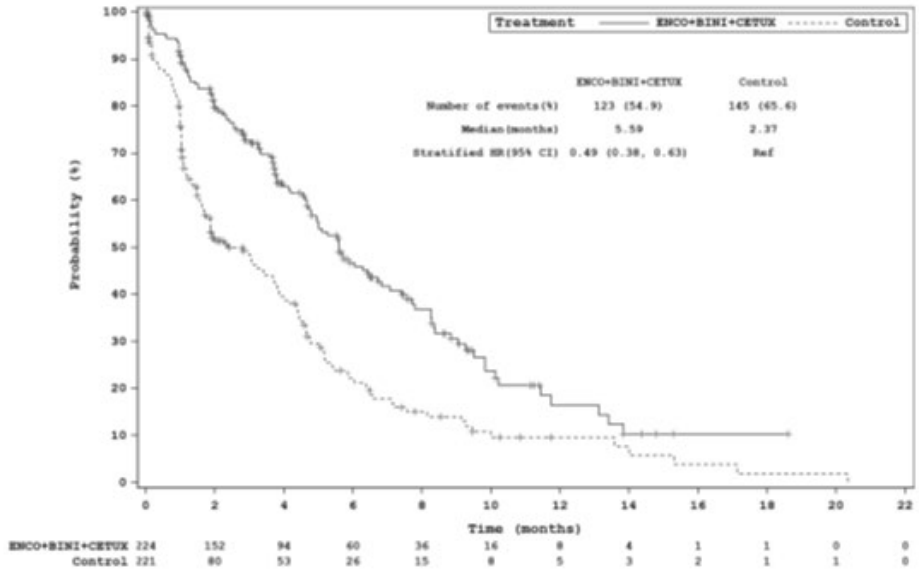
Median EQ-5D-5L VASs at Baseline were identical in the Triplet and Control arms (70 in both). Through Cycle 4, these median scores increased with small fluctuations in both treatment arms. At Cycle 4, median VASs were identical in the 2 treatment arms.

Table 45: EQ-5D-5L Compliance Summary by Time Window and Treatment, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

	ENCO+BINI+CETUX (N = 224)		Control (N = 221)	
Visit	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]
Baseline	224	211 (94.2)	221	199 (90.0)
CYCLE 2 DAY 1	205	191 (93.2)	154	135 (87.7)
CYCLE 4 DAY 1	142	124 (87.3)	46	39 (84.8)
CYCLE 6 DAY 1	80	70 (87.5)	18	15 (83.3)
CYCLE 8 DAY 1	49	43 (87.8)	11	8 (72.7)
CYCLE 10 DAY 1	26	24 (92.3)	6	4 (66.7)
CYCLE 12 DAY 1	14	13 (92.9)	3	2 (66.7)
CYCLE 14 DAY 1	7	7 (100.0)	1	0
CYCLE 16 DAY 1	6	5 (83.3)	0	0
CYCLE 18 DAY 1	4	1 (25.0)	0	0
CYCLE 20 DAY 1	2	1 (50.0)	0	0
CYCLE 22 DAY 1	1	0	0	0
END OF TREATMENT	146	82 (56.2)	184	88 (47.8)
30 DAY FOLLOW UP		24		22

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib; EQ-5D-5L = EuroQoL-5 Dimension-5 Level examination
[a] Includes instruments fully or partially completed.
Source: Table 14.2-8.1

Figure 20: Kaplan-Meier Plot of Time to Definitive 10% Deterioration in EQ-5D-5L VAS, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; EQ-5D-5L = EuroQoL-5 Dimension-5 Level examination; HR = hazard ratio; Ref = reference; VAS = visual analog score
Note: Definitive 10% deterioration is defined as at least 10% relative to Baseline worsening of the corresponding scale score with no later improvement above this threshold observed while on treatment or death due to any cause.
Source: Figure 14.2-6.10

PGIC

Compliance with the PGIC assessment was slightly higher in the Triplet arm (68% to 87%) than in the Control arm (67% to 83%) from Baseline through Cycle 4 (Table 46).

Table 46: PGIC Compliance Summary by Time Window and Treatment, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

	ENCO+BINI+CETUX (N = 224)		Control (N = 221)	
Visit	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]
Baseline	224	153 (68.3)	221	149 (67.4)
CYCLE 2 DAY 1	205	178 (86.8)	154	118 (76.6)
CYCLE 4 DAY 1	142	120 (84.5)	46	38 (82.6)
CYCLE 6 DAY 1	80	68 (85.0)	18	12 (66.7)
CYCLE 8 DAY 1	49	42 (85.7)	11	7 (63.6)
CYCLE 10 DAY 1	26	24 (92.3)	6	4 (66.7)
CYCLE 12 DAY 1	14	14 (100.0)	3	2 (66.7)
CYCLE 14 DAY 1	7	7 (100.0)	1	0
CYCLE 16 DAY 1	6	4 (66.7)	0	0
CYCLE 18 DAY 1	4	1 (25.0)	0	0
CYCLE 20 DAY 1	2	1 (50.0)	0	0
CYCLE 22 DAY 1	1	0	0	0
END OF TREATMENT	146	72 (49.3)	184	79 (42.9)
30 DAY FOLLOW UP		21		21

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib
[a] Includes instruments fully or partially completed.
Source: Table 14.2-8.1

Table 47: Patient Global Impression of Change Summary by Time Window and Treatment, Triplet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

		Randomized Portion	
Visit	Response to PGIC Questionnaire	ENCO+ BINI+ CETUX (N=224)	Control (N=221)
CYCLE 2 DAY 1	Very Much Improved	18/205 (8.8)	8/154 (5.2)
	Much Improved	40/205 (19.5)	15/154 (9.7)
	Minimally Improved	50/205 (24.4)	33/154 (21.4)
	No change	55/205 (26.8)	46/154 (29.9)
	Minimally Worse	13/205 (6.3)	10/154 (6.5)
	Much Worse	2/205 (1.0)	5/154 (3.2)
	Very Much Worse	0/205	1/154 (0.6)
CYCLE 4 DAY 1	Very Much Improved	15/142 (10.6)	2/46 (4.3)
	Much Improved	42/142 (29.6)	11/46 (23.9)
	Minimally Improved	33/142 (23.2)	13/46 (28.3)
	No change	21/142 (14.8)	8/46 (17.4)
	Minimally Worse	7/142 (4.9)	3/46 (6.5)
	Much Worse	2/142 (1.4)	1/46 (2.2)
	Very Much Worse	0/142	0/46

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib
Source: Table 14.2-8.10

Doublet Arm vs. Control Arm

EORTC QLQ-C30

Compliance with the EORTC QLQ-C30 assessment was slightly higher in the Doublet arm (88% to 96%) than in the Control arm (85% to 91%) from Baseline through Cycle 4 (Table 48).

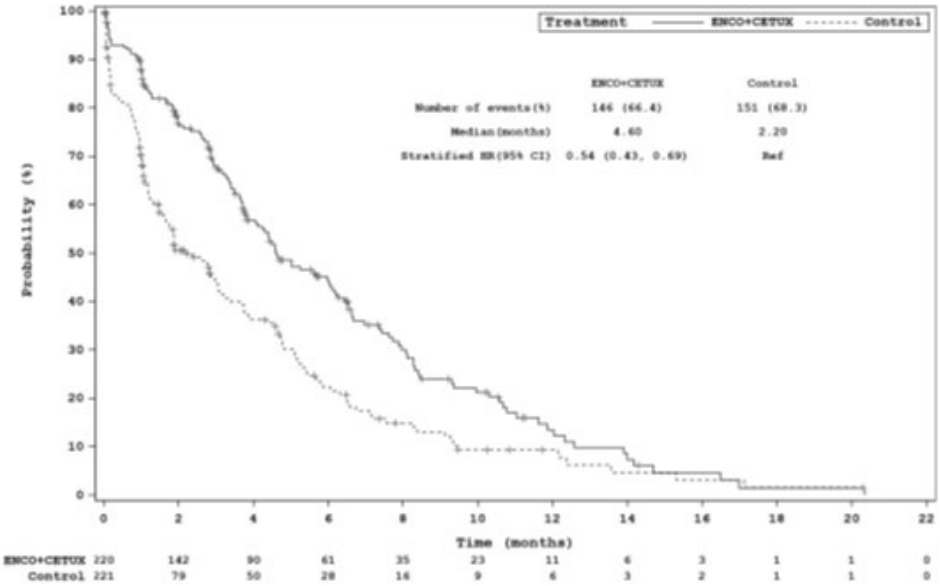
Median EORTC QLQ-C30 global health status scores at Baseline were identical in the Doublet and Control arms (67 in both). Through Cycle 4, median scores remained at or near Baseline levels in both treatment arms. At Cycle 4, median global health status scores were identical in the 2 treatment arms.

Table 48: EORTC QLQ-C30 Compliance Summary by Time Window and Treatment, Doublet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

	ENCO+ CETUX (N=220)		Control (N = 221)	
Visit	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]
Baseline	220	202 (91.8)	221	200 (90.5)
CYCLE 2 DAY 1	203	195 (96.1)	154	134 (87.0)
CYCLE 4 DAY 1	132	116 (87.9)	46	39 (84.8)
CYCLE 6 DAY 1	68	64 (94.1)	18	15 (83.3)
CYCLE 8 DAY 1	45	42 (93.3)	11	8 (72.7)
CYCLE 10 DAY 1	28	24 (85.7)	6	4 (66.7)
CYCLE 12 DAY 1	19	18 (94.7)	3	2 (66.7)
CYCLE 14 DAY 1	8	7 (87.5)	1	0
CYCLE 16 DAY 1	5	3 (60.0)	0	0
CYCLE 18 DAY 1	3	3 (100.0)	0	0
CYCLE 20 DAY 1	3	1 (33.3)	0	0
CYCLE 22 DAY 1	1	1 (100.0)	0	0
END OF TREATMENT	142	81 (57.0)	184	87 (47.3)
30 DAY FOLLOW UP		19		22

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer's core quality of life questionnaire
[a] Includes instruments fully or partially completed.
Source: Table 14.2-8.1

Figure 21: Kaplan-Meier Plot of Time to Definitive 10% Deterioration in EORTC QLQ-C30 Global Health Status, Doublet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer's core quality of life questionnaire; HR = hazard ratio; Ref = reference
Note: Definitive 10% deterioration is defined as at least 10% relative to Baseline worsening of the corresponding scale score with no later improvement above this threshold observed while on treatment or death due to any cause.
Source: Figure 14.2-6.1

FACT-C

As was observed with the EORTC QLQ-C30 assessment, compliance with the FACT-C assessment was slightly higher in the Doublet arm (87% to 97%) than in the Control arm (85% to 91%) from Baseline through Cycle 4 (Table 49).

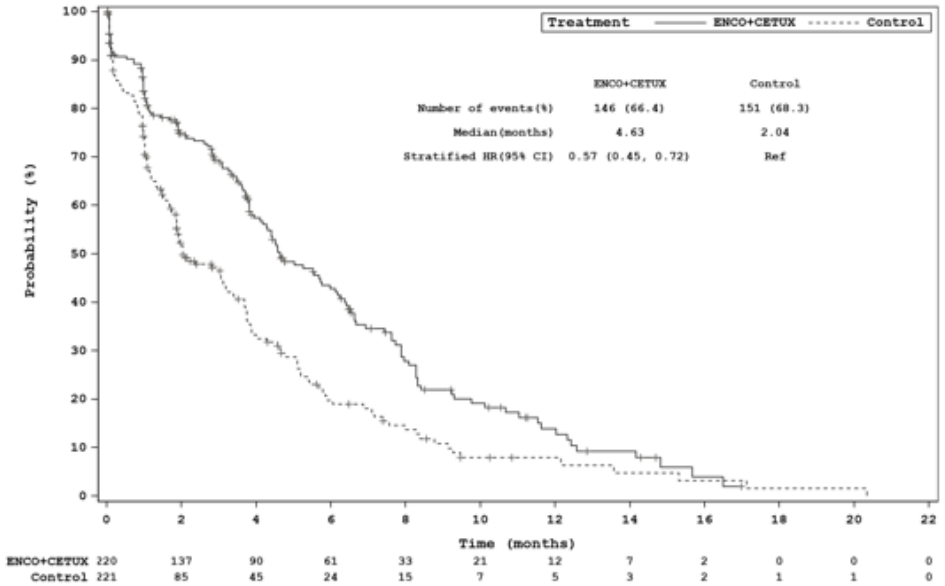
Median FACT-C functional well-being scores at Baseline were similar in the Doublet and Control arms (Doublet = 16 and Control = 17; Table 14.2-8.6). Through Cycle 4, the median score remained at or near Baseline levels in the Doublet arm and decreased with small fluctuations in in the Control arm. At Cycle 4, the median functional well-being score was higher in the Doublet arm than the Control arm.

Table 49: FACT-C Compliance Summary by Time Window and Treatment, Doublet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

	ENCO+ CETUX (N=220)		Control (N = 221)	
Visit	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]
Baseline	220	202 (91.8)	221	200 (90.5)
CYCLE 2 DAY 1	203	196 (96.6)	154	134 (87.0)
CYCLE 4 DAY 1	132	115 (87.1)	46	39 (84.8)
CYCLE 6 DAY 1	68	63 (92.6)	18	15 (83.3)
CYCLE 8 DAY 1	45	41 (91.1)	11	9 (81.8)
CYCLE 10 DAY 1	28	24 (85.7)	6	4 (66.7)
CYCLE 12 DAY 1	19	18 (94.7)	3	2 (66.7)
CYCLE 14 DAY 1	8	7 (87.5)	1	0
CYCLE 16 DAY 1	5	3 (60.0)	0	0
CYCLE 18 DAY 1	3	3 (100.0)	0	0
CYCLE 20 DAY 1	3	1 (33.3)	0	0
CYCLE 22 DAY 1	1	1 (100.0)	0	0
END OF TREATMENT	142	81 (57.0)	184	88 (47.8)
30 DAY FOLLOW UP		19		22

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib; FACT-C = Functional Assessment of Cancer Therapy – Colorectal Cancer
[a] Includes instruments fully or partially completed.
Source: Table 14.2-8.1

Figure 22: Kaplan-Meier Plot of Time to Definitive 10% Deterioration in FACT-C Functional Well-being Subscale, Doublet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; FACT-C = Functional Assessment of Cancer Therapy – Colon Cancer; HR = hazard ratio; Ref = reference
Note: Definitive 10% deterioration is defined as at least 10% relative to Baseline worsening of the corresponding scale score with no later improvement above this threshold observed while on treatment or death due to any cause.
Source: Figure 14.2-6.5

EQ-5D-5L

Compliance with the EQ-5D-5L assessment was slightly higher in the Doublet arm (86% to 95%) than in the Control arm (85% to 90%) from Baseline through Cycle 4 (Table 50).

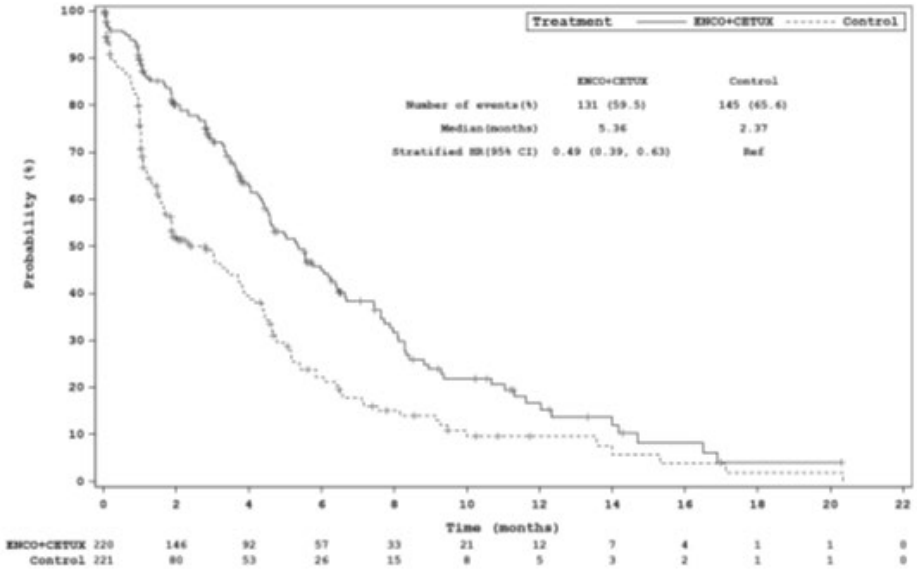
Median EQ-5D-5L VASs at Baseline were identical in the Doublet and Control arms (70 in both). Through Cycle 4, these median scores increased in both treatment arms. At Cycle 4, the median VAS was higher in the Doublet arm than the Control arm.

Table 50: EQ-5D-5L Compliance Summary by Time Window and Treatment, Doublet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

	ENCO+ CETUX (N=220)		Control (N = 221)	
Visit	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]
Baseline	220	204 (92.7)	221	199 (90.0)
CYCLE 2 DAY 1	203	193 (95.1)	154	135 (87.7)
CYCLE 4 DAY 1	132	114 (86.4)	46	39 (84.8)
CYCLE 6 DAY 1	68	62 (91.2)	18	15 (83.3)
CYCLE 8 DAY 1	45	42 (93.3)	11	8 (72.7)
CYCLE 10 DAY 1	28	24 (85.7)	6	4 (66.7)
CYCLE 12 DAY 1	19	18 (94.7)	3	2 (66.7)
CYCLE 14 DAY 1	8	7 (87.5)	1	0
CYCLE 16 DAY 1	5	3 (60.0)	0	0
CYCLE 18 DAY 1	3	3 (100.0)	0	0
CYCLE 20 DAY 1	3	1 (33.3)	0	0
CYCLE 22 DAY 1	1	1 (100.0)	0	0
END OF TREATMENT	142	79 (55.6)	184	88 (47.8)
30 DAY FOLLOW UP		18		22

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib; EQ-5D-5L = EuroQoL-5 Dimension-5 Level examination
[a] Includes instruments fully or partially completed.
Source: Table 14.2-8.1

Figure 23: Kaplan-Meier Plot of Time to Definitive 10% Deterioration in EQ-5D-5L VAS, Doublet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; EQ-5D-5L = EuroQoL-5 Dimension-5 Level examination; HR = hazard ratio; Ref = reference; VAS = visual analog score
Note: Definitive 10% deterioration is defined as at least 10% relative to Baseline worsening of the corresponding scale score with no later improvement above this threshold observed while on treatment or death due to any cause.
Source: Figure 14.2-6.10

PGIC

Compliance with the PGIC assessment was slightly higher in the Doublet arm (69% to 89%) than in the Control arm (67% to 83%) from Baseline through Cycle 4 (Table 51).

Table 51: PGIC Compliance Summary by Time Window and Treatment, Doublet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

	ENCO+ CETUX (N=220)		Control (N = 221)	
Visit	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]
Baseline	220	152 (69.1)	221	149 (67.4)
CYCLE 2 DAY 1	203	180 (88.7)	154	118 (76.6)
CYCLE 4 DAY 1	132	111 (84.1)	46	38 (82.6)
CYCLE 6 DAY 1	68	59 (86.8)	18	12 (66.7)
CYCLE 8 DAY 1	45	40 (88.9)	11	7 (63.6)
CYCLE 10 DAY 1	28	24 (85.7)	6	4 (66.7)
CYCLE 12 DAY 1	19	18 (94.7)	3	2 (66.7)
CYCLE 14 DAY 1	8	7 (87.5)	1	0
CYCLE 16 DAY 1	5	3 (60.0)	0	0
CYCLE 18 DAY 1	3	3 (100.0)	0	0
CYCLE 20 DAY 1	3	1 (33.3)	0	0
CYCLE 22 DAY 1	1	1 (100.0)	0	0
END OF TREATMENT	142	74 (52.1)	184	79 (42.9)
30 DAY FOLLOW UP		14		21

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib
[a] Includes instruments fully or partially completed.
Source: Table 14.2-8.1

Table 52: Patient Global Impression of Change Summary by Time Window and Treatment, Doublet Arm vs. Control Arm (Randomized Phase 3, Full Analysis Set)

		Randomized Portion	
Visit		ENCO+ CETUX (N=220)	Control (N=221)
CYCLE 2 DAY 1	Very Much Improved	10/203 (4.9)	8/154 (5.2)
	Much Improved	53/203 (26.1)	15/154 (9.7)
	Minimally Improved	55/203 (27.1)	33/154 (21.4)
	No change	50/203 (24.6)	46/154 (29.9)
	Minimally Worse	12/203 (5.9)	10/154 (6.5)
	Much Worse	0/203	5/154 (3.2)
	Very Much Worse	0/203	1/154 (0.6)
CYCLE 4 DAY 1	Very Much Improved	14/132 (10.6)	2/46 (4.3)
	Much Improved	41/132 (31.1)	11/46 (23.9)
	Minimally Improved	26/132 (19.7)	13/46 (28.3)
	No change	26/132 (19.7)	8/46 (17.4)
	Minimally Worse	4/132 (3.0)	3/46 (6.5)
	Much Worse	0/132	1/46 (2.2)
	Very Much Worse	0/132	0/46

Abbreviations: CETUX = cetuximab; ENCO = encorafenib
Source: Table 14.2-8.10

Triplet Arm vs. Doublet Arm

EORTC QLQ-C30

Compliance with the EORTC QLQ-C30 assessment was similar in the Triplet arm (88% to 94%) and Doublet arm (88% to 96%) from Baseline through Cycle 6 (Table 53).

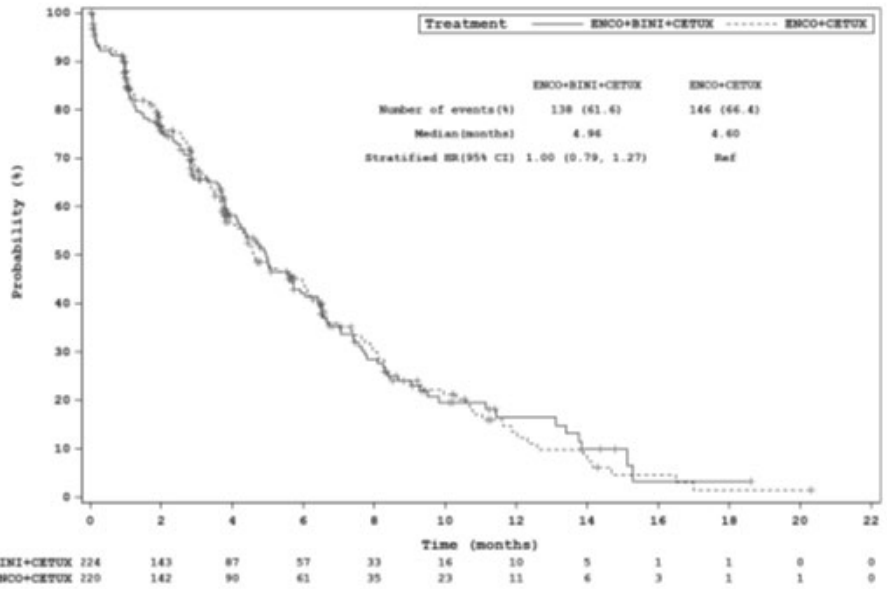
Median EORTC QLQ-C30 global health status scores at Baseline were identical in the Triplet and Doublet arms (67 in both; Table 14.2-8.4). Through Cycle 8, these scores remained unchanged from Baseline levels in the Triplet arm and increased slightly in the Doublet arm. **At Cycle 8, the median global health status score was higher in the Doublet arm than the Triplet arm**.

Table 53: EORTC QLQ-C30 Compliance Summary by Time Window and Treatment, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Full Analysis Set)

	ENCO+BINI+CETUX (N = 224)		ENCO+ CETUX (N=220)	
Visit	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]
Baseline	224	210 (93.8)	220	202 (91.8)
CYCLE 2 DAY 1	205	193 (94.1)	203	195 (96.1)
CYCLE 4 DAY 1	142	125 (88.0)	132	116 (87.9)
CYCLE 6 DAY 1	80	71 (88.8)	68	64 (94.1)
CYCLE 8 DAY 1	49	42 (85.7)	45	42 (93.3)
CYCLE 10 DAY 1	26	24 (92.3)	28	24 (85.7)
CYCLE 12 DAY 1	14	14 (100.0)	19	18 (94.7)
CYCLE 14 DAY 1	7	7 (100.0)	8	7 (87.5)
CYCLE 16 DAY 1	6	5 (83.3)	5	3 (60.0)
CYCLE 18 DAY 1	4	1 (25.0)	3	3 (100.0)
CYCLE 20 DAY 1	2	1 (50.0)	3	1 (33.3)
CYCLE 22 DAY 1	1	0	1	1 (100.0)
END OF TREATMENT	146	81 (55.5)	142	81 (57.0)
30 DAY FOLLOW UP		24		19

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer's core quality of life questionnaire
[a] Includes instruments fully or partially completed.
Source: Table 14.2-8.1

Figure 24: Kaplan-Meier Plot of Time to Definitive 10% Deterioration in EORTC QLQ-C30 Global Health Status, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer's core quality of life questionnaire; HR = hazard ratio; Ref = reference
Note: Definitive 10% deterioration is defined as at least 10% relative to Baseline worsening of the corresponding scale score with no later improvement above this threshold observed while on treatment or death due to any cause.
Source: Figure 14.2-6.1

FACT-C

As was observed with the EORTC QLQ-C30 assessment, compliance with the FACT-C assessment was similar in the Triplet arm (88% to 94%) and Doublet arm (87% to 97%) from Baseline through Cycle 6 (Table 54).

Median FACT-C functional well-being scores at Baseline were identical in the Triplet and Doublet arms (16 in both; Table 14.2-8.6). Through Cycle 8, these scores remained at or near Baseline levels in the Triplet

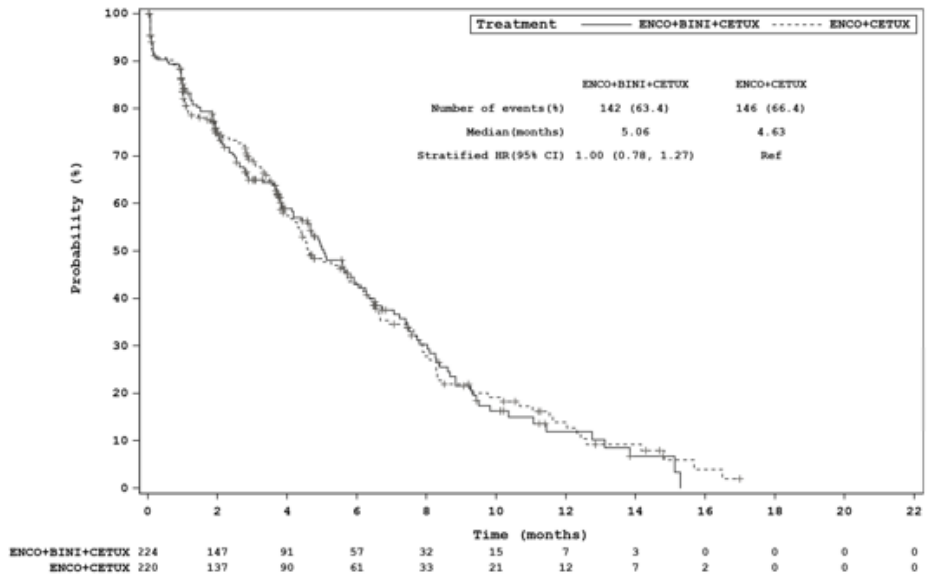
arm and decreased with small fluctuations in the Doublet arm. At Cycle 8, the median functional well-being score was higher in the Triplet arm than the Doublet arm.

Table 54: FACT-C Compliance Summary by Time Window and Treatment, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Full Analysis Set)

	ENCO+BINI+CETUX (N = 224)		ENCO+ CETUX (N=220)	
Visit	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]
Baseline	224	211 (94.2)	220	202 (91.8)
CYCLE 2 DAY 1	205	192 (93.7)	203	196 (96.6)
CYCLE 4 DAY 1	142	125 (88.0)	132	115 (87.1)
CYCLE 6 DAY 1	80	71 (88.8)	68	63 (92.6)
CYCLE 8 DAY 1	49	43 (87.8)	45	41 (91.1)
CYCLE 10 DAY 1	26	24 (92.3)	28	24 (85.7)
CYCLE 12 DAY 1	14	14 (100.0)	19	18 (94.7)
CYCLE 14 DAY 1	7	7 (100.0)	8	7 (87.5)
CYCLE 16 DAY 1	6	5 (83.3)	5	3 (60.0)
CYCLE 18 DAY 1	4	1 (25.0)	3	3 (100.0)
CYCLE 20 DAY 1	2	1 (50.0)	3	1 (33.3)
CYCLE 22 DAY 1	1	0	1	1 (100.0)
END OF TREATMENT	146	81 (55.5)	142	81 (57.0)
30 DAY FOLLOW UP		24		19

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib; FACT-C = Functional Assessment of Cancer Therapy – Colorectal Cancer
[a] Includes instruments fully or partially completed.
Source: Table 14.2-8.1

Figure 25: Kaplan-Meier Plot of Time to Definitive 10% Deterioration in FACT-C Functional Well-being Subscale, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; FACT-C = Functional Assessment of Cancer Therapy – Colon Cancer; HR = hazard ratio; Ref = reference
Note: Definitive 10% deterioration is defined as at least 10% relative to Baseline worsening of the corresponding scale score with no later improvement above this threshold observed while on treatment or death due to any cause.
Source: Figure 14.2-6.5

EQ-5D-5L

Compliance with the EQ-5D-5L assessment was similar in the Triplet arm (87% to 94%) and Doublet arm (86% to 95%) from Baseline through Cycle 6 (Table 55).

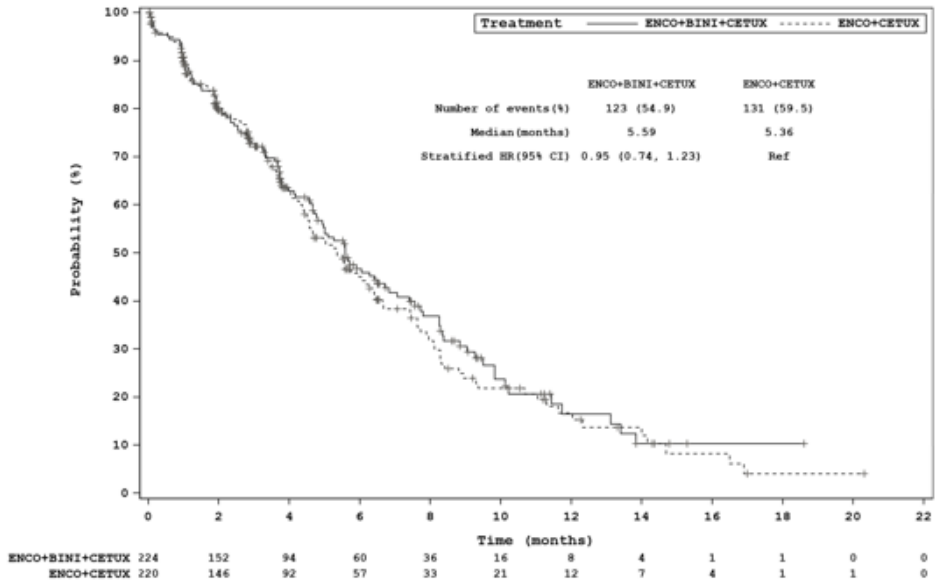
Median EQ-5D-5L VASs at Baseline were identical in the Triplet and Doublet arms (70 in both). Through Cycle 8, these median scores increased with small fluctuations in both treatment arms. At Cycle 8, the median VAS was slightly higher in the Triplet arm than the Doublet arm.

Table 55: EQ-5D-5L Compliance Summary by Time Window and Treatment, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Full Analysis Set)

	ENCO+BINI+CETUX (N = 224)		ENCO+ CETUX (N=220)	
Visit	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]
Baseline	224	211 (94.2)	220	204 (92.7)
CYCLE 2 DAY 1	205	191 (93.2)	203	193 (95.1)
CYCLE 4 DAY 1	142	124 (87.3)	132	114 (86.4)
CYCLE 6 DAY 1	80	70 (87.5)	68	62 (91.2)
CYCLE 8 DAY 1	49	43 (87.8)	45	42 (93.3)
CYCLE 10 DAY 1	26	24 (92.3)	28	24 (85.7)
CYCLE 12 DAY 1	14	13 (92.9)	19	18 (94.7)
CYCLE 14 DAY 1	7	7 (100.0)	8	7 (87.5)
CYCLE 16 DAY 1	6	5 (83.3)	5	3 (60.0)
CYCLE 18 DAY 1	4	1 (25.0)	3	3 (100.0)
CYCLE 20 DAY 1	2	1 (50.0)	3	1 (33.3)
CYCLE 22 DAY 1	1	0	1	1 (100.0)
END OF TREATMENT	146	82 (56.2)	142	79 (55.6)
30 DAY FOLLOW UP		24		18

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib; EQ-5D-5L = EuroQoL-5 Dimension-5 Level examination
[a] Includes instruments fully or partially completed.
Source: Table 14.2-8.1

Figure 26: Kaplan-Meier Plot of Time to Definitive 10% Deterioration in EQ-5D-5L VAS, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Full Analysis Set)



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; ENCO = encorafenib; EQ-5D-5L = EuroQoL-5 Dimension-5 Level examination; HR = hazard ratio; Ref = reference; VAS = visual analog score
Note: Definitive 10% deterioration is defined as at least 10% relative to Baseline worsening of the corresponding scale score with no later improvement above this threshold observed while on treatment or death due to any cause.
Source: Figure 14.2-6.10

PGIC

Compliance with the PGIC assessment was similar in the Triplet arm (68% to 87%) and Doublet arm (69% to 89%) from Baseline through Cycle 6 (Table 56).

Table 56: PGIC Compliance Summary by Time Window and Treatment, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Full Analysis Set)

	ENCO+BINI+CETUX (N = 224)		ENCO+ CETUX (N=220)	
Visit	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]	Number of patients still on treatment	Number of patients who filled out instrument n (%)[a]
Baseline	224	153 (68.3)	220	152 (69.1)
CYCLE 2 DAY 1	205	178 (86.8)	203	180 (88.7)
CYCLE 4 DAY 1	142	120 (84.5)	132	111 (84.1)
CYCLE 6 DAY 1	80	68 (85.0)	68	59 (86.8)
CYCLE 8 DAY 1	49	42 (85.7)	45	40 (88.9)
CYCLE 10 DAY 1	26	24 (92.3)	28	24 (85.7)
CYCLE 12 DAY 1	14	14 (100.0)	19	18 (94.7)
CYCLE 14 DAY 1	7	7 (100.0)	8	7 (87.5)
CYCLE 16 DAY 1	6	4 (66.7)	5	3 (60.0)
CYCLE 18 DAY 1	4	1 (25.0)	3	3 (100.0)
CYCLE 20 DAY 1	2	1 (50.0)	3	1 (33.3)
CYCLE 22 DAY 1	1	0	1	1 (100.0)
END OF TREATMENT	146	72 (49.3)	142	74 (52.1)
30 DAY FOLLOW UP		21		14

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib
[a] Includes instruments fully or partially completed.
Source: Table 14.2-8.1

Table 57: Patient Global Impression of Change Summary by Time Window and Treatment, Triplet Arm vs. Doublet Arm (Randomized Phase 3, Full Analysis Set)

		Randomized Portion	
Visit		ENCO+ BINI+ CETUX (N=224)	ENCO+ CETUX (N=221)
CYCLE 2 DAY 1	Very Much Improved	18/205 (8.8)	10/203 (4.9)
	Much Improved	40/205 (19.5)	53/203 (26.1)
	Minimally Improved	50/205 (24.4)	55/203 (27.1)
	No change	55/205 (26.8)	50/203 (24.6)
	Minimally Worse	13/205 (6.3)	12/203 (5.9)
	Much Worse	2/205 (1.0)	0/203
	Very Much Worse	0/205	0/203
CYCLE 4 DAY 1	Very Much Improved	15/142 (10.6)	14/132 (10.6)
	Much Improved	42/142 (29.6)	41/132 (31.1)
	Minimally Improved	33/142 (23.2)	26/132 (19.7)
	No change	21/142 (14.8)	26/132 (19.7)
	Minimally Worse	7/142 (4.9)	4/132 (3.0)
	Much Worse	2/142 (1.4)	0/132
	Very Much Worse	0/142	0/132
CYCLE 8 DAY 1	Very Much Improved	10/49 (20.4)	5/45 (11.1)
	Much Improved	10/49 (20.4)	14/45 (31.1)
	Minimally Improved	9/49 (18.4)	7/45 (15.6)
	No change	11/49 (22.4)	11/45 (24.4)
	Minimally Worse	2/49 (4.1)	2/45 (4.4)
	Much Worse	0/49	1/45 (2.2)
	Very Much Worse	0/49	0/45

Abbreviations: BINI = binimetinib; CETUX = cetuximab; ENCO = encorafenib
Source: Table 14.2-8.10

Of note, Patient-reported Outcomes were no subject for update within the newly submitted addendum to the CSR ARRAY-818-302.

Ancillary analyses

Safety Lead-in Efficacy Results

Efficacy in the CSLI, comprising patients from the SLI and JSLI cohorts, was assessed using the SLI Efficacy Set (n = 36) and is summarized in Table 58.

Table 58: Safety Lead-in Efficacy Results (SLI Efficacy Set)

Efficacy Parameter	Results N = 36
Confirmed ORR by Investigator (95% CI)[a]	52.8% (35.5, 69.6)
Confirmed ORR by BICR (95% CI)[a]	41.7% (25.5, 59.2)
DOR by Investigator, median (95% CI)[b]	6.47 months (4.17, 11.07)
DOR by BICR, median (95% CI)[b]	8.15 months (2.79, NR)
TTR by Investigator, median (95% CI)[b]	1.45 months (1.38, 1.64)
TTR by BICR, median (95% CI)[b]	1.45 months (1.38, 1.64)
PFS by Investigator, median (95% CI)[b]	8.08 months (5.59, 9.30)
PFS by BICR, median (95% CI)[b]	5.59 months (4.44, 9.30)
OS, median (95% CI)[b]	15.28 months (9.66, 22.90)

Abbreviations: BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SLI = Safety Lead-in; TTR = time to response

[a] The CIs for ORR were computed using Clopper-Pearson's method.

[b] Greenwood formula is used for CIs of Kaplan-Meier estimates for DOR, TTR, PFS and OS.

Source: Table 14.2-1.5; Table 14.2-1.14; Table 14.2-2.4; Table 14.2-3.5; Table 14.2-3.13; Table 14.2-4.3; Table 14.2-4.6; Table 14.2-5.3; Table 14.2-5.6

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial BEACON

Title: BEACON CRC Study			
Study identifier	ARRAY-818-302		
Design	Randomized (1:1:1) controlled, open label with a single arm safety lead-in		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Date of Data Cutoff: 11 February 2019 Date First Patient Randomized: 04 May 2017 Date of First Informed Consent (Safety Lead-in): 09 October 2016 not applicable
Hypothesis (randomized)	Superiority Triplet vs. Control		
Treatments groups	Control (1)		Irinotecan based chemotherapy + cetuximab until progression in planned (646-651)/3 patients
	Doublet (2)		Enco300 + cetuximab until progression in planned (646-651)/3 patients
	Triplet (3)		Combo*300 + cetuximab until progression in planned (646-651)/3 patients
Endpoints and definitions	OS ORR (BICR)	primary co-primary	Each in the comparison (1) vs. (3), sample size estimation based on OS, ORR added as co-primary with protocol amendment 6

	OS (1) vs. (2) OS (2) vs. (3) ORR (inv.) TTR, DOR PFS PFS2 QoL	each Key secondary secondary secondary secondary secondary secondary secondary	Comparisons of Control vs. Doublet, and Doublet vs. Triplet, are labelled key secondary, ORR parameters (and comparisons) not being subject of the (co-) primary endpoint are labelled as secondary endpoints; QoL determined with overall 5 separate questionnaires
	Safety PK Interactions	secondary	Parameters occurring in the list of secondary endpoints but deemed to be no efficacy endpoints of the BEACON trial

Data cutoff date	11 February 2019			
Results and Analysis				
Analysis description	**Primary Analysis (formally 1 vs. 3 only; bold below)**			
Analysis population and time point description	Intent to treat (FAS, randomized part; **n=665**) Phase III Response Efficacy Set (**n=331**) for Co-Primary endpoint 'confirmed BICR ORR'			
Descriptive statistics and estimate variability	Treatment group	Control (1)	Doublet (2)	Triplet (3)
	Number of subject	221	220	224
	OS (months) $P_{(1 vs 2)}$ = .0002 $P_{(2 vs 3)}$= .0582 **$P_{(1 vs 3)}$ = .0001**	**5.32**	8.41	**9.03**
	95%-CI	[4.76; 6.57]	[7.46; 11.04]	[8.02; 11.43]
	Number of subject	107	113	111
	ORR (BICR)	**1.9%**	20.4%	**26.1 %**
	95% CI	[0.2; 6.6]	[13.4; 29.0]	[18.2; 35.3]
Descriptive statistics and variability **secondary** endpoint/analysis	**PFS** (BICR) (months); FAS (n= 665)	1.51	4.21	4.30
	95%-CI	[1.45; 1.71]	[3.71; 5.36]	[4.14; 5.19]
Notes	Due to the high actual number of secondary analyses, comparisons, and endpoints, the display of results is limited to the endpoints OS, ORR, and PFS since considered the most relevant for the scope of a summary			
Analysis description	Comparison control vs. triplet, OS in FAS and ORR, and OS of Doublet vs Control in phase III efficacy set, are formally primary analyses of primary endpoints and key secondary endpoint.			

* COMBO in the meaning of the terminology used in the COLUMBUS trial (https://clinicaltrials.gov/ct2/show/NCT01909453)

Summary of update:

Data cutoff date	**15 August 2019**			
Results and Analysis				
Analysis description	**Primary Analysis (formally 1 vs. 3 only; bold below); precisely: Analyses reported on January 21, 2020**			
Analysis population and time point description	Intent to treat (FAS, randomized part; **n=665**) Phase III Response Efficacy Set (**n=331**) for Co-Primary endpoint 'confirmed BICR ORR'			
	Treatment group	Control (1)	Doublet (2)	Triplet (3)

Descriptive statistics and estimate variability	Number of subject	221	220	224
	OS (months) $P_{(1 \text{ vs } 2)}$ = n.r.** $P_{(2 \text{ vs } 3)=}$ n.r. **$P_{(1 \text{ vs } 3)}$ = n.r**	**5.9**	9.3	**9.3**
	95%-CI	[5.1; 6.57]	[8.0; 11.3]	[8.2; 10.8]
	Number of subject	107	113	111
	ORR (BICR)	**1.8%**	19.5%	**26.8%**
	95% CI	[0.5; 4.6]	[14.5; 25.4]	[21.1; 33.1]
Descriptive statistics and variability **secondary** endpoint/analysis	**PFS** (months); FAS (n= 665)	1.5	4.3	4.5
	95%-CI	[1.5; 1.9]	[4.1; 5.5]	[4.2; 5.5]
Notes	Due to the high actual number of secondary analyses, comparisons, and endpoints, the display of results is limited to the endpoints OS, ORR, and PFS since considered the most relevant for the scope of a summary			
Analysis description	The primary analysis of the study was Triplet vs. Control for OS in the Full Analyses Set and ORR of Triplet vs. Control in the phase III Response Efficacy Set. In the 15 Aug. 2019 updated analyses are descriptive only.			

* COMBO in the meaning of the terminology used in the COLUMBUS trial (https://clinicaltrials.gov/ct2/show/NCT01909453)

** (currently) not reported

Supportive study(ies)

Within this WSP application dossier some "supportive" (for efficacy of Triplet) studies have been submitted. Their supportive character is displayed best in terms of the CO as follows:

"The clinical development programme for encorafenib in combination with binimetinib in metastatic BRAF V600E mutant CRC, comprises data from **5** clinical trials.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal trial of this application, randomized phase of BEACON trial, is an overall well designed randomized controlled international clinical study. Randomisation was generally appropriate. It is noted that neither center nor region was a stratification factor. The number of in- and exclusion criteria each is remarkably high. Overall, however, this list of criteria is considered both sensitive and adequate for the objective of the trial.

The randomized part of the trial had two primary objectives of which the first, i.e. the comparison of the activity of Triplet vs. Control arm in terms of OS, is the regulatory most relevant.

Of note is that the comparison of Doublet vs. Control arm, in terms of OS, is a key secondary endpoint only whereas the comparison of Triple vs Doublet arm, i.e. the contribution to binimetinib to the overall activity (in terms of ORR, PFS, and OS), is only among the other secondary endpoints.

OS is a robust and appropriate primary endpoint in a trial in which late or last line therapy is investigated, particularly in therapeutic situations where, after treatment failure/progression, no live prolonging therapeutic option is available.

A design issue is, however, that it is a 1:1:1 randomized of different combinations whereas the primary analysis (and the sample size estimation) is based on the hypothesis that Triplet (i.e. cetuximab/binimetinib/encorafenib) is superior to Control. No hypothesis of the trial is that Triplet is superior to Doublet.

Efficacy data and additional analyses

The randomized part of BEACON met its primary objective (superiority of Triplet vs. Control in terms of OS) in the primary analysis with a data cut-off of 11 February 2019.

Robustness and sensitivity analyses support the rejection of the null hypothesis.

Also secondary endpoints in terms of ORR and PFS support the conclusion that triplet, compared to control, is an antineoplastic active and in pretreated BRAF+ mCRC patients efficacious combination treatment. The same discussion applies with the rejection of the null hypothesis of the randomized part of BEACON as there is no difference in-between cetuximab/chemotherapy (Control) and cetuximab/encorafenib (Doublet).

Endpoints are fitting with the objectives. The primary endpoint OS is per se adequate for the scope of a pivotal phase III confirmatory trial in a 2nd/3rd line therapeutic situation without relevant therapeutic alternatives which could promise live prolonging effects. Since the primary analysis of the primary endpoint (OS) is focusing on the comparison Triplet vs. Control arm it can be stated that the investigation of the contribution of binimetinib to the overall effect of the Triplet (i.e. the comparison Doublet vs. Triplet arm/therapy) is not the primary goal of the BEACON trial.

The choice of the co-primary endpoint of ORR has to be considered critically from a regulatory point. The main argument for its investigation is that "*ORR allows for a more rapid assessment of potential benefit and may also be an important measure of clinical benefit. In addition, the assessment of ORR by a BICR ensures the consistency and reliability of results.*" This is considered problematic since if a (potential) benefit is more rapidly assessed, confirmation of this benefit may suffer by a too early stopping of the trial (because one of two primary endpoints is reached).

Finally, the usage of the endpoint DOR is not supported although knowing that this is an endpoint meanwhile in widespread use. Informative value of DOR, compared to the information content in PFS, becomes nearly negligible if responses are infrequent, and even in a population with a high frequency of responders DOR does not measure effects in the reminder population of non-responders. As a secondary endpoint, however, it is acceptable.

An additional analysis with data cut-off 15 August 2019 was available to the applicant and was submitted during the procedure.

The updated results show that the primary analysis was already mature. Medians and hazard ratios are essentially the same in both analyses. The latter is more mature with overall 294 (OS) events out of 445 pts (66.1%). The HR of 0.60 can be translated in a 3.4 months prolonged median overall survival for the Triplet vs Control.

Overall, the sensitivity analyses and in particular the sub-group analyses allow the conclusion that the result as to the primary analysis (comparison of Triple vs. control treatment) of the primary endpoint OS is robust.

The supportive analyses performed ultimately confirm that baseline prognostic factors are actually prognostic factors (independent from treatment arm).

The issue of patients in the Control arm randomized but not treated seems to have slightly biased the result as to the primary endpoint. The median OS for the two patients in the Triplet arm is formally 4.76 months, thus smaller than the OS of patients randomized to the Control arm (but not treated) and at the lowest end of the 95%-CI in this population. In essence, seemingly fitter patients decided not to take randomized Control treatment than the reminder accepting treatment with the randomized control.

In essence it should be noted that the updated data are consistent and confirm the initial results showing in particular a considerably higher number of (confirmed) CR and PR in the Triplet arm (compared to Control).

This display of DOR result in a population with overall few responses is interpreted as DOR not adding information in comparison to the more traditional endpoint PFS.

The analysis of PFS is more meaningful than analysis of DOR (and TTR), in particular in a population with relatively few responses. The analysis presented for PFS, thus, allows the conclusion that the overall population of patients in the triplet arm had a clear clinical benefit compared to the control arm which consists more in a delay of progression than in quick and long enduring responses. The updated PFS analysis underlines that the primary analysis was already mature. Medians are nearly not affected (4.3 and 4.5 months vs. 1.51 and 1.5 months respectively).

The updated analysis of the primary endpoint, comparison Doublet vs. Control, has some effects on the median OS in the doublet arm. With the updated analysis, the OS in the doublet arm is essentially the same as in the Triplet arm.

A HR of 0.95 and a ratio of medians of 1.0 allow the conclusion that Doublet and Triplet do not differ from an efficacy perspective. Which is also supported by the K-M curve. Thus, binimetinib does not seem to contribute to the effect of Triplet (compared to Doublet) on OS.

ORR was numerically higher for Triplet compared to the Doublet regimen whereas DOR is numerically longer for Doublet. PFS is considered as the more relevant endpoint compared to ORR and DOR.

PFS in the doublet and triplet arm has remained essentially the same. The numerical differences seen in the (updated) comparison of Triplet vs. Doublet regarding the endpoints ORR and DOR are not clinically relevant.

Overall, this updated analysis underlines that the primary analysis was robust. Efficacy conclusions made on the originally available primary analysis remain virtually unaffected by the update. However, the strong trend favouring Triplet compared to Doublet in terms of primary endpoint OS can no longer be observed in the updated results. It does not preclude that both Triplet and Doublet can be considered efficacious in BRAF+ mCRC patients (each compared to cetuximab plus chemotherapy). However, the MAH withdrew the binimetinib part of the application for B/R reasons, thus, applying only for the Doublet therapy.

2.4.4. Conclusions on the clinical efficacy

The results from the BEACON/ARRAY study have demonstrated a prolonged survival for both Triplet and Doublet regimen compared to the control arm in patients with metastatic colorectal cancer with a BRAF V600E mutation, who have received prior systemic therapy.

2.5. Clinical safety

Introduction

Following the positive opinion of the Committee for Medicinal Products for Human Use (CHMP)on 26 July 2018, the European Commission (EC) approved two marketing authorization applications on 20 September 2018 for MEKTOVI (binimetinib) and BRAFTOVI (encorafenib) to be used in combination for the treatment of adult patients with unresectable or metastatic melanoma with a B-Raf Proto-Oncogene, Serine/Threonine Kinase (*BRAF*) V600 mutation (BRAFTOVI [encorafenib] MAA EU/1/18/1314; MEKTOVI [binimetinib] MA EU/1/18/1315) based on results from the COLUMBUS Phase 3 Study CMEK162B2301.

Binimetinib and encorafenib are orally bioavailable kinase inhibitors that target two different kinases in the Rat Sarcoma Viral Oncogene Homologue (RAS)/Serine/Threonine-Protein Kinase (RAF)/Mitogen-Activated Protein Kinase (MEK)/Extracellular Signal-Regulated Kinase (ERK) pathway.

- Binimetinib (also known as MEK162 or ARRY-438162) is a potent and selective allosteric, ATP uncompetitive small-molecule inhibitor of kinases MEK 1 and MEK 2.
- Encorafenib (also known as LGX818) is a potent and selective adenosine tri-phosphate (ATP) competitive small-molecule inhibitor of mutant *BRAF* V600 kinase that suppresses the RAS/RAF/MEK/ERK pathway in tumour cells expressing several mutated forms of BRAF kinase (V600E/D/K).

Within this work sharing-procedure initially the following extensions of indication were applied for:

- *Binimetinib is indicated, in combination with encorafenib and cetuximab, for the treatment of adult patients with mCRC with a BRAF V600E mutation, who have received prior systemic therapy.*
- *Encorafenib is indicated, in combination with binimetinib and cetuximab, for the treatment of adult patients with mCRC with a BRAF V600E mutation, who have received prior systemic therapy.*

Safety analysis

In the initial application safety data from 5 clinical studies in patients with BRAF-mutant mCRC (N=602) were included in the analysis of safety.

Pivotal Study - ARRAY-818-302 (BEACON):

Patients with BRAF V600E-mutant mCRC treated with the Triplet regimen at recommended doses of encorafenib 300 mg QD + binimetinib 45 mg BID + the standard weekly cetuximab regimen (N=259) and patients with BRAF V600E-mutant mCRC treated with the Doublet regimen at doses of encorafenib 300 mg QD + standard cetuximab QW (N=216) vs investigator's choice (control arm).

Supportive studies

- CLGX818X2103: Patients with BRAF V600-mutant mCRC treated at combination doses of encorafenib 100 mg QD to 450 mg QD + standard cetuximab QW(N=76)
- CMEK162X2110: Patients with BRAF V600-mutant mCRC treated at combination doses of encorafenib 200 mg QD to 600 mg QD + binimetinib 45 mg BID (N=17).
- CLGX818X2101: Patients with BRAF V600-mutant mCRC treated with single-agent doses of encorafenib 300 mg QD or 450 mg QD (N=18)
- ARRAY-162-111: Patients with BRAF-mutant mCRC treated with single-agent doses of binimetinib 45 mg BID or 60 mg BID (N=16)

Safety data from two separate parts of the pivotal study (ARRAY-818-302) were pooled and four supportive studies were presented separately (CLGX818X2103, CMEK162X2110, CLGX818X2101 and ARRAY-162-111) as the doses of encorafenib in these studies were different.

The "Triplet" population consists of safety data from 259 patients in the Phase 3 randomised Triplet arm of Study ARRAY-818-302 (n=222 patients) and the CSLI (n=37 patients) with BRAF V600E-mutant mCRC treated with encorafenib 300 mg QD + binimetinib 45 mg BID + cetuximab dosed as per its approved label. The pooling of data from patients receiving the Triplet combination in different portions of the ARRAY-818-302 Study enables the summarization of safety data in the greatest possible number of patients, allowing more robust subgroup analyses, frequency estimates for rarer events and detection of less common potential ADRs (for further information regarding the pivotal study please be referred to the efficacy section).

Table S1: Safety data in mCRC (pivotal study and supportive studies)

Study	Design / Population	Cut-off Date	Treatment Groups	Safety Population
ARRAY-818-302 (BEACON, pivotal trial)	A Multicenter, randomized, open-label, 3-Arm **Phase 3 Study** Of Encorafenib + Cetuximab +/- Binimetinib vs. Irinotecan / Cetuximab or FOLFIRI /Cetuximab **in Patients with BRAF V600E Mutant Metastatic Colorectal Cancer**	11 Feb 2019 (Respectively 15 Aug 2019 (see Part 2))	Combined safety lead-in of the triplet combination (CSLI) Binimetinib 45 mg BID + Encorafenib 300 mg QD + Cetuximab (as per approved label) (Triplet) Encorafenib 300 mg QD + Cetuximab (as per approved label) (Doublet) Control Therapy	37 222 (224) 216 (220) 193 (221)
CLGX8182103 (supportive Encorafenib + Cetuximab Study)	**A Phase 1b/2**, multi-center, Open-label, Dose-escalation Study of LGX818 and Cetuximab or LGX818, BYL719 and Cetuximab **in Patients with BRAF Mutant Metastatic Colorectal Cancer**	5 Jan 2018	Encorafenib 100 mg QD To 450 mg QD + cetuximab dosed as per its approved label (Phase 1b) Encorafenib 200 mg QD + cetuximab dosed as per its approved label (Phase 2)	26 50

CMEK162X2110 (supportive Encorafenib + Binimetinib Study)	**Phase 1b/2,** multi-center, Open-label, Dose Escalation Study of Encorafenib in Combination With Binimetinib **in adult Patients with BRAF V600- dependent advanced solid tumours (N=189)**	31 Aug 2015	Encorafenib 200 mg QD to 600 mg QD + binimetinib 45 mg BID (dose-escalation phase) Encorafenib 450 mg QD + binimetinib 45 mg BID (expansion phase) Encorafenib 600 mg QD + binimetinib 45 mg BID (expansion phase)	6 4 7
CLGX818X2101 (supportive single-agent Encorafenib study)	**Phase 1**, multicenter, open-label, dose-escalation study of Encorafenib in **adult patients with locally advanced or metastatic BRAF mutation-positive melanomas and mCRC (N=107)**	18 Aug 2014	encorafenib 300 mg QD encorafenib 450 mg QD	6 12
ARRAY-162-111 (supportive single-agent Binimetinib study)	**A Phase 1** dose-escalation study of binimetinib in **patients with advanced solid tumour followed by expansion cohorts in patients with advanced or metastatic biliary cancer or BRAF- or KRAS-mutant metastatic colorectal cancer (N=93)**	completed	binimetinib 60 mg BID (dose-escalation phase) binimetinib 45 mg BID (expansion phase)	1 15

In addition, to discuss the additive toxicity of cetuximab to the Triplet (and Doublet) regimens, data from three supportive clinical trials in patients with unresectable or metastatic melanoma (Study CMEK162B2301, CLGX818X2102 and CLGX818X2101) are included in this submission. Within these data, the safety profile of encorafenib 300 mg QD single-agent (Enco 300P) and binimetinib 45 mg BID + encorafenib 300 mg QD (Combo 300) respectively binimetinib 45 mg BID + encorafenib 450 mg QD (Combo 450 RP)is described:

- Patients with metastatic BRAF V600 melanoma, previously naïve to BRAF inhibitors, treated with encorafenib 300 mg QD pooled from studies CMEK162B2301 [Part 1], CLGX818X2102 and

CLGX818X2101) at a data cut-off date of 09 November 2016 (Encorafenib monotherapy safety pool, Enco300°P, N=217)

- Patients with metastatic BRAF V600 melanoma, previously naïve to BRAF inhibitors treated with encorafenib 300 mg QD plus binimetinib 45 mg BID (Combo 300) enrolled in study CMEK162B2301 Part 2 at a data cut-off date of 9 November 2016 (N=257)
- Patients with metastatic BRAF V600 melanoma, previously naïve to BRAF inhibitors, treated at the registered recommended dose of encorafenib is 450 mg once daily in combination with binimetinib 45 mg BID, pooled from studies CMEK162B2301 [Part 1], CLGX818X2102 and CLGX818X2101) at a data cut-off date of 09 November 2016 (restricted combination pool, Combo 450°RP, N=274)

It is acknowledged that the supportive studies in melanoma are conducted in different disease settings (different tumour types and stages of disease), hence with different durations of exposure and in the context of different tumour related symptoms.

Table S2: Supportive Safety data in Melanoma

Study	Design / Population	Cut-off Date	Treatment Groups	Safety Population
CMEK162B2301 (COLUMBUS, (supportive Encorafenib + Binimetinib Study)	2-part **phase 3**, randomized, open label, multicenter study of LGX818 (Enco) + MEK162 (Bini) versus vemurafenib and LGX818 (Enco) monotherapy in **patients with unresectable or metastatic BRAF V600 mutant melanoma**	Cut-off part I: 19 May 2016 Cut-off part I: 9 Nov 2016	Binimetinib 45 mg BID + encorafenib 450 mg QD (Combo 450) Binimetinib 45 mg BID + encorafenib 300 mg QD (Combo 300) Encorafenib 300 mg QD (Enco 300)	274 257 192
CLGX8182101 (supportive single-agent Encorafenib study)	**A Phase I,** Multi-center, Open-label, Dose-Escalation Study of Oral LGX818 in **Adult Patients with Locally Advanced or Metastatic BRAF Mutant Melanoma**	18 Aug 2014	Enco 50 mg to 700 mg QD and 75 mg to 150 mg BID (Dose-escalation) Enco 300 mg or 450 mg QD (Dose-expansion)	54 35
CLGX8182102 (supportive single-agent Encorafenib study)	**A Phase II,** Multi-center, Open-label Study of Single-agent LGX818 Followed by a Rational Combination with Targeted Agents After Progression on LGX818, to Overcome Resistance in **Adult Patients with Locally Advanced or Metastatic BRAF V600 Melanoma**	31 Aug 2015	Encorafenib 300 mg QD	15

Known safety issues

Single-agent Encorafenib

The maximum well-tolerated dose of encorafenib when given as a single agent is 300 mg QD. Encorafenib 300 mg QD as a single agent is associated with an increased risk of certain adverse reactions compared to when used in combination with 45 mg binimetinib. Among pooled population of melanoma patients receiving single agent encorafenib 300 mg QD, AEs reported most frequently (≥25% of patients) were hyperkeratosis, alopecia, PPES, fatigue, rash, arthralgia, dry skin, nausea, myalgia, headache, vomiting and pruritus.

Encorafenib is primarily metabolised and eliminated by the liver; patients with mild to severe hepatic impairment may have increased exposure over the range of inter-patient variability exposure. It is

recommended that encorafenib is used with caution, at a reduced dose in patients with mild impairment and that patients should be closely monitored (see BRAFTOVI [encorafenib] SmPC, Sections 4.2, 4.4 and 5.2). Because of missing clinical data in patients with moderate and severe hepatic impairment, encorafenib is not recommended in these two sub-populations. An encorafenib dose adjustment to 300 mg QD is proposed in subjects with mild hepatic impairment.

Based on in vitro studies, encorafenib is a substrate of CYP3A4 as well as both an inhibitor and inducer of CYP3A4. Clinical results from a dedicated drug-drug interaction study with encorafenib and CYP3A inhibitors indicated concomitant administration of encorafenib with strong or moderate CYP3A inhibitors may increase encorafenib plasma concentration. If concomitant use with a strong CYP3A inhibitor is necessary, patients should be carefully monitored for safety (see BRAFTOVI [encorafenib] SmPC, Sections 4.4 and 4.5). Caution should be exercised if a moderate CYP3A inhibitor is co-administered with encorafenib (see BRAFTOVI [encorafenib] SmPC, Section 4.5).

While encorafenib is a relatively potent reversible inhibitor of UGT1A1 in vitro, no differences in binimetinib exposure have been observed clinically when binimetinib was co-administered with encorafenib. Encorafenib potentially inhibits a number of transporters. Agents that are substrates of renal transporters OAT1, OAT3, OCT2 or agents that are substrates of the hepatic transporters OATP1B1, OATP1B3, OCT1 or substrates of BCRP or P-gp may have increased exposure and should be therefore co-administered with caution. Concomitant medication restrictions were included in clinical trials based on potential drug interactions.

Single-agent Binimetinib

The maximum well-tolerated dose of binimetinib when given as a single agent is 45 mg BID. Among patients with melanoma receiving single-agent binimetinib 45 mg BID across multiple clinical trials, the most common AEs (≥20%, all grades) were blood CK increased (45%), diarrhoea (43%), dermatitis acneiform (42%), oedema peripheral (41%), rash (34%), nausea (30%) and fatigue (27%). Blood CK increased and hypertension was the only Grade 3/4 AEs reported in ≥5% of patients in the Bini P population and at a higher incidence (≥2% difference) compared to the Combo 450 RP population (20.8% vs 5.5%).

The exposure of binimetinib is not significantly altered in subjects with mild hepatic impairment but is increased 2-fold in subjects with moderate and severe hepatic impairment. Overall, the risk for binimetinib to be a cause of or be affected by significant drug-drug interactions is predicted to be low ().

Cetuximab

Known safety issues for cetuximab are presented in the cetuximab prescribing information (Erbitux [cetuximab] SmPC). The most common adverse reactions (≥ 40% of patients, all grades) reported in patients with mCRC receiving cetuximab monotherapy with best supportive care were rash/desquamation (95%), fatigue (91%), nausea (64%), pain-other (59%), dry skin (57%), constipation (53%), dyspnoea (49%), pruritus (47%), neuropathy-sensory (45%), diarrhoea (42%) and vomiting (40%).

The main known adverse drug reactions associated with the administration of cetuximab, as per the product SmPC include:

- Gastrointestinal symptoms (diarrhoea, nausea and vomiting)
- Mucositis (including severe mucositis that may lead to epistaxis)
- Increased in liver enzymes (ALAT, ASAT and ALP)
- Skin reactions including acne like rash, pruritus, dry skin, desquamation, hypertrichosis, nail disorders, Stevens-Johnson syndrome/toxic epidermal necrolysis

- Superinfection of skin lesion
- Dehydration
- Electrolytes disturbances (hypocalcaemia and hypomagnesemia),
- Eyes disorders (conjunctivitis, keratitis, blepharitis)
- Deep venous thrombosis, pulmonary embolism
- Interstitial lung disease
- Headache
- Aseptic meningitis
- Infusion related reactions

In the course of the WSP the binimetinib application was - with regard to the updated data (cut-off 15 August 2019) of the pivotal study (ARRAY-818-302) - withdrawn.

Thus finally the following extension of indication was applied for:

- *Encorafenib is indicated, in combination with binimetinib and cetuximab, for the trea*tm*ent of adult patients with mCRC with a BRAF V600E mutation, who have received prior systemic therapy.*

The dossier was updated accordingly.

In the scope of this variation, initially the development of encorafenib and binimetinib in combination with cetuximab was assessed. Therefore, the known safety profile of encorafenib and binimetinib in the melanoma indication, the known safety profile of cetuximab as well as the results from the pivotal study ARRAY-818-302 provide the most clinical relevant safety data.

Due to a quite small number of enrolled subjects in the targeted dose and regimen, the safety information from further supportive studies in mCRC is limited and thus, these studies are not described /assessed any further within this AR.

Primarily, the safety profile of the triplet arm (encorafenib, binimetinib and cetuximab) respectively the doublet arm (encorafenib and cetuximab) will be compared with the control arm (Cetuximab and Irinotecan or FOLFIRI) (for further discussion regarding this issue please be referred to the sections below, e.g. overall adverse events and ADRs in the target population).

As requested by the CHMP in a recent scientific advice, additionally the contribution of cetuximab to the safety profile of encorafenib monotherapy as well as to the safety profile of the combination therapy (Encorafenib/Binimetinib) is discussed within the data from three supportive clinical trials in patients with unresectable or metastatic melanoma (CMEK162B2301, CLGX8182101 and CLGX8182102). However, it should be kept in mind that those supportive studies were conducted in different disease settings (different tumour types and stages of disease), hence with different durations of exposure and in the context of different tumour related symptoms. These aspects limit robust evaluation of the contribution of cetuximab (for further discussion regarding this issue please be referred to the sections below e.g. contribution of Cetuximab to the safety and tolerability of the doublet and the triplet arm).

In addition, the contribution of Binimetinib to the safety profile of the combination Encorafenib/Cetuximab is assessed within the results of the comparison of the doublet and triplet arm of the pivotal study (for further discussion regarding this issue please be referred to the sections below, e.g. contribution of Binimetinib to the safety and tolerability of the triplet arm).

It should be noted, that within the pivotal study, a combined safety lead in (CSLI) Phase was performed to justify the triplet combination in the proposed dose. Dose-limiting toxicities were observed in six patients (17.6%). As this was acceptable, the randomized was started. Within this assessment, the data of safety lead in Phase was not assessed separately as the number of treated patients in the CSLI was small (37 patients). However, mainly a pooled triplet arm population (CLSI (37 patients) +Triplet arm of randomized part (222 patients), Triplet Population (259 patients)) was assessed.

As stated above, in the course of this variation the binimetinib application was – with regard to the updated data (cut-off 15 August 2019) of the pivotal study (ARRAY-818-302) – withdrawn and the dossier was updated accordingly.

The safety assessment was therefore updated as follow:

- Part 1 consists of the initial assessment

-Part 2 summarises the updated data of the pivotal study. However, this part includes mainly but not exclusively the assessment of the safety profile of the doublet combination (respectively of encorafenib) only.

2.5.1. Part 1

Patient exposure

As of the most recent edition of the binimetinib IB (11 March 2019; Edition 16), a total of 2907 healthy subjects and patients have received at least 1 dose of binimetinib including 229 healthy subjects, 17 subjects with hepatic impairment, 6 subjects with renal dysfunction, 164 patients with rheumatoid arthritis and 2491 patients with advanced cancer (943 patients who received single-agent binimetinib and 1548 patients who received binimetinib combination therapy.

As of the most recent edition of the encorafenib IB (20 June 2019; Edition 11), a total of 1549 healthy subjects and patients have received at least 1 dose of encorafenib including 97 healthy subjects, 7 subjects with hepatic impairment and 1445 patients and advanced cancer (410 patients who received single-agent encorafenib and 1046 patients who received encorafenib combination therapy, with 11 patients who received both single-agent encorafenib and encorafenib + binimetinib combination therapy and 4 patients who received encorafenib + binimetinib combination therapy in 2 different studies).

In patients with metastatic melanoma, the specific combination of binimetinib plus encorafenib has been evaluated:

- in 274 patients with metastatic melanoma (BRAF-inhibitors naïve) at the recommended doses of 450 mg QD encorafenib and 45 mg BID binimetinib (Combo 450 RP)
- in 257 who received encorafenib in combination with binimetinib at doses of 300 mg QD encorafenib and 45 mg BID binimetinib (Combo 300)

In patients with BRAF V600 E mutant CRC, the Triplet combination of 45 mg BID for binimetinib, 300 mg QD for encorafenib and cetuximab dosed weekly as per its approved label has been evaluated for safety in 259 patients (Triplet°P population).

Duration of exposure

Table S3: Duration of Exposure to Study Treatment – Randomised Phase 3 (ARRAY-818-302)

	ENCO+BINI+CETUX				ENCO+CETUX			
Parameter	ENCO (N=222)	BINI (N=222)	CETUX (N=222)	ENCO+ BINI+ CETUX (N=222)	ENCO (N=216)	CETUX (N=216)	ENCO+ CETUX (N=216)	Control (N=193)
Duration of Exposure (weeks)								
n	222	222	222	222	216	216	216	193
Mean	19.01	18.93	19.05	19.22	18.85	18.89	19.01	9.68
SD	15.049	15.014	15.039	15.008	15.321	15.300	15.277	9.148
Median	15.7	15.7	15.8	15.9	14.0	14.0	14.0	6.3
Min, Max	0.1, 89.1	0.1, 89.1	1.0, 89.1	1.0, 89.1	0.1, 89.7	1.0, 89.7	1.0, 89.7	1.0, 52.4
Duration of Exposure (weeks), n (%)								
<4 weeks	23 (10.4)	24 (10.8)	22 (9.9)	21 (9.5)	12 (5.6)	12 (5.6)	11 (5.1)	36 (18.7)
4- <8 weeks	30 (13.5)	29 (13.1)	31 (14.0)	30 (13.5)	43 (19.9)	42 (19.4)	43 (19.9)	77 (39.9)
8- <12 weeks	27 (12.2)	27 (12.2)	27 (12.2)	28 (12.6)	29 (13.4)	29 (13.4)	27 (12.5)	30 (15.5)
12- <16 weeks	34 (15.3)	34 (15.3)	33 (14.9)	33 (14.9)	35 (16.2)	37 (17.1)	37 (17.1)	18 (9.3)
16- <20 weeks	29 (13.1)	30 (13.5)	30 (13.5)	29 (13.1)	29 (13.4)	27 (12.5)	29 (13.4)	12 (6.2)
20- <24 weeks	20 (9.0)	20 (9.0)	19 (8.6)	19 (8.6)	13 (6.0)	15 (6.9)	14 (6.5)	8 (4.1)
24- <28 weeks	10 (4.5)	10 (4.5)	11 (5.0)	13 (5.9)	9 (4.2)	7 (3.2)	7 (3.2)	2 (1.0)
28- <32 weeks	11 (5.0)	12 (5.4)	11 (5.0)	10 (4.5)	8 (3.7)	9 (4.2)	10 (4.6)	1 (0.5)
32- <36 weeks	12 (5.4)	10 (4.5)	12 (5.4)	12 (5.4)	9 (4.2)	10 (4.6)	8 (3.7)	2 (1.0)
36- <40 weeks	9 (4.1)	9 (4.1)	8 (3.6)	9 (4.1)	9 (4.2)	8 (3.7)	10 (4.6)	3 (1.6)
40- <44 weeks	3 (1.4)	3 (1.4)	4 (1.8)	4 (1.8)	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)
44- <48 weeks	3 (1.4)	3 (1.4)	3 (1.4)	2 (0.9)	4 (1.9)	4 (1.9)	4 (1.9)	2 (1.0)
48- <52 weeks	4 (1.8)	4 (1.8)	4 (1.8)	5 (2.3)	6 (2.8)	6 (2.8)	6 (2.8)	1 (0.5)
52- <104 weeks	7 (3.2)	7 (3.2)	7 (3.2)	7 (3.2)	9 (4.2)	9 (4.2)	9 (4.2)	1 (0.5)

Source: **ARRAY-818-302 CSR Table 14.3-1.3.1**

BINI: binimetinib; CETUX: cetuximab; CSLI: combined safety lead in; ENCO: encorafenib; SD: standard deviation

Triplet°P: Randomised Phase 3 and CSLI (Pooled)

Relative Dose intensity

Table S4: Dose Intensity and Relative Dose Intensity – Randomised Phase 3 ARRAY-818-302)

	Randomised Phase 3								
	ENCO + BINI + CETUX			ENCO + CETUX		CONTROL			
	ENCO N=222	BINI N=222	CETUX N=222	ENCO N=216	CETUX N=216	CETUX N=193	Irinotecan N=193	Folinic Acid N=107	5-FU N=107
Dose intensity (mg/day)									
n	222	222	222	216	216	193	193	107	107
Mean	251.02	70.69	409.42	266.82	413.20	378.68	234.04	507.56	3163.70
SD	59.050	21.015	100.255	58.614	95.709	118.420	83.188	194.659	1425.544
Median	273.3	78.6	416.0	294.1	415.8	382.5	239.8	525.0	3132.0
Min, Max	32.1, 300.9	4.0, 90.3	25.3, 792.0	27.3, 301.8	100.0, 896.0	0.0, 724.0	0.0, 403.2	0.0, 880.0	0.0, 6150.0
Relative dose intensity (%)									
n	222	222	221	216	216	193	193	107	107
Mean	83.67	78.54	85.83	88.94	87.79	78.47	73.54	71.88	65.97
SD	19.683	23.350	16.487	19.538	15.729	21.552	23.487	25.593	27.667
Median	91.1	87.3	91.2	98.0	93.2	85.4	75.7	75.2	73.2

	Randomised Phase 3								
	ENCO + BINI + CETUX			ENCO + CETUX		CONTROL			
	ENCO N=222	BINI N=222	CETUX N=222	ENCO N=216	CETUX N=216	CETUX N=193	Irinotecan N=193	Folinic Acid N=107	5-FU N=107
Min, Max	10.7, 100.3	4.5, 100.3	5.9, 102.6	9.1, 100.6	14.9, 113.0	0.0, 103.6	0.0, 103.4	0.0, 102.3	0.0, 106.5
Relative dose intensity (%), n (%)									
<50%	18 (8.1)	27 (12.2)	11 (5.0)	14 (6.5)	9 (4.2)	21 (10.9)	30 (15.5)	18 (16.8)	27 (25.2)
50 - <80%	54 (24.3)	66 (29.7)	45 (20.3)	27 (12.5)	36 (16.7)	59 (30.6)	81 (42.0)	47 (43.9)	46 (43.0)
80 - <100%	108 (48.6)	107 (48.2)	130 (58.6)	108 (50.0)	139 (64.4)	88 (45.6)	61 (31.6)	25 (23.4)	24 (22.4)
=100%	41 (18.5)	21 (9.5)	6 (2.7)	66 (30.6)	3 (1.4)	9 (4.7)	8 (4.1)	5 (4.7)	3 (2.8)
>100%	1 (0.5)	1 (0.5)	30 (13.5)	1 (0.5)	29 (13.4)	16 (8.3)	13 (6.7)	12 (11.2)	7 (6.5)

Source: **ARRAY-818-302 CSR Table 14.3-1.1.1**

5-FU: 5-fluorouracil; BINI: binimetinib; CETUX: cetuximab; ENCO: encorafenib; SD: standard deviation

Study drug modifications

In Study ARRAY-818-302, the percentage of patients requiring more than one reduction or interruption of study drug was higher in the Triplet arm (46.4% binimetinib, 40.1% encorafenib, 23.9% cetuximab) as compared with the Doublet arm (20.8% encorafenib, 17.1% cetuximab) and the Control arm (14%, cetuximab, 16% irinotecan, 7.5% FA and 36.4% 5-FU). In the Triplet arm, 46.4%, 50.9% and 32.9% of patients had at least one dose interruption of encorafenib, binimetinib or cetuximab due to an AE, respectively, and 17.6%, 27.0% and 5.9% of patients had at least one dose reduction of encorafenib, binimetinib and cetuximab, respectively. Due to the varying dosing schedules of the IV-administered agents in the Control arm and the differences in the duration of exposure, it is difficult to make comparisons of dose interruptions and/or reductions in the Triplet and Doublet arms to the Control arm;

however, the percentage of patients requiring ≥ 1 reduction or interruption of cetuximab, administered in all three treatment arms, was 41.9% for the Triplet arm, 38.4% for the Doublet arm and 26.4% for the Control arm.

In the Doublet arm, 37% and 38.4% of patients had at least one dose interruption of encorafenib and cetuximab, respectively, and 10.3% and 4.2% of patients had at least one dose reduction of encorafenib and cetuximab, respectively. Cetuximab dose in the Control arm was reduced at least once in 6.2% of patients and interrupted in 0.5% of patients.

Adverse events

Overall adverse events

The methods of collecting and analysing AEs in the pivotal study included in the safety analysis are shown in Table S7.

Table S7: Methods of collecting and analysing AEs

Study	MedDRA Version used for Coding of AEs/SAEs		Severity Assessment NCI CTCAE Version	AE collection methods
	SCS/ISS	CSR		
ARRAY-818-302	21.0	21.0	4.03	Collected treatment-related SAEs after prescreening informed consent was provided, all AEs/SAEs after the main study informed consent was provided through 30 days after the last dose, and only treatment-related SAEs after 30 days. Severity of AEs was to be assessed according to CTCAE Grades 1 to 5. Progression of malignancy (including fatal outcome), if documented by use of appropriate method (e.g. per RECIST for solid tumours), was not to be reported as an SAE. An abnormal laboratory value was recorded as an AE if considered clinically significant, induced clinical signs or symptoms, required concomitant therapy or required changes in study treatment.

Safety was assessed throughout the study and included collection of all non-serious AEs and SAEs; regular laboratory evaluations (haematology, coagulation, clinical chemistry, urinalysis, and pregnancy tests); regular physical examinations, dermatologic examinations, ophthalmic examinations and cardiac assessments (ECGs, ECHO/MUGA scans); and recording of ECOG PS, vital signs and body weight.

Table S8 provides an overview of AEs by treatment group for the ARRAY-818-302 TripletºP Population, the CSLI and the randomised Phase 3 treatment arms.

Table S8: Overall summary of Adverse Events by treatment (ARRAY-818-302 Safety Set)

Patients with, n (%)	Triplet°P	CSLI	Randomised Phase 3		
	ENCO+ BINI+ CETUX (N=259)	ENCO+ BINI+ CETUX (N=37)	ENCO+ BINI+ CETUX (N=222)	ENCO+ CETUX (N=216)	Control (N=193)
AEs leading to Death on treatment	9 (3.5)	0 (0.0)	9 (4.1)	7 (3.2)	8 (4.1)
at least one AE regardless of causality	254 (98.1)	37 (100.0)	217 (97.7)	212 (98.1)	188 (97.4)
Grade ≥3	154 (59.5)	26 (70.3)	128 (57.7)	108 (50.0)	117 (60.6)
at least one AE with suspected any study drug relationship	244 (94.2)	36 (97.3)	208 (93.7)	191 (88.4)	176 (91.2)
Grade ≥3	90 (34.7)	16 (43.2)	74 (33.3)	42 (19.4)	76 (39.4)
at least one SAE regardless of causality	115 (44.4)	22 (59.5)	93 (41.9)	71 (32.9)	71 (36.8)
Grade ≥3	100 (38.6)	17 (45.9)	83 (37.4)	61 (28.2)	64 (33.2)
at least one SAE with suspected any study drug relationship	46 (17.8)	10 (27.0)	36 (16.2)	20 (9.3)	25 (13.0)
Grade ≥3	33 (12.7)	5 (13.5)	28 (12.6)	13 (6.0)	22 (11.4)
at least one AE leading to discontinuation of any study drug regardless of causality	41 (15.8)	8 (21.6)	33 (14.9)	25 (11.6)	33 (17.1)
Grade ≥3	25 (9.7)	3 (8.1)	22 (9.9)	22 (10.2)	24 (12.4)
at least one AE leading to discontinuation of any study drug with suspected study drug relationship	26 (10.0)	7 (18.9)	19 (8.6)	9 (4.2)	23 (11.9)
Grade ≥3	13 (5.0)	2 (5.4)	11 (5.0)	8 (3.7)	15 (7.8)
at least one AE leading to discontinuation of all study treatment regardless of causality	18 (6.9)	2 (5.4)	16 (7.2)	18 (8.3)	22 (11.4)
Grade ≥3	14 (5.4)	1 (2.7)	13 (5.9)	16 (7.4)	18 (9.3)
at least one AE leading to discontinuation of all study treatment with suspected study drug relationship	8 (3.1)	2 (5.4)	6 (2.7)	6 (2.8)	12 (6.2)
Grade ≥3	6 (2.3)	1 (2.7)	5 (2.3)	5 (2.3)	9 (4.7)
at least one AE requiring dose reduction of any study drug regardless of causality	84 (32.4)	16 (43.2)	68 (30.6)	22 (10.2)	58 (30.1)
Grade ≥3	35 (13.5)	5 (13.5)	30 (13.5)	8 (3.7)	29 (15.0)
at least one AE requiring dose reduction of any study drug with suspected study drug relationship	82 (31.7)	15 (40.5)	67 (30.2)	21 (9.7)	56 (29.0)
Grade ≥3	33 (12.7)	4 (10.8)	29 (13.1)	8 (3.7)	29 (15.0)
at least one AE requiring dose interruption of any study drug regardless of causality	176 (68.0)	30 (81.1)	146 (65.8)	98 (45.4)	103 (53.4)
Grade ≥3	101 (39.0)	18 (48.6)	83 (37.4)	65 (30.1)	69 (35.8)
at least one AE requiring dose interruption of any study drug with suspected study drug relationship	140 (54.1)	26 (70.3)	114 (51.4)	57 (26.4)	74 (38.3)
Grade ≥3	64 (24.7)	10 (27.0)	54 (24.3)	33 (15.3)	46 (23.8)
at least one AE requiring additional therapy regardless of causality	246 (95.0)	37 (100.0)	209 (94.1)	200 (92.6)	180 (93.3)
Grade ≥3	132 (51.0)	20 (54.1)	112 (50.5)	91 (42.1)	94 (48.7)
at least one AE requiring additional therapy with suspected any study drug relationship	228 (88.0)	36 (97.3)	192 (86.5)	155 (71.8)	160 (82.9)
Grade ≥3	66 (25.5)	11 (29.7)	55 (24.8)	28 (13.0)	51 (26.4)

Source: **ARRAY-818-302 CSR Table 14.3.1-1.1.1**
AE: adverse event; BINI: binimetinib; CETUX: cetuximab; CSLI: combined safety lead in; CSR: clinical study report; ENCO: encorafenib; SAE: serious adverse event
Triplet°P: Randomised Phase 3 and CSLI (Pooled)

An overview of Relevant Adverse Events, Regardless of Study Drug Relationship, Adjusted for Patient-month Exposure (EAIRs), is provided in Table S9.

Table S9: Relevant Adverse Events, Regardless of Study Drug Relationship, Adjusted for Patient-month Exposure, by Preferred Term (EAIR ⩾5 in any Phase 3 arm or Study population) (ARRAY-818-302 Safety Set)

		Triplet°P	CSLI	Randomised Phase 3		
Preferred Term°		**ENCO+ BINI+ CETUX (N=259)**	**ENCO+ BINI+ CETUX (N=37)**	**ENCO+ BINI+ CETUX (N=222)**	**ENCO+ CETUX (N=216)**	**Control (N=193)**
Any preferred term	**n (%)**	**254 (98.1)**	**37 (100.0)**	**217 (97.7)**	**212 (98.1)**	**188 (97.4)**
	Exposure (mo)	**48.16**	**3.48**	**44.68**	**58.94**	**35.68**
	EAIR	**527.36**	**1062.44**	**485.66**	**359.69**	**526.91**
Diarrhoea	n (%)	165 (63.7)	28 (75.7)	137 (61.7)	72 (33.3)	93 (48.2)
	Exposure (mo)	514.69	91.27	423.43	689.41	195.88
	EAIR	32.06	30.68	32.36	10.44	47.48
Dermatitis acneiform	n (%)	133 (51.4)	25 (67.6)	108 (48.6)	63 (29.2)	76 (39.4)
	Exposure (mo)	586.58	80.92	505.66	659.42	242.04
	EAIR	22.67	30.89	21.36	9.55	31.40
Nausea	n (%)	122 (47.1)	22 (59.5)	100 (45.0)	74 (34.3)	80 (41.5)
	Exposure (mo)	716.78	132.99	583.79	680.05	226.99
	EAIR	17.02	16.54	17.13	10.88	35.24
Vomiting	n (%)	103 (39.8)	18 (48.6)	85 (38.3)	46 (21.3)	56 (29.0)
	Exposure (mo)	941.31	207.93	733.37	790.57	312.08
	EAIR	10.94	8.66	11.59	5.82	17.94
Fatigue	n (%)	93 (35.9)	20 (54.1)	73 (32.9)	65 (30.1)	53 (27.5)
	Exposure (mo)	839.20	153.36	685.83	694.70	283.93
	EAIR	11.08	13.04	10.64	9.36	18.67
Anaemia	n (%)	96 (37.1)	16 (43.2)	80 (36.0)	35 (16.2)	37 (19.2)
	Exposure (mo)	998.80	236.45	762.35	861.24	335.61
Abdominal pain	n (%)	79 (30.5)	14 (37.8)	65 (29.3)	49 (22.7)	48 (24.9)
	Exposure (mo)	1006.19	214.77	791.43	806.05	336.07
	EAIR	7.85	6.52	8.21	6.08	14.28
Decreased appetite	n (%)	77 (29.7)	14 (37.8)	63 (28.4)	58 (26.9)	52 (26.9)
	Exposure (mo)	1053.77	259.15	794.61	751.93	340.99
	EAIR	7.31	5.40	7.93	7.71	15.25
Constipation	n (%)	69 (26.6)	14 (37.8)	55 (24.8)	33 (15.3)	35 (18.1)
	Exposure (mo)	1065.59	246.18	819.42	852.47	331.27
	EAIR	6.48	5.69	6.71	3.87	10.57
Asthenia	n (%)	61 (23.6)	6 (16.2)	55 (24.8)	46 (21.3)	49 (25.4)
	Exposure (mo)	1131.66	305.15	826.51	779.60	292.67
	EAIR	5.39	1.97	6.65	5.90	16.74
Dry skin	n (%)	65 (25.1)	19 (51.4)	46 (20.7)	24 (11.1)	13 (6.7)
	Exposure (mo)	978.76	189.01	789.75	850.63	355.45
	EAIR	6.64	10.05	5.82	2.82	3.66
Pyrexia	n (%)	60 (23.2)	15 (40.5)	45 (20.3)	35 (16.2)	27 (14.0)
	Exposure (mo)	1037.27	208.76	828.52	809.30	359.56
	EAIR	5.78	7.19	5.43	4.32	7.51
Rash	n (%)	45 (17.4)	3 (8.1)	42 (18.9)	25 (11.6)	27 (14.0)
	Exposure (mo)	1131.43	325.52	805.91	815.11	323.58
	EAIR	3.98	0.92	5.21	3.07	8.34
Stomatitis	n (%)	37 (14.3)	6 (16.2)	31 (14.0)	12 (5.6)	44 (22.8)
	Exposure (mo)	1167.15	308.40	858.74	880.72	311.98
	EAIR	3.17	1.95	3.61	1.36	14.10
Vision blurred	n (%)	37 (14.3)	12 (32.4)	25 (11.3)	8 (3.7)	1 (0.5)
	Exposure (mo)	1099.01	214.08	884.93	911.70	386.66
	EAIR	3.37	5.61	2.83	0.88	0.26
Arthralgia	n (%)	32 (12.4)	9 (24.3)	23 (10.4)	41 (19.0)	1 (0.5)
	Exposure (mo)	1147.07	263.98	883.09	783.44	381.93
	EAIR	2.79	3.41	2.60	5.23	0.26
Blood CK increased	n (%)	33 (12.7)	13 (35.1)	20 (9.0)	1 (0.5)	3 (1.6)

		Triplet°P	CSLI	Randomised Phase 3		
Preferred Term[a]		**ENCO+ BINI+ CETUX (N=259)**	**ENCO+ BINI+ CETUX (N=37)**	**ENCO+ BINI+ CETUX (N=222)**	**ENCO+ CETUX (N=216)**	**Control (N=193)**
	Exposure (mo)	1133.86	231.89	901.98	938.71	385.91
	EAIR	2.91	5.61	2.22	0.11	0.78
Neutropenia	n (%)	4 (1.5)	1 (2.7)	3 (1.4)	1 (0.5)	36 (18.7)
	Exposure (mo)	1297.77	336.59	961.18	936.41	309.36
	EAIR	0.31	0.30	0.31	0.11	11.64
Back pain	n (%)	33 (12.7)	8 (21.6)	25 (11.3)	22 (10.2)	23 (11.9)
	Exposure (mo)	1220.14	319.64	900.50	893.83	353.87
	EAIR	2.70	2.50	2.78	2.46	**6.50**
Hypokalaemia	n (%)	18 (6.9)	3 (8.1)	15 (6.8)	13 (6.0)	27 (14.0)
	Exposure (mo)	1291.76	337.58	954.18	912.20	368.82
	EAIR	1.39	0.89	1.57	1.43	**7.32**
Headache	n (%)	22 (8.5)	6 (16.2)	16 (7.2)	42 (19.4)	5 (2.6)
	Exposure (mo)	1174.18	278.34	895.84	820.37	381.80
	EAIR	1.87	2.16	1.79	5.12	1.31

Source: **ARRAY-818-302 CSR Table 14.3.1-1.45.1**
BINI: binimetinib; CETUX: cetuximab; CK: creatine phosphokinase; CSLI: combined safety lead in; CSR: clinical study report;
EAIR: exposure adjusted incidence rate; ENCO: encorafenib; mo: months; MedDRA: Medical Dictionary for Regulatory Activities.
[a] From MedDRA version 21.0.
n (%): number of patients reporting the event (patient incidence (%).
Exposure time for a patient without the specific event is the treatment duration, whereas the exposure time for a subject with the specific event is the treatment duration up to the start date (inclusive) of the first occurrence of the specific event.
EAIR (Exposure adjusted incidence rate per 100 patient-months=(n*100)/(total exposure time).
Terms are sorted in descending EAIR of Randomised Phase 3 ENCO+BINI+CETUX column.
Triplet°P: Randomised Phase 3 and CSLI (Pooled).

Triplet arm vs Control arm

In general, EAIRs (exposure adjusted incidence rate) were lower in the Triplet arm than in the Control arm, with the following events having a difference of >10 per 100 patient-months: diarrhoea (32.36 Triplet vs 47.48 Control), dermatitis acneiform (21.36 vs 31.40), nausea (17.13 vs 35.24), asthenia (6.65 vs 16.74), stomatitis (3.61 vs 14.10) and neutropenia (0.31 vs 11.64).

Doublet arm vs Control arm

In general, EAIRs were lower in the Doublet arm than in the Control arm, with the following events having a difference of >10 per 100 patient-months: diarrhoea (10.44 Doublet vs 47.48 Control), dermatitis acneiform (9.55 vs 31.40), nausea (10.88 vs 35.24), vomiting (5.82 vs 17.94) asthenia (5.90 vs 16.74) and stomatitis (1.36 vs 14.10) and neutropenia (0.11 vs 11.64).

Adverse Events by Time of Onset and/or Duration

The incidence of AEs over various periods was assessed for the first month of treatment, for months 2 and 3 and for the first 3, 6 and 12 months of study treatment.

In the Triplet, Doublet and Control arms of the randomised Phase 3 population, 9.5%, 5.1% and 18.7% of patients, respectively received treatment for less than 4 weeks.

In the first month of treatment, AEs of any grade were reported in 95.9% of patients in the Triplet arm, 93.1% in the Doublet arm and 95.9% in the Control arm (Grade >3 AEs: 28.4%, 22.2% and 39.4%, respectively).

In the first 3 months of treatment, the prevalence of AEs of any grade was the same for the Triplet and Doublet (97.7% in both) and Control (97.4%) arms. However, Grade >3 AEs were more commonly reported in the Control arm (48.7%) than in the Triplet or Doublet arms (37.8% vs 33.8%, respectively).

Comparing the data reported during the first month vs months 2 and 3 of treatment, the overall incidence was reduced in all treatment arms (Triplet: from 95.9%% to 79.3%; Doublet: from 93.1% to 81.0%; Control: from 95.9% to 64.8%) whilst the overall incidences of Grade >3 events were similar in the Triplet (from 28.4 to 27.9%) and the Doublet arm (from 22.2% to 23.6%) but reduced in the Control arm (from 39.4 to 30.1%).

Reduced incidence rates were also reported for all most commonly reported AEs in the Triplet and Control arms, indicating that the majority of events were most frequently occurring in the first month of treatment. Specifically, in the Triplet arm, the incidences of diarrhoea and dermatitis acneiform were reduced by >20% between Month 1 and Months 2 to 3; nausea, fatigue and vomiting were reduced by >10% between the same time periods. Similarly in the Control arm, the incidences of diarrhoea, dermatitis acneiform and nausea were reduced by >20% between Month 1 and Months 2 to 3; fatigue and vomiting were reduced by >10% between the same time periods.

Anaemia in the Triplet arm was the only event with a higher incidence in the Months 2 to 3 period than in the first month of study treatment.

In the Doublet arm, the incidence of the most commonly reported events (fatigue, nausea and diarrhoea) was reduced by >10% between the first month and months 2 to 3 and no AE was reported in Months 2 to 3 at an incidence higher than that reported in the first month of study treatment. All AEs reported in >2% of subjects during Months 2 and 3 had already been reported in the first month of study treatment.

In the first 6 months of treatment, prevalence of AEs of any grade was similar for the three arms (97.7%, 98.1%, and 97.4%). Grade >3 AEs were more commonly reported in the Control arm (51.8%) than in the Triplet or Doublet arms (45.5% vs 40.7%, respectively).

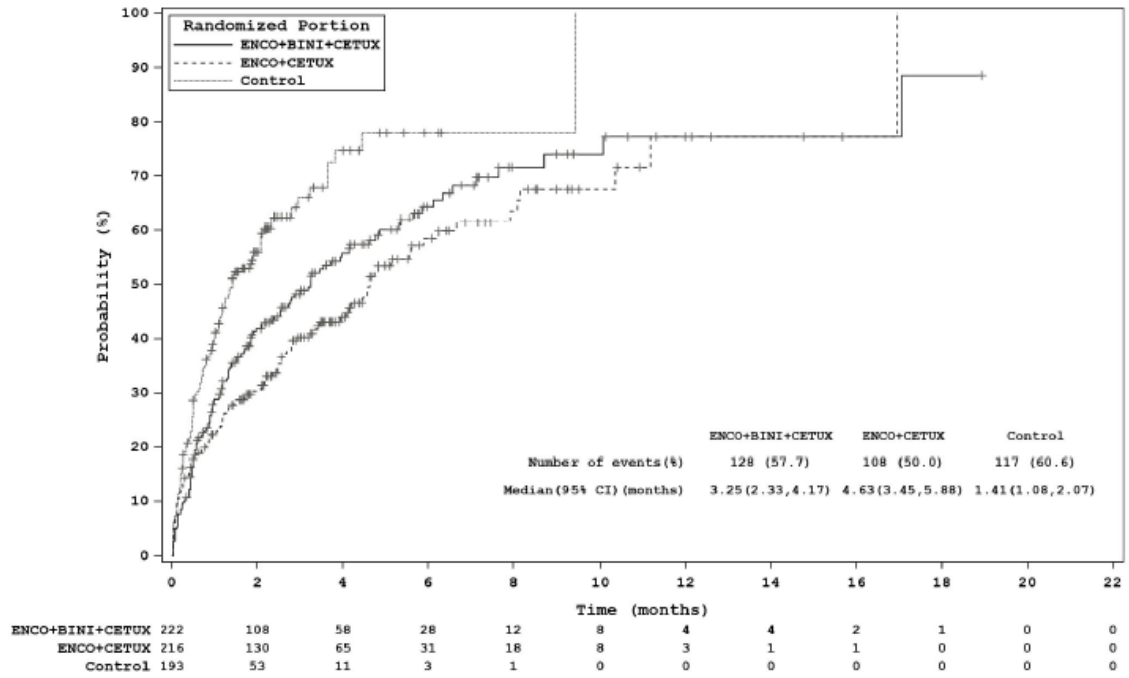
23.0% of patients in the Triplet arm, 23.6% in the Doublet arm and 5.2% in the Control arm received at least 6 months (24 weeks) of study treatment. Grade >3 events were similar between treatment arms, except anaemia that was reported in 7.7% of the Triplet arm vs 1.9% and 1.0% in the Doublet and Control arms.

During Months 4 to 6 of study treatment, AEs of any grade were observed at a lower incidence than during Months 2 to 3 and this decreased in incidences was similar for the Triplet and Doublet arms (Triplet: from 79.3% to 55.0%; Doublet: from 81.0% to 47.7%). Grade >3 AEs were reported more often in the Triplet arm (23.9%) than in the Doublet arm (15.7%), however both incidences were lower than during the Months 2 to 3 time period.

Prevalence of adverse events of any grade occurring within the first 12 months was similar for the three arms (97.7%, 98.11% and 97.4%). Grade >3 AEs were reported at a lower percentage in the Triplet or Doublet arms as compared to the Control arm (28.4% and 22.2%, vs 39.4% respectively).

With exposure in the three arms being low during Month 7 to Month 12 of study treatment, no comparisons were made between arms for this time.

Figure 1: Kaplan-Meier Plot of Time to Onset of First Grade 3+ Adverse Event (Safety Set)



Adverse drug reactions in the Target indication

The lists of ADRs as presented in Table S10 and Table S11 comprise ADRs included in the Company's Core Data Sheet and are considered distinctive of the encorafenib, binimetinib and cetuximab or encorafenib and cetuximab combinations in mCRC, as well as ADRs of encorafenib and binimetinib retained from the initial MAA.

Upon review and analysis of adverse events of special interest (AESI), no AESI that did not already translate into an ADR in the initial MAA was identified as candidate ADR for the Triplet or the Doublet.

Adverse drug reaction occurred in the Triplet°P of study Array-818-302 in 97.3% of patients with 48.6% Grade ≥3 events. The most frequent ADRs were diarrhoea (63.7%), fatigue (58.3%), acneiform dermatitis (57.9%), nausea (47.1%), abdominal pain (39.8%), vomiting (39.8%), anaemia (37.1%), rash (31.3%), Dry skin (30.9%) decreased appetite (29.6%) and constipation (26.6%).

In the Doublet arm, adverse drug reactions occurred in 96.8% of patients with 24.1% Grade ≥3 events. The most frequent ADRs were fatigue (51.4%), nausea (34.3%), diarrhoea (33.3%), acneiform dermatitis (31.9%), abdominal pain (29.6%), Arthralgia (27.3%), decreased appetite (26.6%) and rash (25.9%).

As mentioned in the methodology for the determination of ADRs, several ADRs identified in the initial MAA were not retained as ADRs for the Triplet and/or the Doublet. The reasons for not retaining an ADR were either that no event was reported for this ADR or that the incidence for this ADR was low and similar to that reported in a population of non-treated mCRC patients or in the general population.

ADRs not retained for the Triplet and the Doublet were:

- Facial paresis - no event
- Photosensitivity - low incidence similar to the general population
- Hypertension - low incidence similar to the incidence in the mCRC population

- Gamma glutamyl transferase increased - low incidence similar to the incidence in the general population or in a cancer population
- Blood alkaline phosphatase (ALP) increased – low incidence similar to the incidence in the mCRC population

ADRs not retained for the Triplet were:

- Lipase increased – no event

ADRs not retained for the Doublet were:

- Uveitis – no event

The ADR hypalbuminaemia was not identified in the initial MAA and is considered an ADR of the Triplet based on multiple criteria analysis, including the difference in incidence rates of overall AEs.

Table S10: Adverse Reactions Occurring in the Triplet°P of ARRAY-818-302

	Any Grade n (%)	Grade ≥3 n (%)
Any ADR	**N(%) Triplet**	**N(%) Triplet**
	252 (97.3)	**126 (48.6)**
Gastrointestinal disorders		
Diarrhoea*	165 (63.7)	24 (9.3)
Nausea*	122 (47.1)	12 (4.6)
Abdominal pain*	103 (39.8)	16 (6.2)
Vomiting*	103 (39.8)	11 (4.2)
Constipation*	69 (26.6)	0 (0.0)
Colitis*	5 (1.9)	2 (0.8)
Pancreatitis*	3 (1.2)	2 (0.8)
Blood and lymphatic system disorders		
Anaemia*	96 (37.1)	42 (16.2)
Investigations		
Blood creatinine increased*	29 (11.2)	7 (2.7)
Hypoalbuminaeamia*	21 (8.1)	5 (1.9)
Blood creatine phosphokinase increased*	33 (12.7)	11 (4.2)
Transaminases increased*	30 (11.6)	6 (2.3)
Skin Disorders		
Acneiform Dermatitis*	150 (57.9)	9 (3.5)
Rash*	81 (31.3)	2 (0.8)

	Any Grade n (%)	Grade ≥3 n (%)
Dry skin*	80 (30.9)	3 (1.2)
Pruritus*	38 (14.7)	1 (0.4)
PPES*	34 (13.1)	0 (0.0)
Erythema	10 (3.9)	1 (0.4)
Skin exfoliation	7 (2.7)	0 (0.0)
Alopecia	5 (1.9)	0 (0.0)
Hyperkeratosis	2 (0.8)	0 (0.0)
Panniculitis*	1 (0.4)	0 (0.0)
Neoplasms benign, malignant and unspecified		
Basal cell carcinoma	1 (0.4)	0 (0.0)
Cutaneous squamous cell carcinoma	1 (0.4)	0 (0.0)
Skin papilloma	1 (0.4)	0 (0.0)
General disorders		
Fatigue*	151 (58.3)	17 (6.6)
Pyrexia*	61 (23.6)	4 (1.5)
Peripheral oedema*	36 (13.9)	1 (0.4)
Metabolism and nutrition disorders		
Decreased appetite	77 (29.7)	6 (2.3)
Musculoskeletal events		
Arthralgia/Musculoskeletal pain*	39 (15.1)	0 (0.0)
Back pain	33 (12.7)	3 (1.2)
Myopathy/Muscular disorders*	43 (16.6)	1 (0.4)
Pain in extremity*	18 (6.9)	0 (0.0)
Rhabdomyolysis*	1 (0.4)	1 (0.4)
Eye Disorders		
Visual impairment*	44 (17.0)	0 (0.0)
RPED*	38 (14.7)	1 (0.4)
Uveitis	1 (0.4)	0 (0.0)
Renal and urinary disorders		
Renal failure	23 (8.9)	9 (3.5)
Nervous System disorders		
Peripheral neuropathy*	42 (16.2)	3 (1.2)
Dizziness	23 (8.9)	0 (0.0)
Headache	22 (8.5)	1 (0.4)
Dysgeusia	17 (6.6)	0 (0.0)
Vascular disorders		
Haemorrhage*	56 (21.6)	10 (3.9)
Venous thromboembolism*	18 (6.9)	10 (3.9)
Cardiac disorders		
Left ventricular dysfunction (Cardiomyopathy)*	15 (5.8)	1 (0.4)
Immune system disorders		
Drug hypersensitivity (Hypersensitivity)*	2 (0.8)	0 (0.0)

Source: **ISS_CRC_add Table 1.1**

ADR: adverse drug reaction; RPED: retinal pigment epithelial detachment.

Grades are based on CTCAE version 4.03.

Terms are sorted in descending frequency of 'Any Grades'

*ADRs identified with * are considered distinctive of the encorafenib, binimetinib and cetuximab combinations in mCRC per Company's Core Datasheet

Table S11: Adverse Reactions Occurring in the Doublet Arm of ARRAY-818-302

	Any Grade n (%)	Grade ≥3
Any ADR	**N(%) Doublet**	**N(%) Doublet**
	209 (96.8)	**52 (24.1)**
Gastrointestinal disorders		
Diarrhoea	72 (33.3)	4 (1.9)
Nausea	74 (34.3)	1 (0.5)
Abdominal pain*	64 (29.6)	9 (4.2)
Vomiting*	46 (21.3)	3 (1.4)
Constipation*	33 (15.3)	0 (0.0)
Pancreatitis*	1 (0.5)	1(0.5)
Investigations		
Anaemia	35 (16.2)	16 (7.4)
Amylase increased	1 (0.5)	0 (0.0)
Lipase increased	1 (0.5)	1(0.5)
Blood creatinine increased*	5 (2.3)	1 (0.5)
Transaminases increased*	18 (8.3)	2 (0.9)
Skin Disorders		
Acneiform Dermatitis	69 (31.9)	2 (0.9)
Rash*	56 (25.9)	0 (0.0)
Dry skin*	29 (13.4)	0 (0.0)
Pruritus*	31 (14.4)	0 (0.0)
PPES	9 (4.2))	1 (0.5)
Skin exfoliation	1 (0.5)	0 (0.0)
Skin hyperpigmentation*	16 (7.4)	0 (0.0)
Hyperkeratosis*	8 (3.7)	0 (0.0)
Erythema	10 (4.6)	1 (0.5)
Alopecia	8 (3.7)	0 (0.0)
Neoplasms benign, malignant and unspecified		
Melanocytic naevus*	31 (14.4)	0 (0.0)
Basal cell carcinoma	1 (0.5)	0 (0.0)
Cutaneous squamous cell carcinoma*	3 (1.4)	0 (0.0)
Skin papilloma*	12 (5.6)	0 (0.0)
New primary melanoma*	3 (1.4)	2 (0.9)
General disorders		
Fatigue	111 (51.4)	16 (7.4)
Peripheral oedema	20 (9.3)	0 (0.0)
Pyrexia*	36 (16.7)	3 (1.4)
Metabolism and nutrition disorders		
Decreased appetite	58 (26.9)	3 (1.4)
Musculoskeletal events		
Arthralgia/Musculoskeletal pain*	59 (27.3)	2 (0.9)
Myopathy/Muscular disorders*	33 (15.3)	1 (0.5)
Back pain	22 (10.2)	2 (0.9)
Pain in extremity*	22 (10.2))	0 (0.0)
Renal and urinary disorders		
Renal failure	4 (1.9)	4 (1.9)
Nervous System disorders		
Peripheral neuropathy*	26 (12.0)	3(1.4)
Dizziness	18 (8.3)	0
Headache*	43 (19.9)	0
Dysgeusia	9 (4.2)	0
Vascular disorders		
Haemorrhage	41 (19.0)	4 (1.9)
Cardiac disorders		
Supraventricular tachycardia	8 (3.7)	3 (1.4)
Psychiatric disorders		
Insomnia*	28 (13.0)	0
Immune system disorders		
Drug hypersensitivity (Hypersensitivity)*	3 (1.4)	2 (0.9)

Source: **ISS_CRC_add Table 1.2**
ADR: adverse drug reaction.
Grades are based on CTCAE version 4.03.
Terms are sorted in descending frequency of 'Any Grades'
*ADRs identified with * are considered distinctive of the encorafenib, binimetinib and cetuximab combinations in mCRC per Company's Core Datasheet

Contribution of Binimetinib to the safety and tolerability of the triplet

The contribution of binimetinib was determined by comparing the Triplet arm versus the Doublet arm of the randomised Phase 3 part of Study ARRAY-818-302, for the following:

- Overall summary of AEs (overall % of AEs, Grade >3 AEs, SAEs, deaths, AEs leading to discontinuation, dose modifications or requiring additional treatment)
- Most frequent AEs regardless of causality (overall and Grade >3).
- SAEs regardless of causality
- Comparison of individual adverse drug reactions in the doublet resp. triplet arm

Overall adverse event profile – Triplet vs Doublet

A similar percentage of patients in the Triplet arm and the Doublet experienced at least one AE (97.7% vs 98.1%).

Incidence rates of Grade ≥ 3 toxicities (57.7% Triplet arm, 50.0% Doublet arm) and SAEs (41.9% Triplet arm, 32.9% Doublet arm) were higher (even though the difference was < 10%) in the Triplet arm.

The incidences of AEs leading to discontinuation of any drug or all study treatment (all grades and Grade >3) were similar in the Triplet and the Doublet arms (14.9% vs 11.6% and 9.9% vs 10.2% respectively).

In the Triplet vs the Doublet, there were more AEs requiring dose reduction of any study drug (30.6% vs 10.2%) and AEs requiring dose interruption of any study drug (65.8% vs 45.4%). A similar percentage of patients experienced an AE requiring additional therapy.

Overall Adverse events

Adverse Events with an Absolute Difference in Incidence of >5.0% between the Triplet Arm and the Doublet Arm, Regardless of Causality, by Preferred Term – Overall and Maximum Grade >3 are presented in Table S12.

Table S12: Adverse Events with an Absolute Difference in Incidence of >5.0% between the Triplet Arm and the Doublet Arm, Regardless of Causality, by Preferred Term – Overall and Maximum Grade >3 (Safety Set)

	Randomised Phase 3				Difference in Incidence (All Grades) (%)
	ENCO + BINI + CETUX N=222		ENCO + CETUX N=216		
Preferred Term[a]	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	
Any adverse event	217 (97.7)	128 (57.7)	212 (98.1)	108 (50.0)	0.4
Diarrhoea	137 (61.7)	22 (9.9)	72 (33.3)	4 (1.9)	28.4
Anaemia	80 (36.0)	37 (16.7)	35 (16.2)	10 (4.6)	19.8
Dermatitis acneiform	108 (48.6)	5 (2.3)	63 (29.2)	1 (0.5)	19.4
Vomiting	85 (38.3)	9 (4.1)	46 (21.3)	3 (1.4)	17.0
Nausea	100 (45.0)	10 (4.5)	74 (34.3)	1 (0.5)	10.7
Dry skin	46 (20.7)	2 (0.9)	24 (11.1)	0	9.6
Constipation	55 (24.8)	0	33 (15.3)	0	9.5
Blood CK increased	20 (9.0)	8 (3.6)	1 (0.5)	0	8.5
Stomatitis	31 (14.0)	1 (0.5)	12 (5.6)	0	8.4
PPE syndrome	28 (12.6)	0	9 (4.2)	1 (0.5)	8.4
Vision blurred	25 (11.3)	0	8 (3.7)	0	7.6
Rash	42 (18.9)	1 (0.5)	25 (11.6)	0	7.3
Abdominal pain	65 (29.3)	13 (5.9)	49 (22.7)	5 (2.3)	6.6
Muscle spasms	17 (7.7)	1 (0.5)	3 (1.4)	0	6.3
Blood creatinine increased	18 (8.1)	5 (2.3)	4 (1.9)	1 (0.5)	6.2
Skin papilloma	0	0	11 (5.1)	0	-5.1
Myalgia	18 (8.1)	0	29 (13.4)	1 (0.5)	-5.3
Insomnia	11 (5.0)	0	24 (11.1)	0	-6.1
Skin hyperpigmentation	1 (0.5)	0	16 (7.4)	0	-6.9
Infusion related reaction	5 (2.3)	1 (0.5)	20 (9.3)	2 (0.9)	-7.0
Skin lesion	1 (0.5)	0	17 (7.9)	0	-7.4
Arthralgia	23 (10.4)	0	41 (19.0)	2 (0.9)	-8.6
Musculoskeletal pain	6 (2.7)	0	27 (12.5)	0	-9.8
Headache	16 (7.2)	0	42 (19.4)	0	-12.2
Melanocytic naevus	1 (0.5)	0	31 (14.4)	0	-13.9

Source: **ARRAY-818-302 CSR Table 14.3.1-1.3.1**
BINI: binimetinib; CETUX: cetuximab; CK: creatine phosphokinase; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; ENCO: encorafenib; PPE: palmar-plantar erythrodysaesthesia.
Grades are based on CTCAE version 4.03.
[a] From MedDRA version 21.0
Preferred terms are presented by descending order of difference in percent incidence between the Randomised Phase 3 ENCO+BINI+CETUX and the ENCO+ CETUX all-grades column.

Serious AEs

The most frequently reported SAEs (>2.0% patients) in the Triplet arm were diarrhoea and pulmonary embolism (3.6% each), acute kidney injury and nausea (3.2% each), intestinal obstruction (2.7%) and ileus (2.3%); in the Doublet arm they were intestinal obstruction (4.6%) and urinary tract infection and cancer pain (2.3%).

For patients with at least one event, the estimated median time to onset of the first SAE was 1.51 months (95% CI: 1.15, 2.10) in the Triplet arm and 1.45 months (95% CI: 0.89, 1.81) in the Doublet arm.

Comparison of individual adverse drug reactions

Musculoskeletal and Connective Tissue Disorders

Table S13a: Summary of Musculoskeletal and Connective Tissue Disorders Adverse Reactions and Associated Preferred Terms in the Triplet°P Population of ARRAY-818-302

	Pooled ENCO+BINI+CETUX (N=259)						
	Any Grade n (%)	Grade ≥3 n (%)				Outcome	
Adverse Drug Reaction			Discontin.	Red/Int	Additional therapy	Rec/Res	Not Rec/Res
Arthralgia/Musculoskeletal pain	39 (15.1)	0 (0.0)	0 (0.0)	5 (1.9)	16 (16.2)	25 (9.7)	9 (3.5)
Back pain	33 (12.7)	3 (1.2)	1 (0.4)	1 (0.4)	23 (8.9)	16 (6.2)	15 (5.8)
Myopathy/Muscular disorders	24 (9.3)	1 (0.4)	0 (0.0)	2 (0.8)	8 (3.1)	15 (5.8)	8 (3.1)
Pain in extremity	18 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.5)	8 (3.1)	8 (3.1)
Rhabdomyolysis	1 (0.4)	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.4)	0 (0.0)

Source: ISS_CRC_add Table 1.1, ISS_CRC_add Table 3.1, ISS_CRC_add Table 4.1 ISS_CRC_add Table 5.1
BINI: binimetinib; CETUX: cetuximab; CTCAE: Common Terminology Criteria for Adverse Events; Discontin: Discontinuation; ENCO: encorafenib; Rec/Res: Recovered/Resolved; Red/Int: Reduction/Interruption.
Grades are based on CTCAE version 4.03.

Table S13b: Summary of Musculoskeletal and Connective Tissue Disorders Adverse Reactions and Associated Preferred Terms in the Doublet Arm of ARRAY-818-302

	ENCO+CETUX (N=216)						
	Any Grade n (%)	Grade ≥3 n (%)				Outcome	
Adverse Drug Reaction			Discontin.	Red/Int	Additional therapy	Rec/Res	Not Rec/Res
Arthralgia/Musculoskeletal pain	59 (27.3)	2 (0.9)	0 (0.0)	7 (3.2)	33 (15.3)	29 (13.4)	25 (11.6)
Back pain	22 (10.2)	2 (0.9)	0 (0.0)	0 (0.0)	15 (6.9)	7 (3.2)	13 (6.0)
Myopathy/Muscular disorders	4 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	3 (1.4)	1 (0.5)
Pain in extremity	22 (10.2)	0 (0.0)	0 (0.0)	2 (0.9)	11 (5.1)	14 (6.5)	8 (3.7)

Source: ISS_CRC_add Table 1.2, ISS_CRC_add Table 3.2 ISS_CRC_add Table 4.2, ISS_CRC_add Table 5.2
CETUX: cetuximab; CTCAE: Common Terminology Criteria for Adverse Events; Discontin: Discontinuation; ENCO: encorafenib; Rec/Res: Recovered/Resolved; Red/Int: Reduction/Interruption.
Grades are based on CTCAE version 4.03.

Nervous System Disorders

Table S14a Summary of Nervous System Disorders Adverse Reactions and Associated Preferred Terms in the Triplet°P Population of ARRAY-818-302

	Pooled ENCO+BINI+CETUX (N=259)						
	Any Grade n (%)	Grade ≥3 n (%)				Outcome	
Adverse Drug Reaction			Discontin.	Red/Int	Additional therapy	Rec/Res	Not Rec/Res
Dizziness	23 (8.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	17 (6.6)	6 (2.3)
Dysgeusia	17 (6.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (3.5)	7 (2.7)
Headache	22 (8.5)	1 (0.4)	0 (0.0)	1 (0.4)	6 (2.3)	18 (6.9)	3 (1.2)
Peripheral neuropathy	42 (16.2)	3 (1.2)	1 (0.4)	2 (0.8)	6 (2.3)	15 (5.8)	25 (9.7)

Source: ISS_CRC_add Table 1.1, ISS_CRC_add Table 3.1, ISS_CRC_add Table 4.1 ISS_CRC_add Table 5.1.
BINI: binimetinib; CETUX: cetuximab; CTCAE: Common Terminology Criteria for Adverse Events; Discontin: Discontinuation; ENCO: encorafenib; Rec/Res: Recovered/Resolved; Red/Int: Reduction/Interruption.
Grades are based on CTCAE version 4.03.

Table S14b Summary of Nervous System Disorders Adverse Reactions and Associated Preferred Terms in the Doublet Population of ARRAY-818-302

Adverse Drug Reaction	ENCO+CETUX (N=216)						
	Any Grade n (%)	Grade ≥3 n (%)	Discontin.	Red/Int	Additional therapy	Outcome	
						Rec/Res	Not Rec/Res
Dizziness	18 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)	11 (5.1)	7 (3.2)
Dysgeusia	9 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.9)	3 (1.4)	6 (2.8)
Headache	43 (19.9)	0 (0.0)	0 (0.0)	1 (0.5)	21 (9.7)	35 (16.2)	6 (2.8)
Peripheral neuropathy	26 (12.0)	3 (1.4)	1 (0.5)	6 (2.8)	7 (3.2)	11 (5.1)	13 (6.0)

Source: ISS_CRC_add Table 1.2, ISS_CRC_add Table 3.2 ISS_CRC_add Table 4.2, ISS_CRC_add Table 5.2
CETUX: cetuximab; CTCAE: Common Terminology Criteria for Adverse Events; Discontin: Discontinuation; ENCO: encorafenib; Rec/Res: Recovered/Resolved; Red/Int: Reduction/Interruption.
Grades are based on CTCAE version 4.03.

Skin and Subcutaneous Tissue Disorders

Table S15a Summary of Skin and Subcutaneous Tissue Disorders Adverse Reactions and Associated Preferred Terms in the Triplet°P Population of ARRAY-818-302

Adverse Drug Reaction	Pooled ENCO+BINI+CETUX (N=259)						
	Any Grade n (%)	Grade ≥3 n (%)	Discontin.	Red/Int	Additional therapy	Outcome	
						Rec/Res	Not Rec/Res
Acneiform dermatitis	150 (57.9)	9 (3.5)	1 (0.4)	14 (5.4)	128 (49.4)	83 (32.0)	50 (19.3)
Alopecia	5 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.8)	2 (0.8)
Dry skin	80 (30.9)	3 (1.2)	0 (0.0)	1 (0.4)	41 (15.8)	36 (13.9)	36 (13.9)
Erythema	10 (3.9)	1 (0.4)	0 (0.0)	2 (0.8)	4 (1.5)	8 (3.1)	2 (0.8)
Hyperkeratosis	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
PPES	34 (13.1)	0 (0.0)	0 (0.0)	2 (0.8)	10 (3.9)	23 (8.9)	8 (3.1)
Panniculitis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)
Pruritus	38 (14.7)	1 (0.4)	0 (0.0)	2 (0.8)	18 (6.9)	25 (9.7)	7 (2.7)
Rash	81 (31.3)	2 (0.8)	0 (0.0)	7 (2.7)	57 (22.0)	48 (18.5)	24 (9.3)
Skin exfoliation	7 (2.7)	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.2)	6 (2.3)	1 (0.4)

Source: ISS_CRC_add Table 1.1, ISS_CRC_add Table 4.1, ISS_CRC_add Table 3.1
BINI: binimetinib; CETUX: cetuximab; CTCAE: Common Terminology Criteria for Adverse Events; Discontin: Discontinuation; ENCO: encorafenib; PPES: Palmar-plantar erythrodysaethesia syndrome Rec/Res: Recovered/Resolved; Red/Int: Reduction/Interruption.
Grades are based on CTCAE version 4.03.

Table S15b Summary of Skin and Subcutaneous Tissue Disorders Adverse Reactions and Associated Preferred Terms in the Doublet Arm of ARRAY-818-302

Adverse Drug Reaction	ENCO+CETUX (N=216)						
	Any Grade n (%)	Grade ≥3 n (%)	Discontin.	Red/Int	Additional therapy	Outcome	
						Rec/Res	Not Rec/Res
Acneiform dermatitis	69 (31.9)	2 (0.9)	0 (0.0)	3 (1.4)	41 (19.0)	38 (17.6)	23 (10.6)
Alopecia	8 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	6 (2.8)
Dry skin	29 (13.4)	0 (0.0)	0 (0.0)	0 (0.0)	10 (4.6)	11 (5.1)	13 (6.0)
Erythema	10 (4.6)	1 (0.5)	0 (0.0)	1 (0.5)	4 (1.9)	6 (2.8)	3 (1.4)
Hyperkeratosis	8 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.9)	2 (0.9)	2 (0.9)
Palmar-plantar erythrodysaethesia syndrome	9 (4.2)	1 (0.5)	0 (0.0)	0 (0.0)	2 (0.9)	4 (1.9)	2 (0.9)
Pruritus	31 (14.4)	0 (0.0)	0 (0.0)	2 (0.9)	15 (6.9)	19 (8.8)	10 (4.6)
Rash	56 (25.9)	0 (0.0)	0 (0.0)	1 (0.5)	26 (12.0)	31 (14.4)	18 (8.3)
Skin exfoliation	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Skin hyperpigmentation	16 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	3 (1.4)	10 (4.6)

Source: ISS_CRC_add Table 1.2, ISS_CRC_add Table 3.2 ISS_CRC_add Table 4.2, ISS_CRC_add Table 5.2
CETUX: cetuximab; CTCAE: Common Terminology Criteria for Adverse Events; Discontin: Discontinuation; ENCO: encorafenib; Rec/Res: Recovered/Resolved; Red/Int: Reduction/Interruption.
Grades are based on CTCAE version 4.03.

Gastrointestinal disorder

Table S16a: Summary of Gastrointestinal Disorders Adverse Reactions and Associated Preferred Terms in the Triplet°P Population of ARRAY-818-302

Adverse Drug Reaction	Pooled ENCO+BINI+CETUX (N=259)						
	Any Grade n (%)	Grade ≥3 n (%)	Discontin.	Red/Int	Additional therapy	Outcome	
						Rec/Res	Not Rec/Res
Abdominal pain	103 (39.8)	16 (6.2)	1 (0.4)	5 (1.9)	60 (23.2)	68 (26.3)	25 (9.7)
Colitis	5 (1.9)	2 (0.8)	0 (0.0)	4 (1.5)	4 (1.5)	5 (1.9)	0 (0.0)
Constipation	69 (26.6)	0 (0.0)	0 (0.0)	1 (0.4)	40 (15.4)	50 (19.3)	16 (6.2)
Diarrhoea	165 (63.7)	24 (9.3)	4 (1.5)	51 (19.7)	100 (38.6)	139 (53.7)	23 (8.9)
Nausea	122 (47.1)	12 (4.6)	4 (1.5)	23 (8.9)	82 (31.7)	94 (36.3)	24 (9.3)
Pancreatitis	3 (1.2)	2 (0.8)	0 (0.0)	1 (0.4)	2 (0.8)	1 (0.4)	1 (0.4)
Vomiting	103 (39.8)	11 (4.2)	1 (0.4)	23 (8.9)	43 (16.6)	90 (34.7)	12 (4.6)

Source: ISS_CRC_add Table 1.1, ISS_CRC_add Table 3.1, ISS_CRC_add Table 4.1, ISS_CRC_add Table 5.1
BINI: binimetinib; CETUX: cetuximab; CTCAE: Common Terminology Criteria for Adverse Events; Discontin: Discontinuation; ENCO: encorafenib; Rec/Res: Recovered/Resolved; Red/Int: Reduction/Interruption.
Grades are based on CTCAE version 4.03.

Table S16b: Summary of Gastrointestinal Disorders Adverse Reactions and Associated Preferred Terms in the Doublet Arm of ARRAY-818-302

Adverse Drug Reaction	ENCO+CETUX (N=216)						
	Any Grade n (%)	Grade ≥3 n (%)	Discontin.	Red/Int	Additional therapy	Outcome	
						Rec/Res	Not Rec/Res
Abdominal pain	64 (29.6)	9 (4.2)	1 (0.5)	0 (0.0)	43 (19.9)	42 (19.4)	17 (7.9)
Constipation	33 (15.3)	0 (0.0)	0 (0.0)	0 (0.0)	21 (19.7)	20 (9.3)	11 (5.1)
Diarrhoea	72 (33.3)	4 (1.9)	1 (0.5)	6 (2.8)	30 (13.9)	64 (29.6)	7 (3.2)
Nausea	74 (34.3)	1 (0.5)	0 (0.0)	9 (4.2)	43 (19.9)	52 (24.1)	18 (8.3)
Pancreatitis	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Vomiting	46 (21.3)	3 (1.4)	0 (0.0)	9 (4.2)	26 (12.0)	39 (18.1)	6 (2.8)

Source: ISS_CRC_add Table 1.2, ISS_CRC_add Table 3.2 ISS_CRC_add Table 4.2, ISS_CRC_add Table 5.2
CETUX: cetuximab; CTCAE: Common Terminology Criteria for Adverse Events; Discontin: Discontinuation; ENCO: encorafenib; Rec/Res: Recovered/Resolved; Red/Int: Reduction/Interruption.
Grades are based on CTCAE version 4.03.

Investigations

Table S17a: Summary of Investigations Adverse Reactions and Associated Preferred Terms in the Triplet°P Population of ARRAY-818-302

Adverse Drug Reaction	Pooled ENCO+BINI+CETUX (N=259)						
	Any Grade n (%)	Grade ≥3 n (%)	Discontin.	Red/Int	Additional therapy	Outcome	
						Rec/Res	Not Rec/Res
Blood alkaline phosphatase increased	5 (1.9)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)	1 (0.4)
Blood creatine phosphokinase increased	33 (12.7)	11 (4.2)	1 (0.4)	9 (3.5)	2 (0.8)	30 (11.6)	3 (1.2)
Blood creatinine increased	29 (11.2)	7 (2.7)	4 (1.5)	18 (6.9)	5 (1.9)	20 (7.7)	8 (3.1)
Hypoalbuminaemia	21 (8.1)	5 (1.9)	0 (0.0)	0 (0.0)	7 (2.7)	14 (5.4)	5 (1.9)
Transaminases increased	30 (11.6)	6 (2.3)	1 (0.4)	5 (1.9)	3 (1.2)	25 (9.7)	5 (1.9)

Source: ISS_CRC_add Table 1.1; ISS_CRC_add Table 17.1; ISS_CRC_add Table 5.1; ISS_CRC_add Table 15.1; ISS_CRC_add Table 3.1
BINI: binimetinib; CETUX: cetuximab; CTCAE: Common Terminology Criteria for Adverse Events; Discontin: Discontinuation; ENCO: encorafenib; Rec/Res: Recovered/Resolved; Red/Int: Reduction/Interruption.
Grades are based on CTCAE version 4.03.

Table S17b: Summary of Investigations Adverse Reactions and Associated Preferred Terms in the Doublet Population of ARRAY-818-302

Adverse Drug Reaction	ENCO+CETUX (N=216)						
	Any Grade n (%)	Grade ≥3 n (%)	Discontin.	Red/Int	Additional therapy	Outcome	
						Rec/Res	Not Rec/Res
Amylase increased	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Blood creatinine increased	5 (2.3)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.9)	2 (0.9)
Lipase increased	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)
Transaminases increased	18 (8.3)	2 (0.9)	2 (0.9)	2 (0.9)	2 (0.9)	10 (4.6)	6 (2.8)

Source: ISS_CRC_add Table 1.2, ISS_CRC_add Table 3.2 ISS_CRC_add Table 4.2, ISS_CRC_add Table 5.2
CETUX: cetuximab; CTCAE: Common Terminology Criteria for Adverse Events; Discontin: Discontinuation; ENCO: encorafenib; Rec/Res: Recovered/Resolved; Red/Int: Reduction/Interruption.
Grades are based on CTCAE version 4.03.

Contribution of Cetuximab to the safety and tolerability of the doublet and the triplet

The contribution of Cetuximab to the safety and tolerability profile of the doublet and the triplet was assessed by comparing the Triplet population of the pivotal study with the Combo 300 Population of part 2 of the COLUMBUS trial (CMEK162B2301) as well as by comparing the doublet population of the pivotal trial with the known ENCO 300 mono population (please be referred to the initial MAA):

Table S18 shows a comparison of the overall AE profile for the above-mentioned population, Table S19 presents the comparison of individual adverse events by PT.

Table S18: Overall AE profile for the Triplet°P /Doublet population of Study ARRAY-818-302 and the Combo 300 arm of study CMEK162B2301 respectively the Enco 300 mono population

		ARRAY-818-302 Triplet°Pooled	CMEK162B2301 Combo 300 Part 2	ARRAY-818-302 Phase 3 Doublet	BRAF Melanoma Enco 300P
		ENCO+ BINI+ CETUX (N=259)	ENCO+ BINI (N=257)	ENCO+ CETUX (N=216)	ENCO (N=217)
On-treatment deaths [a]	All Grades	28 (10.8)	25 (9.7)	31 (14.4)	16 (7.4)
AE	All Grades	254 (98.1)	252 (98.1)	212 (98.1)	216 (99.5)
	Grade 3-4	152 (58.7)	120 (46.7)	106 (49.1)	147 (67.7)
Related AE	All Grades	244 (94.2)	221 (86.0)	191 (88.4)	216 (99.5)
	Grade 3-4	90 (34.7)	64 (24.9)	42 (19.4)	110 (50.7)
SAE	All Grades	115 (44.4)	75 (29.2)	71 (32.9)	71 (32.7)
	Grade 3-4	95 (36.7)	65 (25.3)	59 (27.3)	60 (27.6)
Related SAE	All Grades	46 (17.8)	21 (8.2)	20 (9.3)	34 (15.7)
	Grade 3-4	32 (12.4)	18 (7.0)	13 (6.0)	25 (11.5)
AE leading to treatment discontinuation	All Grades	41 (15.8)	32 (12.5)	25 (11.6)	40 (18.4)
	Grade 3-4	21 (8.1)	23 (8.9)	18 (8.3)	29 (13.4)
AE requiring additional therapy [b]	All Grades	246 (95.0)	211 (82.1)	200 (92.6)	206 (94.9)
	Grade 3-4	130 (50.2)	77 (30.0)	89 (41.2)	120 (55.3)

AE requiring dose adjustment [c]	All Grades	32 (12.4)	31 (12.1)	13 (6.0)	60 (27.6)
	Grade 3-4	5 (1.9)	9 (3.5)	2 (0.9)	20 (9.2)

Source ISS_CRC_add Table 14.3.1-1.1.1;

Abbreviations: AE = adverse event, Combo = encorafenib plus binimetinib; SAE = serious adverse event.

Categories are mutually exclusive. Patients with events in more than 1 category are counted once in each of those categories.

[a] Deaths occuring > 30 days after end of treatment are not included.

[b] Additionnal therapy includes all non drug therapies and concomitant medications.

In the summaries of AEs for CMEK162B2301 Part 2, the 'All Grades' row includes 1 patient with Grade 5 events

[c] Dose adjustment according to worst action taken

Table S19: Adverse Events, regardless of Study Drug Relationship, by PT - Overall and Maximum Grade 3-4 (All Grades difference >10% or Grade >3 difference >2% between Triplet°P and COMBO 300 respectively Doublet and ENCO 300 mono)

Preferred Term[a]	Grades	ARRAY-818-302 Triplet°Pooled ENCO+ BINI+ CETUX (N=259) (4.14 months[b])	CMEK162B2301 Combo 300 Part 2 ENCO+ BINI (N=257) (11.99 months[b])	ARRAY-818-302 Phase 3 Doublet ENCO+ CETUX (N=216) (3.22 months[b])	BRAF Melanoma Enco 300P ENCO (N=217) (6.83 months[b])
Any Adverse Event	All Grades	254 (98.1)	252 (98.1)	212 (98.1)	216 (99.5)
	Grade 3-4	152 (58.7)	120 (46.7)	106 (49.1)	147 (67.7)
Diarrhoea	All Grades	165 (63.7)	73 (28.4)	72 (33.3)	27 (12.4)
	Grade 3-4	24 (9.3)	4 (1.6)	4 (1.9)	3 (1.4)
Dermatitis acneiform	All Grades	133 (51.4)	4 (1.6)	63 (29.2)	9 (4.1)
	Grade 3-4	5 (1.9)	0	1 (0.5)	0
Nausea	All Grades	122 (47.1)	70 (27.2)	74 (34.3)	82 (37.8)
	Grade 3-4	12 (4.6)	4 (1.6)	1 (0.5)	8 (3.7)
Vomiting	All Grades	103 (39.8)	39 (15.2)	46 (21.3)	60 (27.6)
	Grade 3-4	11 (4.2)	1 (0.4)	3 (1.4)	9 (4.1)
Anaemia	All Grades	96 (37.1)	24 (9.3)	35 (16.2)	16 (7.4)
	Grade 3-4	42 (16.2)	7 (2.7)	10 (4.6)	5 (2.3)
Fatigue	All Grades	93 (35.9)	57 (22.2)	65 (30.1)	60 (27.6)
	Grade 3-4	9 (3.5)	2 (0.8)	9 (4.2)	4 (1.8)
Abdominal pain	All Grades	79 (30.5)	27 (10.5)	49 (22.7)	13 (6.0)
	Grade 3-4	14 (5.4)	3 (1.2)	5 (2.3)	4 (1.8)
Decreased appetite	All Grades	77 (29.7)	24 (9.3)	58 (26.9)	48 (22.1)
	Grade 3-4	6 (2.3)	1 (0.4)	3 (1.4)	1 (0.5)
Dry skin	All Grades	65 (25.1)	21 (8.2)	24 (11.1)	68 (31.3)
	Grade 3-4	2 (0.8)	0	0	0
Rash	All Grades	45 (17.4)	18 (7.0)	25 (11.6)	46 (21.2)
	Grade 3-4	2 (0.8)	2 (0.8)	0	4 (1.8)
Stomatitis	All Grades	37 (14.3)	6 (2.3)	12 (5.6)	15 (6.9)
	Grade 3-4	1 (0.4)	0	0	1 (0.5)
Blood creatinine increased	All Grades	29 (11.2)	8 (3.1)	4 (1.9)	5 (2.3)
	Grade 3-4	7 (2.7)	1 (0.4)	1 (0.5)	0

Preferred Term[a]	Grades	ARRAY-818-302 Triplet°Pooled ENCO+ BINI+ CETUX (N=259) (4.14 months[b])	CMEK162B2301 Combo 300 Part 2 ENCO+ BINI (N=257) (11.99 months[b])	ARRAY-818-302 Phase 3 Doublet ENCO+ CETUX (N=216) (3.22 months[b])	BRAF Melanoma Enco 300P ENCO (N=217) (6.83 months[b])
Alanine aminotransferase increased	All Grades	21 (8.1)	29 (11.3)	12 (5.6)	11 (5.1)
	Grade 3-4	4 (1.5)	12 (4.7)	0	2 (0.9)
Aspartate aminotransferase increased	All Grades	20 (7.7)	21 (8.2)	8 (3.7)	8 (3.7)
	Grade 3-4	5 (1.9)	11 (4.3)	1 (0.5)	1 (0.5)
Hypokalaemia	All Grades	18 (6.9)	1 (0.4)	13 (6.0)	5 (2.3)
	Grade 3-4	6 (2.3)	0	2 (0.9)	2 (0.9)
Acute kidney injury	All Grades	12 (4.6)	2 (0.8)	4 (1.9)	3 (1.4)
	Grade 3-4	7 (2.7)	0	4 (1.9)	1 (0.5)
Pulmonary embolism	All Grades	12 (4.6)	3 (1.2)	3 (1.4)	1 (0.5)
	Grade 3-4	10 (3.9)	3 (1.2)	3 (1.4)	1 (0.5)
Alopecia	All Grades	5 (1.9)	33 (12.8)	8 (3.7)	123 (56.7)
	Grade 3-4	0	0	0	0
Gamma-glutamyltransferase increased	All Grades	3 (1.2)	36 (14.0)	3 (1.4)	25 (11.5)
	Grade 3-4	1 (0.4)	12 (4.7)	3 (1.4)	11 (5.1)

Source: **ISS_CRC_add Table 14.3.1-1.92; ISS_CRC_add Table 14.3.1-1.93**

BINI: binimetinib; CETUX: cetuximab; CSLI: combined safety lead in; CSR: clinical study report; ENCO: encorafenib; MedDRA: Medical Dictionary for Regulatory Activities.

[a] MedDRA version 21.0 has been used for the reporting of adverse events in Study ARRAY-818-302 and version 19.0 in Study CMEK162B2301

[b] Median duration of exposure.

Duration of exposure ([Date of last (non-zero) dose of study drug] – [date of first dose of study drug] + 1)

Terms are sorted in descending frequency of 'All grades' ARRAY-818-302 Triplet°Pooled column.

Serious adverse event and deaths

Serious adverse events

Table S20: Serious Adverse Events, Regardless of Study Drug Relationship, by Preferred Term and Treatment – Overall and Grade ≥3 (≥1% in the Triplet°P population or any Phase 3 treatment arm) (ARRAY-818-302 Safety Set)

	Randomised Phase 3 + CSLI (Pooled)		CSLI		Randomised Phase 3					
	ENCO + BINI + CETUX N = 259		ENCO + BINI + CETUX N = 37		ENCO + BINI + CETUX N = 222		ENCO + CETUX N = 216		CONTROL N = 193	
Preferred Term	All Grades n (%)	Grade 3+ n (%)	All Grades n (%)	Grade 3+ n (%)	All Grades n (%)	Grade 3+ n (%)	All Grades n (%)	Grade 3+ n (%)	All Grades n (%)	Grade 3+ n (%)
Any SAE	115 (44.4)	100 (38.6)	22 (59.5)	17 (45.9)	93 (41.9)	83 (37.4)	71 (32.9)	61 (28.2)	71 (36.8)	64 (33.2)
Diarrhoea	9 (3.5)	7 (2.7)	1 (2.7)	0 (0.0)	8 (3.6)	7 (3.2)	0 (0.0)	0 (0.0)	10 (5.2)	7 (3.6)
Pulmonary embolism	9 (3.5)	8 (3.1)	1 (2.7)	1 (2.7)	8 (3.6)	7 (3.2)	3 (1.4)	3 (1.4)	4 (2.1)	4 (2.1)
Acute kidney injury	7 (2.7)	5 (1.9)	0 (0.0)	0 (0.0)	7 (3.2)	5 (2.3)	4 (1.9)	4 (1.9)	1 (0.5)	1 (0.5)
Nausea	8 (3.1)	5 (1.9)	1 (2.7)	0 (0.0)	7 (3.2)	5 (2.3)	3 (1.4)	1 (0.5)	1 (0.5)	1 (0.5)
Intestinal obstruction	6 (2.3)	5 (1.9)	0 (0.0)	0 (0.0)	6 (2.7)	5 (2.3)	10 (4.6)	9 (4.2)	7 (3.6)	5 (2.6)
Ileus	5 (1.9)	4 (1.5)	0 (0.0)	0 (0.0)	5 (2.3)	4 (1.8)	3 (1.4)	3 (1.4)	2 (1.0)	2 (1.0)
Abdominal pain	4 (1.5)	4 (1.5)	0 (0.0)	0 (0.0)	4 (1.8)	4 (1.8)	3 (1.4)	3 (1.4)	4 (2.1)	3 (1.6)
Anaemia	5 (1.9)	5 (1.9)	1 (2.7)	1 (2.7)	4 (1.8)	4 (1.8)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)
Pyrexia	6 (2.3)	3 (1.2)	2 (5.4)	0 (0.0)	4 (1.8)	3 (1.4)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Bacteraemia	3 (1.2)	3 (1.2)	0 (0.0)	0 (0.0)	3 (1.4)	3 (1.4)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)
Hepatic failure	3 (1.2)	3 (1.2)	0 (0.0)	0 (0.0)	3 (1.4)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Large intestine perforation	4 (1.5)	4 (1.5)	1 (2.7)	1 (2.7)	3 (1.4)	3 (1.4)	2 (0.9)	2 (0.9)	2 (1.0)	1 (0.5)
Rectal haemorrhage	4 (1.5)	2 (0.8)	1 (2.7)	0 (0.0)	3 (1.4)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	4 (1.5)	4 (1.5)	1 (2.7)	1 (2.7)	3 (1.4)	3 (1.4)	3 (1.4)	3 (1.4)	2 (1.0)	2 (1.0)
Small intestinal obstruction	3 (1.2)	3 (1.2)	0 (0.0)	0 (0.0)	3 (1.4)	3 (1.4)	2 (0.9)	2 (0.9)	4 (2.1)	4 (2.1)
Vomiting	5 (1.9)	3 (1.2)	2 (5.4)	0 (0.0)	3 (1.4)	3 (1.4)	2 (0.9)	0 (0.0)	3 (1.6)	3 (1.6)
Bile duct obstruction	2 (0.8)	2 (0.8)	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.9)	3 (1.4)	3 (1.4)	2 (1.0)	2 (1.0)
Urinary tract infection	6 (2.3)	5 (1.9)	4 (10.8)	3 (8.1)	2 (0.9)	2 (0.9)	5 (2.3)	5 (2.3)	1 (0.5)	1 (0.5)
Cancer pain	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	5 (2.3)	4 (1.9)	1 (0.5)	1 (0.5)
Large intestinal obstruction	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	3 (1.4)	3 (1.4)	0 (0.0)	0 (0.0)
Respiratory failure	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	3 (1.6)	2 (1.0)
Subileus	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	3 (1.6)	3 (1.6)
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)	1 (0.5)	0 (0.0)	0 (0.0)
Febrile neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.6)	5 (2.6)
Infusion-related reaction	3 (1.2)	1 (0.4)	3 (8.1)	1 (2.7)	0 (0.0)	0 (0.0)	3 (1.4)	2 (0.9)	2 (1.0)	1 (0.5)

Abbreviations: BINI = binimetinib; CETUX = cetuximab; CSLI = Combined Safety Lead-in; ENCO = encorafenib; SAE = serious adverse event
Preferred terms are presented in descending order of frequency in the Randomised Phase 3 ENCO+BINI+CETUX all-grades column.
Source: **ARRAY-818-302 CSR Table 14.3.1-1.8.1**

Death

Table S21: Deaths Occurring On-study or Within 30 Days of End of Treatment by System Organ Class and Preferred Term (ARRAY-818-302 Safety Set)

	Randomized Phase 3 + CSLI (Pooled)	CSLI	Randomized Phase 3		
Primary SOC Preferred term	ENCO+BINI + CETUX N = 259	ENCO+BINI + CETUX N = 37	ENCO+BINI + CETUX N = 222	ENCO + CETUX N = 216	CONTROL N = 193
Number of patients with on-treatment death	28 (10.8)	5 (13.5)	23 (10.4)	32 (14.8)	26 (13.5)
General disorders and administration site conditions	16 (6.2)	4 (10.8)	12 (5.4)	20 (9.3)	15 (7.8)
Disease progression	14 (5.4)	4 (10.8)	10 (4.5)	20 (9.3)	15 (7.8)
Death	2 (0.8)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	4 (1.5)	0 (0.0)	4 (1.8)	2 (0.9)	1 (0.5)
Gastrointestinal perforation	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Ileus	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Intestinal obstruction	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Large intestine perforation	1 (0.4)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)
Gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Subileus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.9)	1 (2.7)	4 (1.8)	6 (2.8)	3 (1.6)
Colorectal cancer metastatic	2 (0.8)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)
Malignant neoplasm progression	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Neoplasm progression	1 (0.4)	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)
Colon cancer	1 (0.4)	1 (2.7)	0 (0.0)	2 (0.9)	0 (0.0)
Colon cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.5)
Colorectal cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)
Hepatobiliary disorders	2 (0.8)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)
Hepatic failure	2 (0.8)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)
Cardiac disorders	1 (0.4)	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)
Cardiac arrest	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Cardio-respiratory arrest	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)
Immune system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Anaphylactic reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	2 (1.0)
Peritonitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Cerebral ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	2 (1.0)
Aspiration	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)
Respiratory distress	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)

Abbreviations: incl = including; BINI = binimetinib; CETUX = cetuximab; CSLI = Combined Safety Lead-in; ENCO = encorafenib; PT = preferred term; SOC = system organ class

System organ classes and PTs within an SOC are sorted in descending frequency in the Randomized Phase 3 ENCO+BINI+CETUX column.

Deaths during treatment or within 30 days of last study treatment are included.

Source: **ARRAY-818-302 CSR Table 14.3.1-1.40**

The AEs that resulted in death were:

Triplet arm: hepatic failure (three patients [1.4%]), gastrointestinal perforation, ileus, intestinal obstruction, large intestinal perforation, cardiac arrest and death (one patient [0.5%] each).

Doublet arm: aspiration (two patients [0.9%]), intestinal obstruction, large intestine perforation, gastrointestinal haemorrhage, cardio-respiratory arrest and sepsis (one patient [0.5%] each]

Control arm: subileus, cardio-respiratory arrest, anaphylactic reaction, lung infection, peritonitis, pneumocystis jirovecii pneumonia, cerebral ischaemia and respiratory failure (one patient [0.5%] each).

A clinical review of the 23 on-treatment deaths that were considered due to events other than disease progression in Phase 3 showed that 15 of these patients (7 Triplet arm, 5 Doublet arm, 3 Control Arm) also had evidence of disease progression.

Laboratory findings

Haematology

Table 22a presents a summary of newly occurring or worsening abnormal haematology and coagulation laboratory values based on CTCAE grade (overall and maximum Grade >3) reported for >1.0% of patients in any Phase 3 treatment arm.

Table 22a: Newly Occurring or Worsening Haematology and Coagulation Laboratory Abnormalities– Overall and Maximum Grade > 3 (>1.0% in Any Phase 3 Treatment Arm; ARRAY-818-302 Safety Set)

	Triplet*P		CSLI		Randomised Phase 3					
	ENCO + BINI+ CETUX N=259		ENCO + BINI+ CETUX N=37		ENCO + BINI+ CETUX N=222		ENCO+ CETUX N=216		CONTROL N=193	
Laboratory Parameter	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Activated Partial Thromboplastin Time (sec), Hyper	46 (17.8)	5 (1.9)	9 (24.3)	1 (2.7)	37 (16.7)	4 (1.8)	26 (12.0)	2 (0.9)	13 (6.7)	1 (0.5)
Haemoglobin (g/L), Hypo	145 (56.0)	24 (9.3)	23 (62.2)	2 (5.4)	122 (55.0)	22 (9.9)	69 (31.9)	10 (4.6)	84 (43.5)	8 (4.1)
Haemoglobin (g/L), Hyper	2 (0.8)	1 (0.4)	1 (2.7)	1 (2.7)	1 (0.5)	0	5 (2.3)	1 (0.5)	1 (0.5)	1 (0.5)
Lymphocytes (10^9/L), Hypo	32 (12.4)	10 (3.9)	7 (18.9)	4 (10.8)	25 (11.3)	6 (2.7)	50 (23.1)	14 (6.5)	59 (30.6)	9 (4.7)
Lymphocytes (10^9/L), Hyper	12 (4.6)	0	1 (2.7)	0	11 (5.0)	0	2 (0.9)	0	3 (1.6)	0
Neutrophils (10^9/L), Hypo	18 (6.9)	1 (0.4)	3 (8.1)	0	15 (6.8)	1 (0.5)	12 (5.6)	1 (0.5)	80 (41.5)	28 (14.5)
Platelets (10^9/L), Hypo	13 (5.0)	0	2 (5.4)	0	11 (5.0)	0	16 (7.4)	2 (0.9)	13 (6.7)	2 (1.0)
Leukocytes (10^9/L), Hypo	13 (5.0)	0	3 (8.1)	0	10 (4.5)	0	17 (7.9)	3 (1.4)	82 (42.5)	17 (8.8)

Source: **ARRAY-818-302 CSR Table 14.3-4.2**
BINI: binimetinib; CETUX: cetuximab; CSLI: combined safety lead in; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; ENCO: encorafenib.
Presented values represent new or worsening post-baseline abnormalities per National Cancer Institute CTCAE v4.03.
Triplet*P: Randomised Phase 3 and CSLI (Pooled)

Chemistry

Table S22b presents a summary of newly occurring or worsening abnormal serum chemistry laboratory values based on CTCAE grade (overall and maximum Grade >3) reported for >5.0% of patients in the pivotal study.

Table S22b: Newly Occurring or Worsening Serum Chemistry Laboratory Abnormalities – Overall and Maximum Grade ⩾3 (Overall incidence ⩾5%)

	Randomised Phase 3 + CSLI (Pooled)		CSLI		Randomised Phase 3					
	ENCO + BINI + CETUX N = 259		ENCO + BINI + CETUX N = 37		ENCO + BINI + CETUX N = 222		ENCO + CETUX N = 216		CONTROL N = 193	
Laboratory Parameter	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Albumin (g/L), Hypo	110 (42.5)	5 (1.9)	22 (59.5)	2 (5.4)	88 (39.6)	3 (1.4)	35 (16.2)	0	45 (23.3)	0
ALP (IU/L), Hyper	61 (23.6)	9 (3.5)	12 (32.4)	3 (8.1)	49 (22.1)	6 (2.7)	37 (17.1)	9 (4.2)	51 (26.4)	12 (6.2)
ALT (IU/L), Hyper	66 (25.5)	7 (2.7)	15 (40.5)	3 (8.1)	51 (23.0)	4 (1.8)	36 (16.7)	0	50 (25.9)	5 (2.6)
AST (IU/L), Hyper	67 (25.9)	8 (3.1)	17 (45.9)	4 (10.8)	50 (22.5)	4 (1.8)	31 (14.4)	3 (1.4)	38 (19.7)	3 (1.6)
Bilirubin (umol/L), Hyper	17 (6.6)	7 (2.7)	5 (13.5)	2 (5.4)	12 (5.4)	5 (2.3)	16 (7.4)	5 (2.3)	16 (8.3)	6 (3.1)
Calcium (mmol/L), Hypo	18 (6.9)	7 (2.7)	5 (13.5)	2 (5.4)	13 (5.9)	5 (2.3)	11 (5.1)	1 (0.5)	7 (3.6)	1 (0.5)
Calcium (mmol/L), Hyper	2 (0.8)	1 (0.4)	0	0	2 (0.9)	1 (0.5)	3 (1.4)	0	0	0
Creatine Kinase (IU/L), Hyper	69 (26.6)	9 (3.5)	17 (45.9)	3 (8.1)	52 (23.4)	6 (2.7)	6 (2.8)	0	13 (6.7)	0
Creatinine (µmol/L), Hyper	199 (76.8)	13 (5.0)	33 (89.2)	3 (8.1)	166 (74.8)	10 (4.5)	109 (50.5)	5 (2.3)	65 (33.7)	2 (1.0)
Glucose (mmol/L), Hypo	20 (7.7)	0	5 (13.5)	0	15 (6.8)	0	9 (4.2)	0	9 (4.7)	0
Glucose (mmol/L), Hyper	10 (3.9)	10 (3.9)	3 (8.1)	3 (8.1)	7 (3.2)	7 (3.2)	12 (5.6)	12 (5.6)	3 (1.6)	3 (1.6)
Potassium (mmol/L), Hypo	35 (13.5)	9 (3.5)	7 (18.9)	4 (10.8)	28 (12.6)	5 (2.3)	26 (12.0)	6 (2.8)	56 (29.0)	9 (4.7)
Potassium (mmol/L), Hyper	25 (9.7)	3 (1.2)	3 (8.1)	0	22 (9.9)	3 (1.4)	16 (7.4)	6 (2.8)	8 (4.1)	0
Magnesium (mmol/L), Hypo	43 (16.6)	3 (1.2)	12 (32.4)	0	31 (14.0)	3 (1.4)	40 (18.5)	0	38 (19.7)	1 (0.5)
Magnesium (mmol/L), Hyper	15 (5.8)	0	5 (13.5)	0	10 (4.5)	0	6 (2.8)	1 (0.5)	5 (2.6)	2 (1.0)
Sodium (mmol/L), Hypo	34 (13.1)	12 (4.6)	9 (24.3)	3 (8.1)	25 (11.3)	9 (4.1)	22 (10.2)	4 (1.9)	22 (11.4)	4 (2.1)
Sodium (mmol/L), Hyper	21 (8.1)	0	2 (5.4)	0	19 (8.6)	0	13 (6.0)	0	9 (4.7)	1 (0.5)
Troponin I (µg/L), Hyper	21 (8.1)	0	4 (10.8)	0	17 (7.7)	0	21 (9.7)	0	6 (3.1)	0
Urate (µmol/L), Hyper	6 (2.3)	1 (0.4)	2 (5.4)	0	4 (1.8)	1 (0.5)	5 (2.3)	2 (0.9)	5 (2.6)	1 (0.5)

Source: **ARRAY-818-302 CSR Table 14.3-4.6**
AE: adverse event; BINI: binimetinib; CETUX: cetuximab; CSLI: combined safety lead in; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; ENCO: encorafenib
Presented values represent new or worsening post-baseline abnormalities per National Cancer Institute CTCAE v.4.03.
Triplet°P: Randomised Phase 3 and CSLI (Pooled)

	Randomized Phase 3 + CSLI (Pooled)	CSLI	Randomized Phase 3		
Laboratory Parameter	ENCO+BINI + CETUX N = 259 n/m (%)	ENCO+BINI + CETUX N = 37 n/m (%)	ENCO+BINI + CETUX N = 222 n/m (%)	ENCO + CETUX N = 216 n/m (%)	CONTROL N = 193 n/m (%)
ALT					
> 5 × ULN	7/254 (2.8)	3/37 (8.1)	4/217 (1.8)	0/211	5/186 (2.7)
AST					
> 5 × ULN	8/254 (3.1)	4/37 (10.8)	4/217 (1.8)	3/209 (1.4)	3/186 (1.6)
Total bilirubin (TBL)					
> 2 × ULN	8/253 (3.2)	3/37 (8.1)	5/216 (2.3)	8/214 (3.7)	8/188 (4.3)
ALP					
> 3 × ULN	14/223 (6.3)	2/32 (6.3)	12/191 (6.3)	18/196 (9.2)	25/176 (14.2)
ALT or AST (AT) and TBL					
AT > 3 × ULN & TBL > 2 × ULN	3/256 (1.2)	2/37 (5.4)	1/219 (0.5)	2/215 (0.9)	4/189 (2.1)
ALP and TBL					
ALP > 3 × ULN & TBL > 2 × ULN	3/255 (1.2)	2/37 (5.4)	1/218 (0.5)	4/214 (1.9)	5/189 (2.6)
ALT or AST and TBL and ALP					
AT > 3 × ULN & TBL > 2 × ULN & ALP < 2 × ULN [a]	0/256	0/37	0/219	0/216	0/189

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AT = ALT or AST; BINI = binimetinib; CETUX = cetuximab; CSLI = Combined Safety Lead-in; ENCO = encorafenib; TBL = total bilirubin; ULN = upper limit of normal
Newly occurring = patients not meeting criterion at Baseline and meeting criterion post-Baseline.
n: number of patients who meet the criteria at least once.
m: number of patients at risk, i.e., with non-missing values at Baseline and with a Baseline value that does not already meet the abnormality.
N: Total number of patients in the treatment group in this analysis set.
[a] These parameters define the case-finding criteria for Hy's Law.
Source: Table 14.3-4.13

Safety in special populations

Subgroups for reporting adverse events

Adverse events by category are summarised and analysed by subgroups of age, race, gender, tumour resection, liver metastases and number of lines of prior therapy.

Age

Table S23: Adverse Event Overview by Age subgroup (<65 vs 65 years)

Parameter Subgroup (<65 or ≥65 years)	Randomised Phase 3 ENCO+BINI+ CETUX (N=222)	 ENCO+CETUX (N=216)	 Control (N=193)
Patients with AEs leading to Death on treatment			
<65	2 (1.4)	5 (3.7)	7 (5.5)
≥65	7 (8.5)	2 (2.4)	1 (1.5)
Patients with at least one AE regardless of causality			
<65	136 (97.1)	130 (97.0)	124 (97.6)
≥65	81 (98.8)	82 (100.0)	64 (97.0)
Patients with at least one AE with suspected any study drug relationship			
<65	131 (93.6)	123 (91.8)	116 (91.3)
≥65	77 (93.9)	68 (82.9)	60 (90.9)
Patients with at least one SAE regardless of causality			
<65	54 (38.6)	40 (29.9)	43 (33.9)
≥65	39 (47.6)	31 (37.8)	28 (42.4)
Patients with at least one treatment-related SAE			
<65	18 (12.9)	9 (6.7)	13 (10.2)
≥65	18 (22.0)	11 (13.4)	12 (18.2)
Patients with at least one AE leading to discontinuation of all study treatment regardless of causality			
<65	10 (7.1)	12 (9.0)	13 (10.2)
≥65	9 (11.0)	8 (9.8)	12 (18.2)
Patients with at least one AE requiring dose reduction of any study drug regardless of causality			
<65	31 (22.1)	14 (10.4)	39 (30.7)
≥65	37 (45.1)	8 (9.8)	19 (28.8)
Patients with at least one AE requiring dose interruption of any study drug regardless of causality			
<65	82 (58.6)	51 (38.1)	64 (50.4)
≥65	64 (78.0)	47 (57.3)	39 (59.1)
Patients with at least one AE leading to discontinuation of any study drug regardless of causality			
<65	16 (11.4)	13 (9.7)	17 (13.4)
≥65	17 (20.7)	12 (14.6)	16 (24.2)
Patients with at least one AE requiring additional therapy regardless of causality			
<65	128 (91.4)	125 (93.3)	119 (93.7)
≥65	81 (98.8)	75 (91.5)	61 (92.4)

Race

Overall, a similar percentage of patients reported an AE in each race subgroup for all treatment arms. More in-depth analysis could be compromised by the small patient numbers in some of the subgroups. Adverse events with >20% difference in incidence between Asian and Caucasian patients in the Triplet arm were nausea (22.2% vs 49.5%) and pyrexia. Based on this data and the limitations inherent to the size of the Asian population, no dose adjustment is recommended/required for patients based on race.

Gender

Incidence of AEs was similar between subgroups for all treatment arms. The 10 most frequently reported PTs were the same for both subgroups (diarrhoea, dermatitis acneiform, nausea, fatigue, vomiting, anaemia, abdominal pain, constipation, decreased appetite, asthenia) and only anaemia and decreased appetite were reported with >10% difference in incidence between the subgroups (anaemia male: 27.9% vs 43.2% female; decreased appetite male 22.1% vs 33.9% female). Incidence of Grade ≥3 AEs and AEs leading to dose reduction was higher in females compared to males for the Triplet arm. The incidence of SAEs, AEs leading to discontinuations and AEs leading to interruptions were similar between subgroups.

Tumour resection

In the Triplet arm no AEs were reported in more patients (>10.0% difference in incidence) with completely resected tumours (n=132) compared with those with partially resected or unresected tumours (n=90): Anaemia and vomiting were reported in more patients with partially resected or unresected

tumours compared with those with completely resected tumours (47.8% vs 28.0% and 44.4% vs 34.1%, respectively).

In the Doublet arm diarrhoea was the only AE reported in more patients (>10.0% difference in incidence) with completely resected tumours (n=122) compared with those with partially resected or unresected tumours (n=94) (39.3% vs 25.5%) and headache the only AE reported in more patients with partially resected or unresected tumours compared with those with completely resected tumours (25.5% vs. 14.8%).

Liver metastases

Adverse events occurred in all liver metastasis subgroups in 96.5%-100.0% of patients in all treatment arms and populations.

Dermatitis acneiform, nausea, diarrhoea, abdominal pain and fatigue were in the ten most commonly reported AEs in all subgroups. Other commonly reported AEs were: for the subgroup of no liver metastases vomiting, anaemia, asthenia, decreased appetite and constipation; for the subgroup of Liver Metastases and AST and ALT <3xULN, vomiting, anaemia, decreased appetite, constipation and dry skin and for the subgroup of Liver Metastases and AST or ALT >3xULN, abdominal pain upper, headache, myalgia, paronychia and pyrexia.

Number of lines of prior therapy

In the Triplet arm AEs reported in more patients who had received one prior line of therapy (n=145) compared with those who had received two or more prior lines of therapy (n=77) (>10.0% difference in incidence) were: nausea (49.7% vs. 36.4%), arthralgia (14.5% vs. 2.6%), pyrexia (24.1% vs. 13.0%) and fatigue (36.6% vs. 26.0%). No AEs were reported in more patients who had received two or more prior lines of therapy compared with those who had received one prior line of therapy (>10.0% difference in incidence).

In the Doublet arm AEs reported in more patients who had received one prior line of therapy (n=143) compared with those who had received two or more prior lines of therapy (n=73) (>10.0% difference in incidence) were: abdominal pain (28.7% vs. 11.0%), dermatitis acneiform (32.9% vs. 21.9%) and arthralgia (22.4% vs. 12.3%). AEs reported in more patients who had received two or more prior lines of therapy compared with those who had received one prior line of therapy were: fatigue (39.7% vs. 25.2%), anaemia (24.7% vs. 11.9%) and constipation (21.9% vs. 11.9%).

Renal impairment

Binimetinib undergoes minimal renal elimination. In the population PK performed with patients with mCRC (Report T2019-00141 and Module 2.7.2 Section 2.7.2.3.3.6), mild, moderate and severe renal impairment was assessed as a categorical covariate using creatinine clearance (CLCR) calculated with Cockcroft-Gault method for assessment. No increase in AUC is evident in the mild group (CRCL from 60 to 89 mL/min) and in the moderate (CRCL from 30 to 59 mL/min)/severe (< 30 mL/min) compared to subjects with normal renal function (≥ 90 mL/min, moderate and severe renal impairment were grouped because of low number of severe patients). These results are consistent with the previous population PK evaluations for binimetinib in monotherapy and in combination with encorafenib suggesting a minimal impact on exposure in mild and moderate renal impairment subjects that is unlikely to be clinically relevant. As specified in the initial MAA and supported by the additional results above, no dose adjustment is recommended/required for subjects with renal impairment.

Encorafenib undergoes minimal renal elimination as well. In the population PK analysis conducted in patients with mCRC (Report T2019-00141), mild (n=111) and moderate (n=30) renal impairment was assessed as a categorical covariate using creatinine clearance (CLCR) calculated with Cockcroft-Gault method for assessment. Limited increase in encorafenib AUC and Cmax were observed in patients with

mild (CRCL from 60 to 89 mL/min) and moderate (CRCL from 30 to 59 mL/min) renal impairment (maximum difference of 11 %) compared to patients with normal renal function (n=251, CRCL ≥ 90 mL/min). Consistently with the initial MAA, no dose adjustment is recommended/required for subjects with mild or moderate renal impairment based on the population PK analysis. A recommended dose has not been established for subjects with severe renal impairment. Encorafenib should be used with caution in these patients.

Hepatic impairment

No additional clinical studies evaluating the impact of hepatic impairment for encorafenib or binimetinib has been completed yet in addition to what has previously been reported in the initial MAA.

Following the request by the CHMP as a post authorisation measure related to the initial encorafenib and binimetinib MAAs, the impact of moderate and severe hepatic impairment in patients on encorafenib + binimetinib PK is planned to be evaluated in study W00090GE101 "Phase 1 study to evaluate the impact of moderate and severe hepatic impairments on the pharmacokinetics and safety of encorafenib in combination with binimetinib in adult patients with unresectable or metastatic BRAF V600-mutant melanoma", whose results are due by December 2023.

In the population PK analysis performed in patients with mCRC (Report T2019-00141), the covariate of hepatic impairment (as defined by the National Cancer Institute organ dysfunction working group classification) indicated no significant trend versus total encorafenib respectively binimetib CL/F or V/F when comparing patients with normal hepatic function with mild hepatic impairmentsubjects. Given the limited number of subjects available in the severe and moderate hepatic impairment categories (N=1 in each category), no evaluation was performed in this group.

In the mild hepatic impairment group, there was a higher percentage of patients (≥10% difference) with the following categories of events regardless of causality, compared with the normal group: Grade ≥3 AEs, SAEs (overall and Grade ≥3) and Grade ≥3 AEs requiring additional therapy. However, AEs and SAEs (overall and Grade ≥3) considered related to study drugs by the investigator were similar. There was no notable difference in the percentage of patients with AEs leading to dose interruption, reduction or discontinuation.

ADRs that were reported in a higher percentage of patients (≥5% difference) in the mild hepatic impairment group compared with the normal group overall were: abdominal pain (45.0% vs 36.4%), haemorrhage (26.3% vs 20.2%), myopathy/muscular disorders (20.0% vs 15.0%), nausea (51.3% vs 44.5%), peripheral neuropathy (20.0% vs 13.3%), peripheral oedema (17.5% vs 12.1%), retinal pigment epithelial detachment (20.0% vs 12.7%), transaminases increased (16.3% vs 8.7%), visual impairment (21.3% vs 15.0%) and vomiting (47.5% vs 36.4%).

Safety related to drug-drug interactions and other interactions

Based on comparisons to historical data, no impact on the PK of encorafenib and binimetinib have been observed when co-administering with cetuximab. Moreover, encorafenib and binimetinib do not appear to impact the PK of cetuximab. Additionally, the lack of PK interaction between binimetinib and encorafenib is confirmed.

As of this application, no new dedicated clinical pharmacology studies have been completed where data has been generated regarding drug interactions for encorafenib or binimetinib compared to what was previously reported in the initial MAA.

Discontinuation /dose reduction due to adverse events

Discontinuation

In Phase 3, the percentage of patients with an AE leading to discontinuation of any study drug of the regimen was 14.9% for the Triplet arm (binimetinib 10.8%, encorafenib 9.5% and cetuximab 11.3%), 11.6% for the Doublet arm (encorafenib 9.7% cetuximab 8.8%) and 17.1% for the Control arm (cetuximab 13.5%).

The most frequently reported AEs leading to discontinuation of any study drug (> 1.0% of patients) in the Triplet arm were diarrhoea and nausea (1.8% each); and in the Control arm they were neutropenia and small intestinal obstruction (1.6% each). In the Doublet arm, no single AE leading to discontinuation of any study drug was reported in > 2 patients.

Triplet arm vs Control arm

Incidence rates of overall and Grade >3 AEs requiring discontinuation of all study treatments were lower in the Triplet compared to the Control arm (overall: 7.2% vs 11.4%; Grade >3: 5.9% vs 9.3%). The most frequently reported AEs leading to discontinuation of all study treatments (≥ 2 patients) by PT in the Triplet arm were hepatic failure and sepsis (0.9% each); and in the Control arm were small intestinal obstruction (1.6%), and general physical health deterioration and infusion-related reaction (1.0% each).

Doublet arm vs Control arm

Incidence rates of overall and Grade >3 AEs requiring discontinuation of all study treatments were lower in the Doublet than in the Control arm (overall: 8.3% vs 11.4%; Grade >3 AEs: 7.4% vs 9.3%). The most frequently reported AEs leading to discontinuation of all study treatments (≥ 2 patients) by PT in the Doublet arm were infusion-related reaction and intestinal obstruction (0.9% each); and in the Control arm they were small intestinal obstruction (1.6%), and general physical health deterioration and infusion-related reaction (1.0% each).

Dose reduction

In randomised Phase 3 part of study Array 818-302, the percentage of patients with AEs leading to dose reduction of any study drug was 30.6% in the Triplet arm, 10.2% in the Doublet arm and 30.1% in the Control arm. The percentage of patients with Grade >3 AEs leading to dose reduction of any study drug was 13.5% in the Triplet arm, 3.7% in the Doublet arm and 15.0% in the Control arm. The percentage of patients with AEs leading to dose reduction of encorafenib was 17.6% in Triplet arm and 8.8% Doublet arm.

Triplet arm vs Control arm

Adverse events leading to dose reduction of any study drug in >2% of patients in the Triplet arm were diarrhoea (binimetinib 9.9%, encorafenib 4.5%, cetuximab 0%), nausea (binimetinib 2.3%, encorafenib 2.3%, cetuximab 0%) and fatigue (binimetinib 2.3%, encorafenib 1.8% cetuximab 0%).Adverse events leading to dose reduction in >2% of patients in the Control arm were diarrhoea, malaise, fatigue, anaemia, neutropenia, neutrophil count decreased and stomatitis. Differences of >2% between the Triplet arm and Control arms were observed for neutropenia (Triplet: 0.0%; Control: 7.8%), neutrophil count decreased (Triplet: 0.0%; Control: 4.1%) and stomatitis (Triplet: 0.0%; Control: 4.1%).

Doublet arm vs Control arm

No AEs leading to dose reduction of any study drug in >2% of patients were observed in the Doublet arm. In the Control arm, AEs leading to dose reduction in >2% of patients were diarrhoea, malaise, fatigue,

neutropenia, neutrophil count decreased and stomatitis. Differences of >2% between the Doublet arm and Control arm were observed for diarrhoea (Doublet: 0.5%; Control: 8.8%), neutropenia (Doublet: 0.0%; Control: 7.8%), neutrophil count decreased (Doublet: 0.5%; Control: 4.1%) and stomatitis (Doublet: 0.0%; Control: 4.1%). In the Doublet arm, the most frequent AEs leading to encorafenib dose reduction were peripheral neuropathy, musculoskeletal pain and asthenia (1.4% each).

Dose interruption

Triplet arm vs Control arm

In the Triplet arm, 65.8% of patients had AEs of any grade leading to dose interruption of any study drug compared with 53.4% in the Control arm. Similar proportions of patients in both treatment arms had Grade ≥3 AEs leading to dose interruption of any study drug (37.4% and 35.8% of patients in the Triplet arm and Control arm, respectively). The following AEs led to dose interruption of any study drug in >5% more patients in the Triplet arm compared to the Control arm: diarrhoea (18.5% vs 9.3%), vomiting (8.6% vs 3.1%), nausea (7.2% vs 1.6%) and anaemia (5.4% vs 1.0%). Two AEs led to dose interruption in >5% fewer patients in the Triplet arm compared to the Control arm: neutropenia (0.5% vs 7.8%) and neutrophil count decreased (0.5% vs 5.7%). The following Grade ≥3 AEs led to dose interruption in >2% more patients in the Triplet arm compared to the Control arm: diarrhoea (8.6% vs 5.2%), vomiting (2.7% vs 0%), nausea (2.7% vs 0%) and anaemia (4.5% vs 0%). Three Grade ≥3 AEs led to dose interruption in >2% fewer patients in the Triplet arm compared to the Control arm: neutropenia (0.5% vs 5.2%), febrile neutropenia (0% vs 2.1%) and neutrophil count decreased (0% vs 4.1%).

Doublet arm vs Control arm

A total of 45.4% in the Doublet arm and 53.4% in the Control arm had AEs of any grade leading to dose interruption of any study drug. A slightly lower proportion of patients in the Doublet arm had Grade ≥3 AEs leading to dose interruption of any study drug compared to the Control arm (30.1% and 35.8%, respectively). Three AEs led to dose interruption of any study drug in >5% fewer patients in the Doublet arm compared to the Control arm: diarrhoea (2.8% vs 9.3%), neutropenia (0% vs 7.8%) and neutrophil count decreased (0.5% vs 5.7%). No AEs led to dose interruption in >5% more patients in the Doublet arm compared to the Control arm. No Grade ≥3 AEs led to dose interruption in >2% more patients in the Doublet arm compared to the Control arm. Three Grade ≥3 AEs led to dose interruption in >2% fewer patients in the Doublet arm compared to the Control arm: diarrhoea (0.5% vs 5.2%), neutropenia (0.0% vs 5.2%), febrile neutropenia (0.0% vs 2.1%) and neutrophil count decreased (0.5% vs 4.1%).

Post marketing experience

An analysis of the spontaneous adverse reactions was performed to determine if there was any significant new safety information. During the reporting intervals (which represents cumulative post-marketing data), 616 spontaneous ADRs have been reported to the MAHs. There have been no serious ADRs received from Non-interventional post-marketing studies or other solicited sources.

An analysis of the spontaneous adverse reactions was performed to determine if there was any significant new safety information. Cumulatively through 11 February 2019, 949 spontaneous adverse reactions in 360 unique cases were retrieved. Of the 949 total ADRs, 883 events in 336 cases were in patients on combination therapy with BRAFTOVI + MEKTOVI, 36 events in 14 cases were in patients on BRAFTOVI single agent and 30 events in 10 cases were in patients on MEKTOVI single agent. Most patients reporting use of single-agent therapy were being treated for the approved indication of metastatic melanoma, and otherwise limited information has been received on the rationale for single-agent use.

Among patients on combination therapy with BRAFTOVI + MEKTOVI, there were 166 SAEs in 83 cases. In patients on BRAFTOVI single agent, there were 3 SAEs in 2 cases; and in patients on MEKTOVI single agent, there were 6 SAEs in 5 cases. The most frequently reported SAE events (≥ 5 events) were PTs of death (27 events), disease progression/malignant neoplasm progression (14 events), pyrexia (5 events) and acute kidney injury (5 events). Most reports of the PT of death were received from family members via specialty pharmacy staff who routinely contact patients to inquire about medication refills. In these cases, the circumstances and timing of death are often not reported and few cases were confirmed by a healthcare professional. None of the reports with PT of death had concurrent ADRs as the cause of death. For kidney-related events, cases were confounded by several clinical factors, including preceding illness leading to dehydration, concomitant medications known to cause abnormalities in kidney function such as clopidogrel, and patient risk factors such as hypertension and diabetes.

Use in unapproved indications occurred in 53 patients on combination therapy with BRAFTOVI + MEKTOVI, 6 patients on BRAFTOVI single agent and 1 patient on MEKTOVI single agent. Greater than half of reports of use in unapproved indications were patients being treated for CRC (N=27). Most events (20 out of 27) reported with use in CRC were non-serious and consistent with the ADRs reported commonly in patients with melanoma. Of the SAEs reported in patients with CRC, 4 reports were of death only as described above, 1 hospitalization only (no other event reported), and 2 events of renal failure with significant case confounders as described above.

In summary, all reported events were consistent with the known and labelled safety profile of encorafenib in combination with binimetinib. There were no novel events reported in patients being treated for unapproved indication.

Periodic Safety Update Reports/Periodic Benefit Risk Evaluation Reports

Since the MAs of encorafenib and binimetinib, two six-monthly Periodic Benefit Risk Evaluation Reports (PBRER) have been submitted to EMA according to the timelines defined in the European GVP Module VII, Section A and published in the List of European Union Reference Dates (EURD List). These reports summarise safety data reported to the marketing authorisation holders (MAHs) from worldwide sources for two 6 month-intervals and cumulatively.

The first PBRERs covered the reporting interval from 27 June 2018 to 26 December 2018 (BRAFTOVI PSUR 1, MEKTOVI PSUR 1) and were submitted to EMA on 6 March 2019. The second and last PBRERs were submitted to EMA on 4 September 2019 and are currently undergoing evaluation as per standard procedure (BRAFTOVI PSUR 2, MEKTOVI PSUR 2). These reports summarise safety data, covering the reporting interval 27-Dec-2018 to 26-Jun-2019, which represents post-marketing safety information, clinical trial experience and reports in the literature during the reporting interval, as well as cumulative safety information.

Since first marketing approval (27-Jun-2018 in USA), cumulative post-marketing exposure is estimated to be 470,930 patient-days for encorafenib.

Since first marketing approval (27-Jun-2018 in USA), cumulative post-marketing exposure is estimated to be 120,521 patient-days for binimetinib.

During the reporting intervals of these PBRERs, no significant new safety findings have been identified which alter the characterisation of previously recognised important identified risks, important potential risks or missing information, as listed in the approved Risk Management Plan version 0.5

During both reporting intervals, regardless of encorafenib / binimetinib use setting, no actions have been taken by the MAHs, regulatory authorities (RAs), Ethics Committees and/or Independent Data Monitoring Committees for safety reasons.

Cumulatively, there have been 137 reports of off-label use, of which 88 for off-label use of encorafenib / binimetinib in patients with colorectal cancer. The majority of these reports were generated fromthe US and did not contain serious adverse reactions. Of the 5 cases containing SAEs assessed as related by the MAH, reported event terms included arthralgia, pyrexia, nausea, vomiting, diarrhea and rash. Analysis of these adverse reactions did not show any evidence for a safety issue, which might be associated with encorafenib use in the setting of this non-approved therapeutic use at the time of these periodic reports.

2.5.2. Part 2

ARRAY-818-302 Updated results (Data cut-off 15 August 2019)

Study ARRAY-818-302 is still ongoing and patients are still under treatment or continue to be followed-up for survival. An updated analysis of the Phase 3 part of the study was conducted at a data cut-off date of 15 August 2019 (i.e. approximately 6 months after the primary analysis data cut-off). This later data cut-off allowed for a follow-up of all randomised patients for at least 6.5 months and provided more mature estimates of efficacy and safety data.

Patient exposure

As of the data cut-off of 15 August 2019:

- The median duration of exposure increased for all arms and remained longer in the Triplet arm (21.0 weeks) and the Doublet arm (19.3 weeks) compared to the Control arm (7.0 weeks).
- Over 40% of patients in the Triplet and the Doublet arms (40.7% and 43.5% respectively) received ≥ 24 weeks of study treatment while only 12.4% of patients in the Control arm received ≥ 24 weeks of study treatment. More than 20% of patients in the Triplet and the Doublet arms (23% and 26.4% respectively) received ≥ 36 weeks of study treatment while only 6.2% of patients in the Control arm received ≥ 36 weeks of study treatment. At the time of data cut-off, almost 6% of patients in the Triplet and Doublet arms had received one year of study treatment.

Table S24: Updated Duration of Exposure to Study Treatment – Randomised Phase 3 (ARRAY-818-302 Safety Set)

	ENCO+BINI+CETUX				ENCO+CETUX			
Parameter	ENCO (N=222)	BINI (N=222)	CETUX (N=222)	ENCO+ BINI+ CETUX (N=222)	ENCO (N=216)	CETUX (N=216)	ENCO+ CETUX (N=216)	Control (N=193)
Duration of Exposure (weeks)								
n	222	222	222	222	216	216	216	193
Mean	24.77	24.67	24.67	25.03	24.91	25.04	25.17	11.66
SD	18.524	18.531	18.472	18.472	18.284	18.240	18.190	11.842
Median	20.7	20.4	20.8	21.0	19.1	19.0	19.3	7.0
Min, Max	0.1, 115.6	0.1, 115.6	1.0, 115.6	1.0, 115.6	0.1, 103.0	1.0, 103.0	1.0, 103.0	1.0, 70.6
Duration of Exposure (weeks), n (%)								
<4 weeks	16 (7.2)	17 (7.7)	15 (6.8)	14 (6.3)	10 (4.6)	10 (4.6)	9 (4.2)	31 (16.1)
≥24 weeks	93 (41.9)	91 (41.2)	92 (41.6)	96 (43.4)	93 (42.9)	93 (43.0)	94 (43.5)	24 (12.5)

Source: **ARRAY-818-302 CSR Addendum Table 14.3-1.3.1**
BINI: binimetinib; CETUX: cetuximab; CSLI: combined safety lead in; ENCO: encorafenib; SD: standard deviation
Triplet*P: Randomised Phase 3 and CSLI (Pooled)

As of the data cut-off of 15 August 2019, 67 patients (10.1%) continued to receive treatment in the randomised Phase 3 portion of the study compared with 193 (30.6%) at the initial analysis data cut-off. The most common reason for discontinuation from study treatment in all arms was PD (61.4%).

Adverse events

Overall adverse events

The overall percentage of patients with AEs was essentially unchanged (within a maximum difference of +1.4%) compared with that previously reported for the same population at the initial analysis (11 February 2019 data cut-off).

Due to the increase in treatment exposure, the percentage of patients who experienced at least one Grade ≥3 AE was increased across all treatment arms, and the percentage who experienced at least one SAE or AE leading to dose modification was increased in the Triplet and Doublet arms:

- Grade ≥3 AEs regardless of causality were increased in all arms (+8.1% in the Triplet arm, +7.4% in the Doublet arm and +3.6% in the Control arm). The percentage of patients experiencing at least one Grade ≥3 event remained similar between the Triplet and the Control arms (respectively 65.8%, 64.2%) and was still lower in the Doublet arm (57.4%).
- SAEs regardless of causality were increased in the Triplet and Doublet arms (+7.6% and +6.9% respectively). The percentage of patients experiencing at least one SAE remained higher in the Triplet arm (49.5%) than the Doublet arm (39.8%). Given the small number of patients remaining on treatment in the Control arm (N=7), comparison is not relevant.
- AEs regardless of causality leading to a dose interruption were increased by +5.8% in the Triplet arm and +4.5% in the Doublet arm but remained lower in the Doublet arm (50.9%) compared with the Triplet (70.3%) arm and with the Control arm (55.4%). AEs regardless of causality leading to a dose reduction were increased by +1.8% in both the Triplet and Doublet arms but

remained lower in the Doublet arm (12.0%) as compared to the Triplet arm (32.4%) and to the Control arm (31.6%).

Table S24: Changes in the overall summary of Triplet and Doublet AEs between the initial and update data cut-off

	11 February cut-off date	15 August cut-off date	Difference
Median duration of Exposure (weeks)	**Triplet:15.9weeks Doublet:14.0Weeks**	**Triplet:21.0Weeks Doublet:19.3 Weeks**	
Triplet arm (n=222)			
Overall incidence of AEs regardless of causality	217 (97.7)	220 (99.1)	+1.4%
Grade ≥3 AEs regardless of causality	128 (57.7)	146 (65.8)	+8.1%
Grade ≥3 AE with suspected any study drug relationship	74 (33.3)	85 (38.3)	+5.0%
SAE regardless of causality	93 (41.9)	110 (49.5)	+7.6%
Grade ≥3 SAE regardless of causality	83 (37.4)	97 (43.7)	+6.3%
Grade ≥3 AE leading to discontinuation of any study drug regardless of causality	22 (9.9)	25 (11.3)	+1.5%
AE leading to discontinuation of all study treatment regardless of causality	16 (7.2)	21 (9.5)	+2.3%
AE requiring dose reduction of any study drug regardless of causality	68 (30.6%)	72 (32.4%)	+1.8%
AE requiring dose reduction of any study drug with suspected study drug relationship	67 (30.2%)	70 (31.5%)	+1.5%
AE requiring dose interruption of any study drug regardless of causality	146 (65.8)	156 (70.3)	+4.5%
Grade ≥3 AE requiring dose interruption of any study drug regardless of causality	83 (37.4)	96 (43.2)	+5.8%
AE requiring dose interruption of any study drug with suspected study drug relationship	114 (51.4)	123 (55.4)	+4.0%
Grade ≥3 AE requiring dose interruption of any study drug with suspected study drug relationship	54 (24.3)	61 (27.5)	+3.2%
Grade ≥3 AE requiring additional therapy regardless of causality	112 (50.5)	129 (58.1)	+7.6%

	11 February cut-off date	15 August cut-off date	Difference
Median duration of Exposure (weeks)	**Triplet:15.9weeks Doublet:14.0Weeks**	**Triplet:21.0Weeks Doublet:19.3 Weeks**	
Doublet arm (n=216)			
Overall incidence of Aes regardless of causality	212 (98.1)	212 (98.1)	+0
Grade ≥3 AEs regardless of causality	108 (50.0)	124 (57.4)	+7.4%
SAE regardless of causality	71 (32.9)	86 (39.8)	+6 ;9%
Grade ≥3 SAE regardless of causality	61 (28.2)	74 (34.3)	+5.1%
AE leading to discontinuation of all study treatment regardless of causality	18 (8.3)	20 (9.3)	+1.0%
AE requiring dose reduction of any study drug regardless of causality	22 (10.2)	26 (12.0)	+1.8%
AE requiring dose reduction of any study drug with suspected study drug relationship	21 (9.7)	25 (11.6)	+1.9%
AE requiring dose interruption of any study drug regardless of causality	98 (45.4)	110 (50.9)	+4.5%
Grade ≥3 AE requiring dose interruption of any study drug regardless of causality	65 (30.1)	72 (33.3)	+3.2%
AE requiring dose interruption of any study drug with suspected study drug relationship	57 (26.4)	65 (30.1)	+3.7%
Grade ≥3 AE requiring additional therapy regardless of causality	91 (42.1)	107 (49.5)	+7.4%

Source: **ARRAY-818-302 CSR Table 14.3.1-1.1.1 and ISS_CRC_u Table 14.3.1-1.1.1**
Considered notable are the following: difference in overall incidence ≥5%, difference in Grade ≥3 incidence ≥2%, difference in tolerability >1%.

Relevant Adverse events regardless the relationship

The overall percentage of patients with AEs was essentially unchanged (within a maximum difference of +1.4%) compared to that previously reported for the same population at the initial analysis data cut-off.

The only relevant differences in incidence (difference in incidence ≥ 5%) were observed for the following:

- in the Triplet arm for the PTs of anaemia (+9.9%), vomiting (+5.8%), and abdominal pain (+4.9%).
- in the Doublet arm for the PTs of vomiting (+6.0%), diarrhoea (+5.1%) and abdominal pain (+5.1%).

The most common AEs were the same at the 11 February initial analysis and the 15 August 2019 data cut-off. Additional AEs were observed due to the longer exposure to treatment:

- In the Triplet arm, the most common AEs (>30%) remained diarrhoea (66.2%), acneiform dermatitis (50.0%), vomiting (44.1%), nausea (48.2%), anaemia (45.9%), fatigue (33.3%) and abdominal pain (34.2%). AEs occurring in ≥20% of patients were: decreased appetite (29.7%), constipation (26.6%), asthenia (27.9%), pyrexia (22.5%), dry skin (21.6%) and –as of the 15 August 2019 data cut-off – rash (20.3%).
- AEs reported at a higher incidence in the Triplet arm (>10.0% difference) than in the Control arm remained diarrhoea (66.2% vs 48.7%), anaemia (45.9% vs 18.7%), dry skin (21.6% vs 8.3%), and vision blurred (12.2% vs 0.5%) and – as of the 15 August 2019 data cut-off – vomiting (44.1% vs 31.6%), acneiform dermatitis (50.0% vs 39.9%) and pruritis (15.3% vs 5.2%). The AEs reported at a lower incidence in the Triplet arm (≥10.0% difference) than in the Control arm remained neutropenia (1.4% vs 18.7%) and neutrophil count decreased (0.9% vs 10.9%).
- In the Doublet arm the most common AEs (>30%) remained nausea (38.0%), diarrhoea (38.4%) and fatigue (33.3%) and – as of the 15 August 2019 data cut-off – decreased appetite (31.0%) and acneiform dermatitis (30.1%). AEs occurring in ≥20% of patients were: abdominal pain (27.8%), vomiting (27.3%), asthenia (24.1%) and – as of the 15 August 2019 data cut-off – arthralgia (22.7%).
- The AEs reported at a higher incidence in the Doublet arm (≥10.0% difference) than in the Control arm remained arthralgia (22.7% vs 1.6%), myalgia (15.3% vs 2.1%), musculoskeletal pain (13.4% vs 2.6%), melanocytic naevus (15.7% vs none) and headache (19.9% vs 2.6%), and – as of the 15 of August 2019 data cut-off – pain in extremity (11.6% vs 1.0%). The AEs reported at a lower incidence in the Doublet arm (>10.0% difference) than in the Control arm remained diarrhoea (38.4% vs 48.7%), stomatitis (6.0% vs 23.3%), neutropenia (1.4% vs 18.7%) and neutrophil count decreased (0.5% vs 10.9%). The difference in incidence of dermatitis acneiform (30.1% vs 39.9%) fell below the threshold of 10% at the 15 August 2019 data cut-off.

Grade ≥3 events increased across the randomised Phase 3 treatment arms: +8.1% in the Triplet arm, +7.4% in the Doublet arm and +3.6% in the Control arm.

- Grade ≥3 events occurred in 65.8% (with 45.9 % Grade 3, 7.7% Grade 4 and 4.1% Grade 5), with a similar percentage (64.2%) in the Control arm (with 44.0 % Grade 3, 11.4% Grade 4 and 5.2% Grade 5) and a lower percentage (57.4%) in the Doublet arm (with 40.3 % Grade 3, 6.0% Grade 4 and 3.7% Grade 5)
- In the Doublet arm the most common Grade ≥ 3 AEs remained anaemia (5.6%) and fatigue (4.2%) and – as of the 15 August 2019 data cut-off – intestinal obstruction (4.6%).

- In the Triplet arm the most common Grade ≥ 3 AEs in the Triplet arm remained anaemia (23.9%), diarrhoea (10.8%) and abdominal pain (6.3%),
- The only relevant differences in incidence of Grade ≥3 events (difference in incidence ≥ 2%) were observed in the Triplet arm for the PT of anaemia (+7.2%). No other noticeable differences in incidences of Grade ≥3 events were observed (maximum difference in incidences ≤1.8% in the Triplet arm and ≤0.9% in the Doublet arm).

In the Phase 3, the time to onset of first Grade ≥3 AE for all patients was longer in the Triplet arm compared to the Control arm (3.25 months [95% confidence interval (CI) 2.33, 4.17] vs 1.41 months [95% CI 1.08, 2.07], respectively) and this time was 4.73 months [95% CI 3.94, 6.44] in the Doublet arm.

A clinical review of the safety data for each individual patient was conducted on new PTs reported in the study between the 11 February 2019 and 15 August 2019 data cut-offs. No new terms of potential clinical significance were identified. No new safety concern was identified following clinical review.

As of the 15 August 2019 data cut-off:

- The overall EAIR of AEs decreased in the Doublet arm (-5 per 100 patient-months) whereas it increased in the Triplet and Control arms (+22.0 per 100 patient-months and +26 per 100 patient-months respectively).
- No PTs reported with an EAIR below 5 per 100 patient-months in the initial analysis were reported with an EAIR ≥5 in the updated analysis, and the EAIRs of AEs shown in Table S25 generally decreased in the 3 study arms in the updated analysis compared to the initial analysis, reflecting that the longer exposure had no relevant impact on the incidence of AEs when adjusted for the duration of exposure to treatment.
- Overall, EAIRs remained lower in the Triplet arm than in the Control arm, with the following events having a difference of >10 per 100 patient-months: diarrhoea (28.45 Triplet vs 39.76 Control), dermatitis acneiform (16.95 vs 28.98), nausea (14.01 vs 32.59) and neutropenia (0.24 vs 10.02). At the 15 August 2019 cut-off, there was no more difference of ≥10 per 100 patient-months for asthenia and stomatitis between the Triplet and Control arms.
- Overall, EAIRs remained lower in the Doublet arm than in the Control arm with the following events having a difference of ≥10 per 100 patient-months: diarrhoea (9.69 Doublet vs 39.68 Control), dermatitis acneiform (7.48 vs 28.98), nausea (9.42 vs 32.59), vomiting (5.78 vs 16.69), stomatitis (1.11 vs 12.13) and neutropenia (0.24 vs 10.02). At the 15 August 2019, there was no more difference of ≥10 per 100 patient-months for asthenia between the Doublet and Triplet arms.

Table S25: Relevant Adverse Events, Regardless of Study Drug Relationship, Adjusted for Patient-month Exposure, by Preferred Term (EAIR ⩾5 in any Phase 3 arm or Study population) (ARRAY-818-302 Safety Set)

		Randomised Phase 3		
Preferred Term[a]		ENCO+ BINI+ CETUX (N=222)	ENCO+ CETUX (N=216)	Control (N=193)
Any preferred term	n (%)	220 (99.1)	212 (98.1)	190 (98.4)
	Exposure (mo)	43.37	59.83	34.37
	EAIR	**507.29**	**354.35**	**552.88**
Diarrhoea	n (%)	147 (66.2)	83 (38.4)	94 (48.7)
	Exposure (mo)	516.70	856.80	236.88
	EAIR	**28.45**	**9.69**	**39.68**
Dermatitis acneiform	n (%)	111 (50.0)	65 (30.1)	77 (39.9)
	Exposure (mo)	654.95	869.03	265.72
	EAIR	**16.95**	**7.48**	**28.98**
Nausea	n (%)	107 (48.2)	82 (38.0)	84 (43.5)
	Exposure (mo)	763.66	870.05	257.74
	EAIR	**14.01**	**9.42**	**32.59**
Vomiting	n (%)	98 (44.1)	59 (27.3)	61 (31.6)
	Exposure (mo)	926.65	1021.11	365.54
	EAIR	**10.58**	**5.78**	**16.69**
Fatigue	n (%)	74 (33.3)	72 (33.3)	54 (28.0)
	Exposure (mo)	902.21	926.75	326.34
	EAIR	**8.20**	**7.77**	16.55
Anaemia	n (%)	102 (45.9)	42 (19.4)	36 (18.7)
	Exposure (mo)	924.39	1111.20	401.25
	EAIR	**11.03**	3.78	**8.97**
Abdominal pain	n (%)	76 (34.2)	60 (27.8)	54 (28.0)
	Exposure (mo)	1008.00	1035.73	388.27
	EAIR	7.54	5.79	13.91
Decreased appetite	n (%)	66 (29.7)	67 (31.0)	56 (29.0)
	Exposure (mo)	1007.11	1012.40	406.28
	EAIR	**6.55**	**6.62**	**13.78**
Constipation	n (%)	63 (28.4)	39 (18.1)	39 (20.2)
	Exposure (mo)	1065.82	1101.67	394.78
	EAIR	**5.91**	3.54	**9.88**
Asthenia	n (%)	62 (27.9)	52 (24.1)	53 (27.5)
	Exposure (mo)	1020.12	1024.82	355.35
	EAIR	**6.08**	**5.07**	**14.91**
Dry skin	n (%)	48 (21.6)	28 (13.0)	16 (8.3)
	Exposure (mo)	992.16	1101.40	421.78
	EAIR	4.84	2.54	3.79
Pyrexia	n (%)	50 (22.5)	40 (18.5)	28 (14.5)
	Exposure (mo)	1054.85	1071.84	429.86
	EAIR	4.74	3.73	**6.51**
Rash	n (%)	45 (20.3)	32 (14.8)	28 (14.5)
	Exposure (mo)	1018.55	1063.29	377.33
	EAIR	4.42	3.01	**7.42**
Stomatitis	n (%)	32 (14.4)	13 (6.0)	45 (23.3)
	Exposure (mo)	1100.48	1170.73	370.96
	EAIR	2.91	1.11	**12.13**
Vision blurred	n (%)	27 (12.2)	10 (4.6)	1 (0.5)
	Exposure (mo)	1140.80	1202.56	466.30
	EAIR	2.37	0.83	0.21

Preferred Term*		Randomised Phase 3		
		ENCO+ BINI+ CETUX (N=222)	ENCO+ CETUX (N=216)	Control (N=193)
Neutropenia	n (%)	3 (1.4)	3 (1.4)	36 (18.7)
	Exposure (mo)	1254.44	1232.07	359.33
	EAIR	0.24	0.24	**10.02**
Back pain	n (%)	34 (15.3)	28 (13.0)	27 (14.0)
	Exposure (mo)	1138.04	1170.50	407.23
	EAIR	2.99	2.39	**6.63**
Hypokalaemia	n (%)	15 (6.8)	13 (6.0)	27 (14.0)
	Exposure (mo)	1235.61	1208.18	442.12
	EAIR	1.21	1.08	**6.11**

Source: **ISS_CRC_u Table 14.3.1-1.45.1**
EAIR: exposure adjusted incidence rate; ENCO: encorafenib; mo: months;
* From MedDRA version 21.0.
n (%): number of patients reporting the event (patient incidence (%).
Exposure time for a patient without the specific event is the treatment duration, whereas the exposure time for a subject with the specific event is the treatment duration up to the start date (inclusive) of the first occurrence of the specific event.
EAIR (Exposure adjusted incidence rate per 100 patient-months=(n*100)/(total exposure time).

Adverse drug reactions in the target indication

The same method to identify ADRs was applied for the 6-month safety update. This included an assessment, both qualitatively and quantitatively of newly reported PTs in the randomised Phase 3 part of study ARRAY-818-302 between the two data cut-off dates to identify any potential new safety concerns or events requiring further consideration as ADRs. Based on this review, no additional ADR was identified, and the list of final ADR groupings remained unchanged.

The most common ADRs (≥25%) for the Doublet remained fatigue (56.9%), nausea (38.0%), diarrhoea (38.4%), acneiform dermatitis (33.3%), abdominal pain (36.6%), arthralgia/musculoskeletal pain (31.5%), decreased appetite (31.0%) and rash (30.6%). At the 15 August 2019 cut-off, vomiting (27.3%) moved above the 25% threshold.

The categories of frequency of each ADR remained the same as for the initial analysis. The differences in incidences (overall and Grade ≥3) in the Doublet arm are summarised in Table S26. The ADRs with a difference in incidence ≥5% were abdominal pain (+7%), vomiting (+6%), diarrhoea and fatigue (+5%).

There were no relevant changes to the tolerability of the Doublet ADRs with

- Nausea and vomiting remaining the two ADRs leading to dose reduction and or interruption in more than 4% of patients, with no discontinuation
- Renal failure and transaminase increased were the two ADRs that led to discontinuation in ≥ 2 patients (0.9%)

Table S26: Profiles of Doublet-based ADRs at initial and updated data cut-off in the Doublet arm (n=216)

	Safety profile		ADR leading to				ADR requiring	
System Organ Class / Preferred Term Doublet arm (n=216)	Overall (Grade ≥3) % (%)		Discontinuation Overall (Grade ≥3) % (%)		Dose reduction/interruption Overall (Grade ≥3) % (%)		additional therapy Overall (Grade ≥3) % (%)	
	11 February COD	15 August COD	11 February COD	15 August COD	11 February COD	15 August COD	11 February COD	15 August COD
Any ADR	96.8 (24.1)	97.7 (28.7)	3.7 (2.8)	3.7 (2.8)	25.0 (13.9)	29.6 (14.8)	83.3 (15.7)	86.6 (19.4)
Neoplasms benign, malignant and unspecified								
Melanocytic naevus	14.4 (0)	15.7 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3.7 (0)	4.6 (0)
Skin papilloma	5.6 (0)	6.9 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3.2 (0)	3.7 (0)
cuSCC	1.4 (0)	1.4 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.9 (0)	0.9 (0)
New primary melanoma	1.4 (0.9)	1.9 (0.9)	0 (0)	0 (0)	0.5 (0.5)	0.5 (0.5)	1.4 (0.9)	1.9 (0.9)
Basal cell carcinoma	0.5 (0)	0.5 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (0)	0.5 (0)
Immune system disorders								
Hypersensitivity	1.4 (0.9)	1.9 (0.9)	0 (0)	0 (0)	0.9 (0.5)	0.9 (0.5)	1.4 (0.9)	1.9 (0.9)
Metabolism and nutrition disorders								
Decreased appetite	**26.9 (1.4)**	**31.0 (1.4)**	0 (0)	0 (0)	0.9 (0)	1.9 (0)	8.3 (0)	10.2 (0)
Psychiatric disorders								
Insomnia	13.0 (0)	13.4 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6.9 (0)	7.9 (0)
Nervous system disorders								
Headache	19.9 (0)	20.4 (0)	0 (0)	0 (0)	0.5 (0)	0.5 (0)	9.7 (0)	10.2 (0)
Neuropathy peripheral	**12.0 (1.4)**	**14.8 (1.9)**	0.5 (0.5)	0.5 (0.5)	2.8 (1.4)	3.2 (1.4)	3.2 (0.5)	3.7 (0.5)
Dizziness	8.3 (0)	9.3 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.4 (0)	1.9 (0)
Dysgeusia	4.2 (0)	4.6 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac disorders								
Supraventricular tachycardia	3.7 (1.4)	4.6 (1.4)	0 (0)	0 (0)	0.9 (0.5)	0.9 (0.5)	1.9 (0.5)	2.3 (0.5)

	Safety profile		ADR leading to				ADR requiring	
System Organ Class / Preferred Term Doublet arm (n=216)	Overall (Grade ≥3) % (%)		Discontinuation Overall (Grade ≥3) % (%)		Dose reduction/interruption Overall (Grade ≥3) % (%)		additional therapy Overall (Grade ≥3) % (%)	
Vascular disorders								
Haemorrhage	**19.0 (1.9)**	**21.3 (1.9)**	0.5 (0)	0.5 (0)	1.4 (0.5)	1.9 (0.5)	6.5 (1.4)	7.9 (1.4)
Gastrointestinal disorders								
Diarrhoea	**33.3 (1.9)**	**38.4 (2.8)**	0.5 (0.5)	0.5 (0.5)	2.8 (0.5)	3.7 (0.5)	**13.9 (1.4)**	**18.1 (1.9)**
Nausea	**34.3 (0.5)**	**38.0 (0.5)**	0 (0)	0 (0)	4.2 (0.5)	5.1 (0.5)	**19.9 (0.5)**	**22.7 (0.5)**
Abdominal pain	**29.6 (4.2)**	**36.6 (5.1)**	0.5 (0.5)	0.5 (0.5)	1.9 (0.9)	3.2 (0.9)	**19.9 (3.2)**	**24.1 (4.2)**
Vomiting	**21.3 (1.4)**	**27.3 (1.4)**	0 (0)	0 (0)	**4.2 (0.9)**	**6.5 (0.9)**	12.0 (0.5)	13.9 (0.5)
Constipation	**15.3 (0)**	**18.1 (0)**	0 (0)	0 (0)	0 (0)	0.5 (0)	9.7 (0)	12.5 (0)
Pancreatitis	0.5 (0.5)	0.5 (0.5)	0 (0)	0 (0)	0.5 (0.5)	0.5 (0.5)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders								
Dermatitis acneiform	31.9 (0.9)	33.3 (0.9)	0 (0)	0 (0)	1.4 (0.9)	2.3 (0.9)	19.0 (0.9)	20.4 (0.9)
Rash	**25.9 (0)**	**30.6 (0.5)**	0 (0)	0 (0)	0.5 (0)	0.5 (0)	**12.0 (0)**	**16.7 (0.5)**
Pruritus	14.4 (0)	15.3 (0)	0 (0)	0 (0)	0.9 (0)	0.9 (0)	6.9 (0)	8.8 (0)
Dry skin	13.4 (0)	15.3 (0)	0 (0)	0 (0)	0 (0)	0.5 (0)	4.6 (0)	6.0 (0)
Skin hyperpigmentation	7.4 (0)	7.4 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (0)	0.5 (0)
Erythema	4.6 (0.5)	6.0 (0.5)	0 (0)	0 (0)	0.5 (0.5)	0.5 (0.5)	1.9 (0.5)	2.8 (0.5)
PPES	4.2 (0.5)	5.1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	0.9 (0)	0.9 (0)
Hyperkeratosis	3.7 (0)	5.6 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.9 (0)	2.8 (0)
Alopecia	3.7 (0)	4.2 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Skin exfoliation	0.5 (0)	0.5 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders								
Arthralgia	**27.3 (0.9)**	**31.5 (1.4)**	0 (0)	0 (0)	3.2 (0.5)	3.7 (0.9)	**15.3 (0.9)**	**18.1 (0.9)**
Myalgia	**15.3 (0.5)**	**17.6 (0.5)**	0 (0)	0 (0)	0.5 (0.5)	0.9 (0.5)	7.9 (0.5)	8.8 (0.5)
Pain in extremity	10.2 (0)	11.6 (0)	0 (0)	0 (0)	0.9 (0)	1.4 (0)	5.1 (0)	6.5 (0)
Back pain	**10.2 (0.9)**	**13.0 (1.4)**	0 (0)	0 (0)	0 (0)	0 (0)	**6.9 (0.9)**	**9.3 (1.4)**
Renal and urinary disorders								
Renal failure	1.9 (1.9)	2.3 (2.3)	0.9 (0.9)	0.9 (0.9)	0.9 (0.9)	0.9 (0.9)	1.4 (1.4)	1.9 (1.9)
General disorders and administration site conditions								
Fatigue	**51.4 (7.4)**	**56.9 (7.9)**	0.5 (0.5)	0.5 (0.5)	5.1 (3.2)	6.0 (3.2)	1.9 (0)	1.9 (0)
Pyrexia	**16.7 (1.4)**	**19.0 (1.9)**	0 (0)	0 (0)	3.7 (1.4)	4.6 (1.9)	**9.7 (1.4)**	**12.0 (1.9)**
Investigations								
Transaminase increased	8.3 (0.9)	8.8 (1.4)	0.9 (0)	0.9 (0)	0.9 (0.9)	1.4 (1.4)	0.9 (0.5)	1.4 (0.9)
Blood creatinine increased	2.3 (0.5)	2.8 (0.5)	0 (0)	0 (0)	0 (0)	0.5 (0)	0.5 (0)	0.5 (0)
Amylase increased	0.5 (0)	0.5 (0)	0 (0)	0 (0)	0.5 (0)	0.5 (0)	0 (0)	0 (0)
Lipase increased	0.5 (0.5)	0.5 (0.5)	0 (0)	0 (0)	0.5 (0)	0.5 (0)	0 (0)	0 (0)
Source: ISS_CRC_add Table 1.2, ISS_CRC_u Table 1.2, ISS_CRC_add Table 3.2, ISS_CRC_u Table 3.2, ISS_CRC_add Table 5.2, ISS_CRC_u Table 5.2, ISS_CRC_add Table 4.2, ISS_CRC_u Table 4.2								

Serious adverse event and deaths

Deaths and SAEs

As of the 15 August 2019 cut-off date, with the longer exposure to study treatment the following was observed:

- The percentage of patients with on-treatment deaths increased by 3.1% in the Triplet arm (7 patients), 2.8% in the Doublet arm (6 patients) and 1.5% in the Control arm (3 patients). Two on-treatment deaths in the Doublet arm were due to AEs: colorectal cancer and tumour obstruction. In the Triplet arm and the Control arm, none of the newly reported deaths was due to an AE.

- The number of patients experiencing SAEs increased by 7.6% of patients in the Triplet arm, 6.9% in the Doublet arm and 3.1% in the Control arm. The overall incidence of Grade 3-4 SAEs increased by 6.3% in the Triplet arm, 6.1% in the Doublet arm and 1.5% in the Control arm
- The most commonly reported SAEs in the Doublet arm remained intestinal obstruction (5.1% vs 3.6% in Control arm), urinary tract infection and cancer pain (each 2.3% vs 0.5% in the Control arm) and – as of the 15 August 2019 data cut-off – abdominal pain (2.3% vs 2.1%). Similarly, the most commonly reported Grade ≥3 SAEs in the Doublet arm remained intestinal obstruction (4.2% vs 2.6% in Control arm), urinary tract infection (2.3% vs 0.5% in the Control arm), cancer pain (1.9% vs 0.5% in the Control arm) and acute kidney injury (1.9% vs 0.5% in the Control arm).
- The most commonly reported SAEs in the Triplet arm remained diarrhoea (4.1% vs 5.2% in the Control arm), pulmonary embolism (3.6% vs 2.6% in the Control arm), acute kidney injury and nausea (each 3.2% vs 0.5% in the Control arm) and – as of the 15 August 2019 data cut-off - intestinal obstruction (5.0% vs 3.6%). Grade ≥3 SAEs remained diarrhoea (3.6% vs 3.6% in the Control arm), pulmonary embolism (3.2% vs 2.6% in the Control arm), acute kidney injury and nausea (each 2.3% vs 0.5% in the Control arm) and intestinal obstruction (4.1% vs 2.6% in the Control arm).
- As of the update, 9 SAEs were reported under new PTs in the randomised Phase 3 population. None of them were assessed as related to study treatment and none were indicative of a new safety signal.

Table S27: Changes in incidence of Serious Adverse Events, Regardless of study drug relationship, by PT (difference ⩾2 patients in any population in ARRAY-818-302 Safety Set)

		Incidence n (%) February cut-off date		Incidence n (%) August cut-off date	
Preferred Term	Study ARRAY-818-302	All grades n (%)	**Grade 3+ n (%)**	All grades n (%)	Grade 3+ n (%)
Intestinal obstruction	Triplet P (n=259)	6 (2.3)	5 (1.9)	11 (4.2)	9 (3.5)
	Triplet arm (n=222)	6 (2.7)	5 (2.3)	11 (5.0)	9 (4.1)
Vomiting	Triplet P (n=259)	5 (1.9)	3 (1.2)	8 (3.1)	5 (1.9)
	Triplet arm (n=222)	3 (1.4)	3 (1.4)	6 (2.7)	5 (2.3)
Urinary tract infection	Triplet P (n=259)	6 (2.3)	5 (1.9)	8 (3.1)	6 (2.3)
	Triplet arm (n=222)	2 (0.9)	2 (0.9)	4 (1.8)	3 (1.4)
Abdominal pain	Doublet arm (n=216)	3 (1.4)	3 (1.4)	5 (2.3)	3 (1.4)
Subileus	Doublet arm (n=216)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)
Ileus	Control arm (n=193)	2 (1.0)	2 (1.0)	4 (2.1)	2 (1.0)

Source: ARRAY-818-302 CSR Table 14.3.1-1.8.1_u
Abbreviations: SAE: serious adverse event; Triplet°P: Randomised Phase 3 and CSLI (Pooled)

Laboratory findings (Haematology and chemistry)

The frequencies of newly reported or worsening clinical laboratory abnormalities remained similar between the two data cut-off dates across all treatment arms.

At the 15 August 2019 cut-off, the most frequently reported (>30.0%) newly occurring or worsening haematology and coagulation abnormalities (all grades) remained (data presented below for the initial analysis first versus the update analysis):

- Triplet arm: decreased haemoglobin (55.0% to 69.4%
- Doublet arm: decreased haemoglobin (31.9% to 39.4%),

- Control arm: decreased haemoglobin (43.5% to 46.1%), decreased leukocytes (42.5% to 46.1%), decreased neutrophils (41.5% to 44.6%) and decreased lymphocytes (30.6% to 33.7%).

The most frequently reported Grade >3 abnormalities remained:

- Triplet arm: decreased haemoglobin (23.4% vs 5.2% in the Control arm)
- Doublet arm: decreased lymphocytes (6.9% vs 5.7% in the Control arm) and decreased haemoglobin (5.6% vs 5.2% in the Control arm)
- Control arm: decreased neutrophils (17.1% vs 1.4% in the Doublet and 0.5% in the Triplet) and decreased leukocytes (9.8% vs 1.9% in the Doublet and 0.0% in the Triplet).

At the 15 August 2019 data cut-off, the most frequently reported (>20.0%) newly occurring or worsening serum chemistry abnormalities (all grades) remained):

- Triplet arm: creatinine (high), albumin (low), CK (high) ALT (high), AST (high), and ALP (high)
- Doublet arm: creatinine (high) and – as of the 15 August 2019 data cut-off – ALP (high) and magnesium (low)
- Control arm: creatinine (high), potassium (low), ALP (high), ALT (high) and albumin (low) and – as of the 15 August 2019 data cut-off – AST (high), magnesium (low)

The most frequently reported Grade >3 abnormalities (in > 2 patients) remained:

- Triplet arm: creatinine (high), sodium (low), glucose (high), ALP (high), CK (high), bilirubin (high), calcium (low), and potassium (low) and – as of the 15 August 2019 data cut-off – albumin (high), AST (high), potassium (high), magnesium (low)
- Doublet arm: glucose (high), ALP (high), potassium (low), potassium (high), bilirubin (high), and creatinine (high) and – as of the 15 August 2019 data cut-off – AST (high)
- Control arm: ALP (high), potassium (low), bilirubin (high), ALT (high) and sodium (low) and – as of the 15 August 2019 data cut-off – AST (high), glucose (high)

Discontinuation /dose reduction due to adverse events

The following changes on treatment tolerability were observed as of the 15 August 2019 data cut-off.

Treatment discontinuations

- Despite a longer duration of exposure, there were no relevant changes in the overall incidence of AEs leading to all or any study treatment discontinuation in any population of the Safety Set (difference <2.5%).
- Incidence rates of overall and Grade≥3 AEs requiring discontinuation of all study treatments remained lower in the Doublet and the Triplet arms than in the Control arm.
    - The most frequently reported AEs leading to discontinuation of all study treatments (≥ 2 patients) by PT remained:
        - in the Doublet arm, infusion-related reaction and intestinal obstruction (0.9%each);
        - in the Triplet arm, hepatic failure and sepsis (0.9% each) and
        - in the Control arm, small intestinal obstruction (1.6%), and general physical health deterioration and infusion-related reaction (1.0% each).

- The percentage of patients with an AE leading to discontinuation of any study drug of the regimen was 16.2% for the Triplet arm (binimetinib 14.0%, encorafenib 12.2% and cetuximab 13.1%), 12.0% for the Doublet arm (encorafenib 9.5% cetuximab 9.7%) and 17.1% for the Control arm (cetuximab 13.0%).

Discontinuation of encorafenib:

As of the 15 August 2019 Data cut-off, the percentage of patients with AEs leading to discontinuation of encorafenib was lower in the Doublet compared to the Triplet arm (respectively 12.2% and 9.5%). The most frequently reported AEs leading to discontinuation of encorafenib (≥ 2 patients) in the Triplet arm were nausea (3 patients [1.4%]) and asthenia, diarrhoea, hepatic failure and sepsis (2 patients [0.9%] each); and in the Doublet arm it was intestinal obstruction (2 patients [0.9%]). In the Triplet arm, many of the AEs leading to discontinuation of encorafenib were also reported as leading to discontinuation of binimetinib.

Discontinuation of cetuximab:

As of the 15 August 2019 Data cut-off, the percentage of patients with AEs leading to discontinuation of cetuximab was higher in the Triplet and Control arms (13.1% and 13.0%) than in the Doublet arm (9.7%). The most frequently reported AEs leading to discontinuation of cetuximab (≥ 2 patients) in the Triplet arm were diarrhoea, hepatic failure, nausea and sepsis (2 patients [0.9%] each); in the Doublet arm they were acute kidney injury, infusion-related reaction and intestinal obstruction (2 patients [0.9%] each); and in the Control arm they were small intestinal obstruction (3 patients [1.6%]) and diarrhoea, general physical health deterioration and infusion related reaction (2 patients [1.0%] each).

Treatment Dose Reductions

- Despite a longer duration of exposure, no noticeable change in the overall incidence of AEs leading to any study treatment dose reduction was reported in any population of the Safety Set (difference <2.0%).
- Incidence rates of overall and Grade ≥3 AEs requiring dose reduction of any study drug remained lower in the Doublet arm (12.0%) than in the Control and Triplet arms (respectively 31.6% and 32.4%).

The most frequently reported AEs leading to dose reduction of any study treatments (≥ 1%) by PT in the Doublet arm remained fatigue, asthenia, musculoskeletal pain, neuropathy peripheral (3 patients 1.4% each); in the Triplet arm they remained diarrhoea (10.4%), nausea and vomiting (2.7% each), fatigue (2.3%), blood CK increased, decreased appetite and dermatitis acneiform (1.8% each), acute kidney injury, anaemia, asthenia, ejection fraction decreased, pyrexia and pustular rash (1.4% each).

Treatment Dose interruptions

As of the 15 August 2019 data cut-off, slight changes in the overall incidences of AEs leading to any study treatment interruption were reported in the Safety Set (difference <5.0%) as compared to the initial analysis, due to a longer duration of exposure:

- The percentage of patients with an AE leading to interruption of any study drug of the regimen remained higher for the Triplet arm (70.3%: binimetinib 14.0%, encorafenib 57.2% and cetuximab 50.5%) compared to the Doublet arm (50.9%: encorafenib 39.4% cetuximab 35.2%) and the Control arm (55.4%: cetuximab 46.1%).
- The most frequently reported AE leading to interruption of any study treatments (≥ 5%) in the Doublet arm was vomiting (6.5%). In the Triplet these AEs remained diarrhoea (18.9%), nausea (8.6%), vomiting (9.0%), anaemia (7.2%), blood CK increased (6.3%) and – as of 15 August 2019 data cut-off – asthenia and pyrexia (5.0% each).

Requirement for Additional therapy

At the 6-month safety update, the overall percentage of patients with AEs requiring additional therapy was similar (within a maximum difference of approximately +3.5%) to that previously reported for the same populations.

2.5.3. Discussion on clinical safety

This variation was initially intended to support a new indication for Encorafenib and Binimetinib in combination with Cetuximab. Thus, for this submission, at first the known safety profile of encorafenib and binimetinib (in the melanoma indication), the known safety profile of cetuximab (in the approved indications) as well as the results from the pivotal study ARRAY-818-302 provide the most clinical relevant safety data. It should be noted that within the pivotal study, a combined safety lead in (CSLI) Phase was performed to justify the triplet combination in the proposed dose. Dose-limiting toxicities were observed in six patients (17.6%). As this was acceptable, the randomized was started. Within the safety assessment, the data of the CSLI Phase was not assessed separately as the number of treated patients in the CSLI was rather small (37 patients). However, initially mainly a pooled triplet arm population (CLSI (37 patients) +Triplet arm of randomized part (222 patients), Triplet Population (259 patients)) was assessed (Cut-off data: 11 February 2019).

Within the course of this work-sharing procedure the binimetinib application was – with regard to the updated data of the pivotal study - withdrawn. Thus, finally mainly the updated data of the doublet arm in comparison to the control arm was assessed (Cut-off data: 15 Aug 2019).

Compared to the control population of the pivotal study (Cetuximab in combination with Irinotecan or FOLFIRI, N=221) the tolerability of both combinations (Triplet, N=261 and Doublet arm, N=220) seems to be acceptable. In general, the reported adverse events were manageable.

The Triplet and the Control had similar overall incidences of AEs, SAEs and AES leading to dose discontinuation, modifications or requiring additional therapy, although EAIRs were lower for the Triplet compared to the Control. Overall, the Doublet had a safety profile consistently more favorable than the Control.

The median duration of exposure was in the Triplet arm (21.0 weeks) and the Doublet arm (19.3 weeks) compared to the Control arm (7.0 weeks).

With regard to the updated data (Cut-off 15 August 2019) it is acknowledged, that, due to the increase in treatment exposure, the percentage of patients who experienced at least one Grade ≥3 AE was increased across all treatment arms, and the percentage who experienced at least one SAE or AE leading to dose modification was increased in the Triplet and Doublet arms. However, in summary the safety profile did not change remarkably.

It is further noted, that in the course of treatment reduced incidence rates were reported for most of the commonly AEs in all treatment arms, indicating that the majority of events were most frequently occurring in the first month of treatment. Of note, anaemia in the Triplet arm was the only event with a higher incidence in the Months 2 to 3 period than in the first month of study treatment.

The median time to onset of first Grade ¾ AEs was longer in the triplet and doublet population than in the population of the control arm.

Upon review and analysis of adverse events of special interest (AESI), no AESI that did not already translate into an ADR in the initial melanoma MAA was identified as candidate ADR for the Triplet or the Doublet combination in the pivotal study. However, it should be kept in mind that - particular for the

triplet combination - the incidence of several adverse drug reactions was remarkably higher in the pivotal study than in the initial MAA.

Already with regards to the data initially presented, the *contribution of binimetinib* showed - possibly, mainly due to additive toxicities between Binimetinib and Cetuximab - a significant negative impact on the safety profile of the triplet combination (compared to the doublet combination):

Incidence rates of Grade ≥ 3 toxicities (57.7% Triplet arm, 50.0% Doublet arm) and SAEs (41.9% Triplet arm, 32.9% Doublet arm) were remarkably higher in the Triplet arm.

Additionally, in the Triplet vs the Doublet arm, there were more AEs requiring dose reduction of any study drug (30.6% vs 10.2%) and AEs requiring dose interruption of any study drug (65.8% vs 45.4%). Skin disorders (particularly dermatitis acneiform) are described with a significant higher incidence in the Triplet Population than in the doublet arm (57.9% vs 31.9%). More patients required a dose reduction / interruption or additional therapy.

Incidences for gastrointestinal disorders, particularly diarrhoea and vomiting (eventually resulting in dehydration) and increased blood creatinine are remarkably higher in the Triplet Population than in the doublet arm (63.7%, 39.8% and 12.7% vs 33.3%, 21.3 and 2.3%). Additional acute renal failure adverse events (possibly as a consequence of dehydration und increased blood creatinine) were reported at a higher incidence (≥ 5% difference) in the Triplet Population than in the Doublet arm, overall (9.5% vs 1.9%) and for Grade >3 (3.6% vs 1.9%). In addition, it should be noted, that (amongst others) the most commonly reported SAEs in the Triplet arm were diarrhoea (3.6%) and acute kidney injury (3.2%).

Left ventricular dysfunction (LVD) AESIs were reported in the Triplet population (Overall: 5.8%, Grade >3: 0.4%). The most frequent PT was ejection fraction decreased (5.0%).

Eye disorders and venous thromboembolism (VTE) are predominantly described in the Triplet population as well (Retinal pigment epithelial detachment 14.7%, visual impairment 17.0%, VTE 6.9%).

Additional, in the Triplet population anaemia (which incorporated the PTs of anaemia and haemoglobin decreased) was a very common ADR (37.1% of patients, with 16.2% Grade ≥3 events and a single patient (0.4%) with Grade° 4 event; 28.2% events required additional therapy, 6.6% led to dose adjustment/study drug interruption and 0.4% led to study drug discontinuation. The incidence of anaemia in the doublet arm was remarkably lower (16.2%).

However, it should be kept in mind, that (similar to the initial MAA of Binimetinib and Encorafenib) within the combination including Binimetinib (Triplet population) the incidence of Arthralgia, Headache, secondary skin neoplasm and insomnia was decreased compared to the combination without Binimetinib (doublet arm).

The assessment of the *contribution of cetuximab* on the safety profile of the combination (encorafenib/ binimetinib) and of the encorafenib monotherapy is, due to several aspects (e.g. different study settings, study populations and durations of exposure), hampered. However, with regards to the data presented, the contribution of cetuximab has – possibly mainly due to additive toxicities between binimetinib and cetuximab - a significant negative impact on the known safety profile of Combo 300. Thus, a clear negative impact is seen regarding the incidences of the following adverse events: diarrhoea, dermatitis acneiform, anaemia, abdominal pain, hypokalaemia and pulmonary embolism. However, it should be kept in mind, that some of those adverse events might be due to the risks of the underlying disease.

In contrast to this, the *contribution of cetuximab* does not seem to have a significant impact on the safety profile of encorafenib mono (300 mg).

With regards to the updated data (Cut-off 15 August 2019) provided by the applicant. The safety profile of the Doublet remained consistently more favourable than the Control and differences observed as of 15

August 2019 were comparable to these observed as of 11 February 2019 both for "raw" frequencies of events and for the corresponding EAIRs.

The most frequent ADRs observed within the doublet combination (encorafenib and cetuximab, cut-off 15 August 2019) were fatigue (56.9%), nausea (38.0%), diarrhoea (38.4%), acneiform dermatitis (33.3%), abdominal pain (36.6%), decreased appetite (31.0%), vomiting (27.3%) Arthralgia (22.7 %) and headache (19.9%).

Based on the submitted data, the combination of encorafenib and cetuximab results in no increased frequency of secondary skin neoplasms with the Doublet in mCRC population.

The percentage of patients with on-treatment deaths was 17.6% in the Doublet arm and 15% in the Control arm. Most of the on-treatment deaths were due to progression of mCRC. The applicant stated that the on-treatment deaths that were considered due to events other than disease progression were not treatment related which can be acceptable based on the narratives.

In line with previous data and based on the population PK analyses performed with patients with mCRC, renal impairment has low impact on PK of encorafenib. In summary, no dose adjustment is recommended/required in mCRC patients with mild or moderate renal impairment.

Overall, based on all the available (pop) PK and clinical data taken together, no dose adjustment is proposed in patients with mild hepatic impairment in the indication mCRC as well.

The analysis of the subgroups, race, gender, tumour resection, liver metastases and number of lines of prior therapy were noted.

Neither cetuximab itself nor the recommended cetuximab premedication, such as diphenhydramine (CYP2D6 inhibitor) or dexamethasone (weak CYP3A4 inducer) have an impact on encorafenib PK. Thus, no changes to the SmPC section of DDIs with CYP inducers or inhibitors are required.

The post-marketing accumulated data for the combination binimetinib / encorafenib remains in accordance with the previous cumulative experience from clinical trials and the safety information presented in the Company Core Data Sheet and in the SmPC.

Based on the evaluation of the cumulative safety data presented in the PBRERs and the benefit-risk analysis, the MAHs did not propose any safety-related changes to the reference safety information or changes to risk minimisation measures at the time of the last PBRER submission.

Information regarding long-term safety follow-up is missing. This maybe captured as an additional pharmacovigilance activity in an upcoming revision of the RMP.

2.5.4. Conclusions on clinical safety

Compared to the control population of the pivotal study (Cetuximab in combination with Irinotecan or FOLFIRI, N=221) the tolerability of both combinations (Triplet, N=261 and Doublet arm, N=220) seems to be slightly better. In general, the reported adverse events were manageable. The safety and tolerability profile of the Doublet is more favourable over the Triplet mainly in terms of gastrointestinal toxicities and anaemia, with lower rates of dose reduction/interruption of encorafenib and cetuximab. Thus, from a safety point of view, the decision to withdraw the binimetinib application is supported.

Adverse drug reactions observed in patients treated with the doublet combination as well as the monitoring and the management of those are adequately presented in the product information.

2.5.5. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The WSA submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update, as follows:

Update the frequencies according to the latest data.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

Safety concerns

Table SVIII.1 Summary of safety concerns for encorafenib

Important identified risks	-	Secondary skin neoplasms: cuSCC and new primary melanoma
Important potential risks	-	QT prolongation
	-	Non-cutaneous malignancies with RAS mutation
	-	Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors
	-	Over-exposure in patients with moderate to severe hepatic impairment
Missing information	-	Use in patients with severe renal impairment

Pharmacovigilance plan

There are no planned/ongoing additional studies, imposed or required by the competent authority, in the pharmacovigilance plan.

Risk minimisation measures

Safety concern	**Risk minimisation measures**
Important identified risks for encorafenib	
Secondary skin neoplasms: cutaneous squamous cell carcinoma and new primary melanoma	Routine: Warning in Section 4.4 of the SmPC and relevant PIL section Listed in Section 4.8 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer

Safety concern	Risk minimisation measures
	Additional: none
Important potential risks for encorafenib	
QT prolongation	Routine: Dose modification recommendations in section 4.2 of the SmPC Warning in Section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none
Non-cutaneous malignancies with RAS mutation	Routine: Dose modification recommendations in section 4.2 of the SmPC Warning in Section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none
Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors	Routine: Warning in section 4.4 of the SmPC and relevant PIL sections Discussion in section 4.5 Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none
Over-exposure in patients with moderate to severe hepatic impairment	Routine: Dose modification recommendations in section 4.2 of the SmPC and PIL relevant section Warning in section 4.4 and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none
Missing information for encorafenib	
Use in patients with severe renal impairment	Routine: Dosing recommendations in section 4.2 of the SmPC Warning in section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the WSA show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Globally, CRC is the fourth most commonly diagnosed cancer worldwide, with about 1.3 million new cases and over 550,000 deaths in 2018 according to the GLOBOCAN database (Bray, 2018). It is also the second most common type of cancer and the second deadliest cancer in Europe with an estimated 500,000 new cases diagnosed in 2018 and around 242,000 deaths (Ferlay, 2018). Approximately 25% of newly diagnosed patients present with metastases and 50% of patients eventually develop metastatic disease (Van Cutsem, 2014).

Despite major treatment advances over the past decades, metastatic colorectal cancer (mCRC) remains a serious, life-threatening condition, with significant years of potential life lost and substantial losses in productivity due to high incidence rates (Bradley, 2011).

Overall survival (OS) for patients with mCRC has now reached durations of 30 months or longer in the most recent generation of randomised clinical trials (Vogel, 2018; Venook, 2014; Loupakis, 2014, Heinemann, 2013); however, the 5-year survival for the 22% of patients who are initially diagnosed with metastatic disease is 14% (SEER, 2018). The key contributors for longer survival are the increase in resection rates of metastases at diagnosis, emerging treatment options in the therapeutic sequence but also improvement of first-line therapies. The standard first-line therapy for metastatic disease consists of a combination of chemotherapy (based on fluoropyrimidine/leucovorin (5-FU/LV) or capecitabine with irinotecan or oxaliplatin, or in combination with both) with targeted agents (monoclonal antibodies targeting the vascular endothelial growth factor (VEGF) – bevacizumab – and the epidermal growth factor receptor (EGFR) – panitumumab and cetuximab) (Vogel, 2018).

At diagnosis, 8 -12% of metastatic colorectal cancers harbour BRAF mutations (Troiani, 2016) with a broad range of estimates ranging from as low as 5% to as high as 21%.These mutations are usually (> 95%) at the V600E codon and essentially mutually exclusive with RAS mutations (Barras, 2017; Bylsma, 2018; Clarke, 2015; Davies, 2002; De Roock, 2010; Sorbye, 2015). BRAF V600 mutations lead to constitutive activation of BRAF kinase and sustained RAS/RAF/MEK/ERK pathway signalling, resulting in increased cell proliferation and survival (Corcoran, 2012). BRAF V600-mutant CRC is considered a distinct subtype of CRC that has unique clinical characteristics and is associated with a worse prognosis, with a negative impact on both overall survival (OS) and progression-free survival (PFS) (Cremolini, 2015; Loupakis, 2014; Ursem, 2018). In a cohort of 524 patients, OS for patients with BRAF-mutant colorectal cancer was 10.4 months compared with 34.7 months for BRAF wild-type patients. In a multivariate

analysis, the hazard ratio (HR) for survival was 10.662 ($p < 0.001$) (Tran, 2011); the situation is similar in patients with failure of prior systemic therapy (De Roock, 2010; Peeters, 2014b), emphasizing the need to develop novel therapeutic approaches.

3.1.2. Available therapies and unmet medical need

Currently, there are no agents specifically indicated for the treatment of patients with BRAF V600E mutant mCRC and all therapies used in this setting have never been tested in dedicated phase 3 studies.

Since BRAF and KRAS mutations are almost always mutually exclusive (De Roock, 2010; Zheng, 2019), patients with BRAF V600E-mutant mCRC have typically been treated with standard of-care regimens for KRAS wild-type (KRASwt) mCRC in the first line setting i.e. a combination of chemotherapy (based on fluoropyrimidine/leucovorin (5-FU/LV) or capecitabine with or without irinotecan, oxaliplatin, or in combination with both) with targeted agents (monoclonal antibodies targeting the vascular endothelial growth factor (VEGF), mostly bevacizumab or the epidermal growth factor receptor (EGFR), i.e. panitumumab and cetuximab) (Vogel, 2018).

Recommended second-line options depend on the first-line treatment regimen. Common second-line regimens include infusional FOLFIRI or irinotecan with or without cetuximab or panitumumab. The combination of irinotecan/cetuximab is one of the options recommended by the ESMO and NCCN for patients who have previously received irinotecan- or oxaliplatin-based combination regimens, and its use in this setting is consistent with current labelling of cetuximab (Van Cutsem, 2016; NCCN V2, 2019). FOLFIRI has also been used in the control arm of several recent Phase 3 studies in the second-line setting in patients with mCRC unselected for specific mutations (Peeters, 2014b; Tabernero, 2015)

The EMA approved the single -agents regorafenib and trifluridine + tipiracil as oral salvage therapies in patients with chemorefractory disease, who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan- based chemotherapy, and antiVEGF- biological therapy and, if patients are RAS wild type, an antiEGFR- therapy, irrespective of KRAS or BRAF mutational status. Current ESMO and NCCN guidelines include these agents as an additional line of therapy in patients with mCRC who have progressed through standard therapies (Van Cutsem, 2016; NCCN V2, 2019). However, they are minimally active with OS ranging from 6.4 to 8.8 months, a PFS of 1.9 to 3.2 months and an ORR of 1% to 6 % in BRAF wild type mCRC (Grothey, 2013; Mayer, 2015).

Standard therapy for BRAF wild-type mCRC, even with the more intensive regimens, produces substantially poorer outcomes in patients with BRAF V600E-mutant mCRC than in patients with BRAF wild-type disease in the first-line setting (Cremolini, 2015; Loupakis, 2014; Ursem, 2018, Venderbosch, 2014). Second-line treatment for BRAF mutant mCRC using available standards of care for BRAF wild type has shown limited benefits with response rates of generally less than 10% (with best response of progressive disease (PD) in the majority of patients at their first assessment), median PFS of approximately 2 months and a median OS ranging from 4 to 6 months, which is about half of the OS observed with BRAF wild-type mCRC (De Roock, 2010; Kopetz, 2017; Loupakis, 2009; Mitani, 2017; Morris, 2014; Peeters, 2014a; Saridaki, 2013; Seymour, 2013; Ulivi, 2012).

The use of single-agent BRAF inhibitors or of a combination of BRAF and MEK inhibitors without the addition of an EGFR inhibitor has shown minimal clinical activity in BRAF V600E-mutant mCRC (Hyman, 2015; Kopetz, 2015), potentially due to feedback reactivation of EGFR (Corcoran, 2012; Prahallad,°2012).

3.1.3. Main clinical studies

Clinical Study ARRAY-818-302 (BEACON) CRC Study: a multicenter, randomized, open-label, 3-arm phase 3 study of encorafenib + cetuximab plus or minus binimetinib vs. irinotecan/cetuximab or infusional 5-fluorouracil (5-fu)/folinic acid (FA)/irinotecan (FOLFIRI)/cetuximab with a safety lead-in of encorafenib + binimetinib + cetuximab in patients with BRAF V600E-mutant metastatic colorectal cancer.

3.2. Favourable effects

In the BEACON trial (cut-off date 11 February 2019), the Doublet, and Triplet combination therapy showed a 4 months prolonged overall survival, and an about 2.8 months prolonged progression free survival, vs. Control.

An updated analysis (15 August 2019 data cut-off) was provided during the procedure, showing consistent results for OS, ORR and PFS compared to the primary analysis. Both the Triplet and Doublet regimens still demonstrated substantial clinical benefit compared to the Control arm across all efficacy endpoints including

- **OS** Doublet: median OS **9.30 months** (95% CI 8.05; 11.30; [HR **0.61**, 95% CI 0.48, 0.77]); Control **5.88 months** (95% CI 5.09; 7.10).
- **PFS** Doublet **4.27 months** (95% CI 4.07; 5.45; [HR **0.44**; 95% CI 0.35; 0.55]); Control **1.54** months (95% CI 1.48; 1.91)
- and **ORR** Doublet: **19.5%** [95% CI 14.5%, 25.4%], Control: **1.8%** [95% CI 0.5%, 4.6%]

and various supportive and subgroup analyses.

3.3. Uncertainties and limitations about favourable effects

With the updated analysis the MAH decided to leave out binimetinib from the MA claim. This is an option which is offered by the design of BEACON trial having prospectively the key secondary objective comparing OS Doublet vs Control.

3.4. Unfavourable effects

No AESI that was not a known ADR in the initial MAA was identified as candidate ADR for the doublet (encorafenib and cetuximab) combination in the pivotal study.

Adverse drug reactions occurred in 97.7% of patients with 28.7% Grade ≥3 events for the doublet combination (encorafenib and cetuximab) at the cut-off date 15 August 2019. The most frequent ADRs were fatigue (56.9%), nausea (38.0%), diarrhoea (38.4%), acneiform dermatitis (33.3%), abdominal pain (36.6%), Arthralgia (31.5%), decreased appetite (31.0%), vomiting (27.3%) and rash (14.8%).

The combination of encorafenib and cetuximab did not result in an increased frequency of secondary skin neoplasms in mCRC population.

The percentage of patients with on-treatment deaths was 17.6% in the Doublet arm and 15% in the Control arm. The adjusted rate of on-treatment AEs resulting in death per 100 patient-months of exposure was 0.74 in the Doublet arm and 2.06 in the Control arm.

The safety profile of the doublet (encorafenib and cetuximab) combination seems to be acceptable and manageable.

3.5. Uncertainties and limitations about unfavourable effects

Long-term safety data is limited. No separate analysis on the safety in these patients has been provided until now.

3.6. Effects Table

Table 2. Effects Table for BEACON trial [Doublet and Control Arm] (15 August 2019)

Effect	Unit	Doublet	Control	Uncertainties / Strength of evidence	References
	Favourable Effects				
OS	months	9.3	5.9	mature	
PFS	months	4.3	1.5	mature	
ORR	%	20	2	open label	
	Unfavourable Effects				
EAIR All grade AEs	Per 100 patient-months	354.35	552.88		See section "clinical safety"
G3/4 AEs (related)	%	21.3	42.5		
	Per 100 patient-months	4.24	28.27		
SAEs (related)	%	9.7	13.0		
	Per 100 patient-months	1.77	5.68		
Discontinuation (related)	%	4.2	11.9		
	Per 100 patient-months	0.72	5.53		
On treatment deaths	%	17.6	15.0		
	Per 100 patient-months	0,74	2.06		
Fatigue	% (G3/4)	33.3 (4.2)	28.0- (4.7)		
	Per 100 patient-months	7.7	16.55		
Diarrhoea	% (G 3/4)	38.4 (2.8)	48.7 (10.4)		
	Per 100 patient-months	9.69	39.68		
Nausea	% (G 3/4)	38.0 (0.5)	43.5 (1.6)		
	Per 100 patient-months	9.42	32.59		
Vomiting	% (G 3/4)	27.3- (1.4)	31.6 (3.1)		
	Per 100	5.78	16.69		

Effect	Unit		Doublet	Control	Uncertainties / Strength of evidence	References
	patient-months					
Dermatitis acneiform	% (G 3/4)		29.2 (0.5)	39.4- (2.6)		
	Per 100 patient-months		7.48	28.98		
Headache	% (G3/4)		19.9 (0.0)	2.6 (0.0)		
	Per 100 patient-months		5.12	1.31		
Abdominal pain	% (G 3/4)		27.8 (3.2)	28.0 (5.2)		
	Per 100 patient-months		5.79	13.91		
Decreased appetite	% (G3/4)		31.0 (1.4)	29.0- (3.2)		
	Per 100 patient-months		6.62	13.78		
Arthralgia	% (G34)		22.7 (1.4)	1.6 (0.0)		
	Per 100 patient-months		5.23	0.26		
Anaemia	% (G3/4)		16.2 (5.6)	19.2 (6.7)		
	Per 100 patient-months		4.06	11.02		
Skin Neoplasm	% (G 3/4)		1.4 (0.0)	0.0 (0.0)		
	Per 100 patient-months		N/A	N/A		
Haemorrhage	% (G 3/4)		19.0 (1.9)	8.8 (0.0)		
	Per 100 patient-months		N/A	N/A		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The survival gain in the BEACON Study shown by the Doublet compared to the Control arm is considered meaningful and compelling.

With a cut-off date **15.08.2019** median OS in the Doublet arm was **3.42** months longer than that in the Control arm, with median OS estimates using Kaplan-Meier methodology of 9.30 months (95% CI: 8.05,

11.30) in the Doublet arm and 5.88 months (95% CI: 5.09, 7.10) in the Control arm (**p < 0.0001**, stratified log-rank test).

Compared to the control population of the pivotal study (Cetuximab in combination with Irinotecan or FOLFIRI, N=221) the tolerability of the doublet combination (N=220) is slightly better. The contribution of cetuximab does not have a significant impact on the known safety profile of encorafenib mono (300 mg). In general, the reported adverse events of the doublet combination were manageable.

3.7.2. Balance of benefits and risks

An OS gain of about 3.4 months for encorafenib (plus cetuximab) vs. standard chemotherapy (plus cetuximab), observed in the updated efficacy analysis of BEACON trial, is meaningful, compelling, robust, mature, and clinically relevant.

Further primary (ORR) and secondary (PFS, a battery of different QoL questioners) endpoints support this assessment within the usual hierarchy of oncological endpoints.

This clinically relevant benefit is also supported by a slightly better tolerability than the control treatment.

3.7.3. Additional considerations on the benefit-risk balance

In accordance with the provisions of Article 14(11) of Regulation (EC) No 726/2004, the MAH had applied for an additional one year marketing protection period in the framework of the Braftovi/Mektovi WS procedure (EMEA/H/C/WS1695).

Further to the withdrawal of the request for extension of indication for the product Mektovi (binimetinib), an update of the claim for an additional one year marketing protection period has been submitted during the procedure excluding binimetinib.

Having considered the data submitted by the MAH, the CHMP considers that the claim that encorafenib (Braftovi) in the claimed indication brings a significant clinical benefit over existing therapies has been sufficiently justified.

3.8. Conclusions

The benefit-risk-balance is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include encorafenib in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy, as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 2.0 is acceptable. Furthermore, the PI is brought in line with the latest QRD template version 10.1.

The worksharing procedure leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the WSA, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers, that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Braftovi-H-C-4580-WS-1695.