Pierre Fabre Médicament
Represented by: Institut de Recherche Pierre Fabre
45, Place Abel Gance
F-92100 Boulogne

CLINICAL STUDY PROTOCOL

The ANCHOR CRC Study: encor**A**fenib, bi**N**imetinib and **C**etuximab in subjects wit**H** previ**O**usly untreated B**R**AF-mutant **C**olo**R**ectal **C**ancer

Phase II, open-label, single arm, multicenter study of encorafenib, binimetinib plus cetuximab in subjects with previously untreated *BRAF* ^{V600E} -mutant Metastatic Colorectal Cancer

Pierre Fabre Study Code: W00090 GE 2 01

EudraCT Number: 2018-000271-32
NCT Number: NCT03693170

Sponsor's Representative: PII

Study Coordinating investigators:

PII

PII

Version 9_.0- 17JUL20

SPONSOR PERSONNEL

PIERRE FABRE MEDICAMENT

Clinical Study Manager

PII

Clinical Study Physician - (Main Medical Contact)

PII

W00090 GE 2 01

APPROVAL FORM

Protocol Version 9 – 17JUL2020

Sponsor's Representative:
Clinical Study Physician: Date: Signature:
PII

Study Coordinating Investigators: Date: Signature
PII

Date: Signature
PII

W00090 GE 2 01

COUNTRY COORDINATING INVESTIGATOR SIGNATURE FORM

Protocol Version 9 – 17JUL2020

Country: ……..

Country Coordinating Investigator:

"Name"	Date:	Signature:

W00090 GE 2 01
INVESTIGATOR SIGNATURE FORM
Protocol Version 9 – X17JUL2020

By my signature below, I Dr / Pr" Name" , hereby confirm that I agree:

- to conduct the trial described in the protocol W00090 GE 2 01, dated 17 July 2020 in compliance with GCP, with applicable regulatory requirements and with the protocol agreed upon by the Sponsor Pierre Fabre Medicament and given approval by the Ethics Committee / IRB;
- to document the delegation of significant study-related tasks and to notify the Sponsor of changes in site personnel involved in the study;
- to comply with the procedure for data recording and reporting;
- to allow monitoring, auditing and inspection;
- to retain the trial-related essential documents until the Sponsor informs that these documents are no longer needed.

Furthermore, I hereby confirm that I will have and will use the available adequate resources, personnel and facilities for conduct this trial.

I have been informed that certain regulatory authorities require the Sponsor Pierre Fabre Medicament to obtain and supply details about the Investigator's ownership interest in the Sponsor or the study treatment, and more generally about his/her financial relationships with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I agree:

- to supply the Sponsor with any information regarding ownership interest and financial relationships with the Sponsor (including those of my spouse and dependent children);
- to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study;
- that the Sponsor may disclose this information about such ownership interests and financial relationships to regulatory authorities.

Date: Signature:

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SYNOPSIS

Name of Sponsor:	**Pierre Fabre Médicament represented by the Institut de Recherche Pierre Fabre (IRPF)**
Name of Finished Product:	**Encorafenib, Binimetinib, Cetuximab**
Title of the Study:	**Phase II, open-label, single arm, multicenter study of encorafenib, binimetinib plus cetuximab in subjects with previously untreated *BRAF*^{V600E} -mutant Metastatic Colorectal Cancer.**
Study Coordinating Investigator:	PII PII
Study Centre(s):	Approximately 70 centers in Europe, North America and Japan
Publication(s) / Rationale:	*BRAF* mutations, which lead to constitutive activation of BRAF kinase and sustained RAS/RAF/MEK/ERK pathway signaling resulting in increased cell proliferation and survival occur in approximately 10% (range, 5–22%) of the unselected colorectal cancer (CRC) population (**Rozek LS et al, 2010**; **Shaukat A et al, 2010**; **Sorbye et al, 2015**) with lower prevalence in more advanced subject populations. The presence of a *BRAF*^{V600E} mutation is considered a marker of poor prognosis in subjects with mCRC (metastatic ColoRectal Cancer) with a median survival of approximately 12 to 14 months in the first line metastatic setting compared to 21 to 25 months for subjects with *BRAF* wild-type (*BRAF*wt) tumors (**Van Cutsem E et al, 2011**; **Sorbye et al, 2015**). *Preclinical data* The combination of binimetinib, encorafenib, and cetuximab was tested in a *BRAF*^{V600E} mutant human colorectal xenograft model. The average reduction in tumor volume across all animals was better in the group that received the triplet compared to the group that received encorafenib and cetuximab. *Clinical data* Consistent with nonclinical data in human colorectal cancer cell models (**Corcoran RB et al, 2010**; **Yang H et al 2012**), BRAF+MEK+EGFR inhibitors result in greater activity than a dual combination BRAF+EGFR of inhibitors in subjects with *BRAF*^{V600E} mCRC (**Van Cutsem E et al, 2015**).

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Publication(s) / Rationale:	There is a large ongoing multicenter randomized phase III study (NCT02928224), the BEACON CRC study, evaluating binimetinib + encorafenib + cetuximab vs encorafenib + cetuximab compared with Investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab in subjects with *BRAF*^{V600E} mutant mCRC whose disease has progressed after 1 or 2 prior regimens in the metastatic setting. A total of 30 subjects were treated in the safety lead-in (SLI), all of whom received binimetinib (45 mg twice day (BID)) + encorafenib (300 mg once daily (QD)) + cetuximab (400 mg/m^2 initial dose then 250 mg/m^2 once weekly (QW)). Among the 29 subjects with *BRAF*^{V600E} mutant tumors (one patient had a *BRAF* non-V600E mutant tumor) the confirmed overall response rate (cORR) was 48% (14/29 patients) and was 62% in patients with one previous line of therapy (10/16 patients) including 8 partial responses (PR) and 2 complete responses (CR); and in those with two prior lines of therapy the cORR was 31%, (4/13) including 3 PR and 1 CR. Preliminary estimate of median progression–free survival (PFS) is 8.0 months (95% confidence interval (CI), 5.6–8.5 months), with 7 of 29 patients (24%) still in follow-up and progression-free at the cut off date. PFS was similar between patients who had 1 vs 2 previous regimens (median, 95% CI, 7.6 [4.0–8.3] vs 8.1 [4.1–10.8] months) (**Van Cutsem E et al, 2018).** The confirmed ORR of 48% and median PFS of 8.0 months with the triplet combination of binimetinib + encorafenib+cetuximab exceeds historical standard-of-care and exceeds the ORR of 22% in a phase II trial of the doublet of encorafenib + cetuximab **(Tabernero J et al, 2016**). The encouraging preliminary efficacy results observed in the SLI part of the BEACON CRC study are consistent with the preclinical data and together justify the evaluation of this triple combination in the first-line setting of this population, which represents a high-unmet medical need.	
Main Study Period:	Nov 2018 – 27 Dec 2020	Clinical Phase: II
Estimated Study Extension Period	28 Dec 2020 – approximately Dec 2021	Study extension From 28 Dec 2020, access to study treatment will be provided through a Study extension to all subjects whom the investigator considers are continuing to benefit from study treatment (i.e. do not experience unacceptable toxicities and none of the treatment discontinuation criteria are met) until: • the last ongoing subject will discontinue study treatments (including 30-day Safety Follow-Up visit) for any reason (unacceptable toxicity, progression of disease, subject's decision, withdrawal of consent, initiation of subsequent anticancer therapy or death), • or binimetinib/encorafenib are commercially available in the first line setting of *BRAF* ^{V600E} mutated mCRC, • or the binimetinib/encorafenib development program is stopped, whichever comes first.
Objectives:	Primary: • To evaluate the antitumor activity of the combination of encorafenib, binimetinib and cetuximab by assessing the confirmed overall response rate (cORR) by local radiologist/investigator assessment in adult subjects with previously untreated *BRAF* V600E-mutant (*BRAF*^{V600E}) metastatic colorectal cancer (mCRC).	
Objectives:	Secondary: • To evaluate the cORR by central radiologist assessment.	

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	• To evaluate the ORR (for confirmed and unconfirmed responses) by local radiologist/investigator and central assessment. • To assess the effect of the combination of encorafenib, binimetinib and cetuximab on the duration of response (DOR). • To assess the effect of the combination of encorafenib, binimetinib and cetuximab on other time-related efficacy parameters: time to response (TTR), progression-free survival (PFS) and overall survival (OS). • To characterize the safety and tolerability of the combination of encorafenib, binimetinib and cetuximab. • To assess the effect on quality of life (QoL). • To explore health care resource utilization. • To describe the pharmacokinetics (PK) of encorafenib, binimetinib, a metabolite of binimetinib (AR00426032) and cetuximab. Exploratory: • To assess the relationship between changes in tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA19-9]) and radiographic response to treatment. • To assess $BRAF^{V600E}$ status in blood circulating tumor DNA (ctDNA) at baseline. • To assess the potential predictive significance of the microsatellite instability (MSI) status in subjects with $BRAF^{V600E}$ mutant mCRC. • To assess blood- and tissue-based predictive biomarkers of activity.
Endpoints	Primary: • cORR as assessed by local radiologist/investigator review as per Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Secondary: • cORR as assessed by central radiologist review as per RECIST 1.1. • ORR (for confirmed and unconfirmed responses) as per local radiologist/investigator and central assessment. • DOR assessed based on local radiologist/investigator and central review. • TTR assessed based on local radiologist/investigator and central review. • PFS assessed based on local radiologist/investigator and central review. • OS. • Type and severity of adverse events (AEs) and serious adverse events (SAEs), changes in hematology and chemistry values, physical examinations, vital signs, electrocardiogram (ECGs) and echocardiogram (ECHO)/ multi-gated acquisition (MUGA) scans and ophthalmological examinations graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 (NCI-CTCAE v4.03). • Change from baseline in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Cancer subjects (QLQ-C30), EuroQol-5D-5L (EQ-5D-5L), and Patient Global Impression of Change (PGIC). • Resource utilization focused on hospitalizations occurring during the study treatment phase. • Plasma concentrations of encorafenib, binimetinib and the active metabolite of binimetinib (AR00426032) and serum concentration of cetuximab. Exploratory: • Changes from baseline in blood CEA and CA19-9 at the beginning of each cycle and at the end of treatment. • $BRAF^{V600E}$ mutation status in ct-DNA at baseline. • MSI status in formalin-fixed paraffin-embedded (FFPE) samples via established PCR assays in tumor sample versus germline control at screening. • Genomic and proteomic analysis of tumor tissue at baseline and at end of treatment (optional tumor tissue sample at end of treatment). • Genomic and proteomic analysis of blood samples at baseline.

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Methodology:	This is a multinational, multicenter, open-label, single-arm phase II study to evaluate the combination of encorafenib, binimetinib and cetuximab in subjects with *BRAF*^{V600E} mutant mCRC who have not received any prior systemic therapy for metastatic disease. Subjects will be eligible for the study based on identification of a *BRAF*^{V600E} mutation in the tumor tissue as determined by local laboratory result obtained at any time prior to Screening. Only polymerase chain reaction (PCR) and next generation sequencing (NGS)-based results will be acceptable. The *BRAF* mutation status must be confirmed by central laboratory no later than 30 days after the first dose of study treatment. In cases where there is discordance between the local assay and central laboratory results, or if the central laboratory is not able to confirm presence of a *BRAF*^{V600E} mutation due to inadequate or poor sample condition or insufficient amount of tumor cells in sample within 30 days of initiating study therapy, subjects may only continue treatment if there is no clinical indication of deterioration or disease progression and the Investigator determines that the subject is deriving benefit. In such instances, subjects must be informed that the *BRAF* mutation status is unconfirmed and must sign a separate informed consent form (ICF) that includes this information and describes alternative treatment options. Main study period design (treatment phase) The Main study period will include two stages according to a two-stage design. **Stage 1**: In the first stage, 40 subjects will be treated. In case of discordance in the results between the local assay and the central laboratory (potential false-positive local result), or lack of *BRAF*^{V600E} confirmation, subject will be replaced for the primary analysis of the futility analysis. If there are 11 or fewer confirmed responses (CR or PR) in the 40 treated subjects with a centrally confirmed *BRAF*^{V600E} mutation, the study will be stopped. Otherwise, additional subjects will enter stage 2 . Stage 2 may be initiated as soon as 40 subjects with a centrally confirmed *BRAF*^{V600E} mutation are treated and confirmed responses are observed in at least 12 subjects. **Stage 2:** 50 additional subjects will be treated, for a total of 90 subjects with a centrally confirmed *BRAF*^{V600E} mutation. In case of discordance in the results between the local assay and the central laboratory (potential false-positive local result), or lack of *BRAF*^{V600E} confirmation, subjects enrolled in the stage two of the trial will be replaced for the primary analysis. If at any time during the study, either in stage 1 or in stage 2, there is discordance between the local assay and the central laboratory in 3 subjects (≥ 3% of the total targeted 90 treated subjects) or impossibility to confirm the *BRAF*^{V600E} mutation in 6 subjects (≥ 6% of the total targeted 90 treated subjects), all subsequent subjects will be required to have *BRAF*^{V600E} determined by the central laboratory prior to study treatment assignment.For the statistical design, please refer to the statistical section hereunder. Treatment will be administered in 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy or death. An independent Data Safety Monitoring Committee (iDSMC) will review the available safety information at regular intervals as defined in the iDSMC charter. Main study period will end, as initially planned, 1 year after the start of study treatment of the last subject enrolled (as the last enrolled subject started study treatment on 27 Dec 2019, Main study period will end on 27 Dec 2020).

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Methodology:	**Study extension period design** After the Main study period (period from first subject screened to 1 year after the start of study treatment of the last subject enrolled), access to study treatment will be provided from 28 Dec 2020 through a Study extension to all subjects whom the investigator considers are continuing to benefit from study treatment (i.e. do not experience unacceptable toxicities and none of the treatment discontinuation criteria are met) until: • the last ongoing subject will discontinue study treatments (including 30-day Safety Follow-Up visit) for any reason (unacceptable toxicity, progression of disease, subject's decision, withdrawal of consent, initiation of subsequent anticancer therapy or death), • or binimetinib/encorafenib are commercially available in the first line setting of *BRAF* ^{V600E} mutated mCRC, • or the binimetinib/encorafenib development program is stopped, whichever comes first.
Number of subjects:	Target: 90 treated*subjects Stage 1: 40 treated subjects; Stage 2: 50 treated subjects. *In case of discordance in the results between the local assay and the central laboratory (potential false-positive local result), or lack of *BRAF*^{V600E} confirmation, subject will be replaced. If at any time there is lack of confirmation of the *BRAF*^{V600E} mutation in a total of 6 subjects (≥ 6% of the total targeted 90 treated subjects) or discordance between the local assay and thecentral laboratory in 3 subjects (≥ 3% of the total targeted 90 treated subjects), all subsequent subjects will be required to have *BRAF*^{V600E} determined by the central laboratory prior to study treatment assignment.
Diagnosis and Criteria for eligibility	Each subject fulfilling all the inclusion criteria and none of the exclusion criteria will be eligible. **Inclusion Criteria** 1. Provide a signed and dated informed consent document. 2. Male or female ≥ 18 years of age at time of informed consent. 3. Histologically or cytologically confirmed CRC that is metastatic and unresectable at time of study entry (i e. not suitable for complete surgical resection at screening). 4. Presence of *BRAF*^{V600E} mutation in tumor tissue previously determined by a local assay at any time prior to screening. Notes: *a. Only PCR and NGS-based local assays results will be acceptable.* *b. If at any time there is lack of confirmation of the BRAF*^{V600E} *mutation in a total of 6 subjects (≥ 6% of the total targeted 90 treated subjects) or discordance between the local assay and the central laboratory in 3 subjects (≥ 3% of the total targeted 90 treated subjects), all subsequent subjects will be required to have BRAF*^{V600E} *determined by the central laboratory prior to study treatment assignment.* *c. Central testing cannot be repeated to resolve discordances with a local result once the central laboratory delivers a definitive result (positive or negative).*

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	d. If the result from the central laboratory is indeterminate or the sample is deemed inadequate for testing, additional samples should be submitted (archival material only). *e. If more than 1 discordant result from any local laboratory leads to subject enrollment, subsequent results from this local laboratory will not be accepted for further subject enrollment.* 5. Eligible to receive cetuximab per locally approved label with regards to tumor RAS status. *e.g. In agreement with EU label, evidence of wild type RAS (KRAS and NRAS) in EU countries.* 6. Able to provide a sufficient amount of representative tumor specimen (primary or metastatic, archival or newly obtained) for testing of BRAF and RAS mutation status. *Note FFPE tumor tissue block or a minimum of 10 slides, optimally up to 15 slides* 7. Evidence of measurable disease, as per RECIST 1.1. *Note Lesions in areas of prior radiotherapy or other loco-regional therapies are considered measurable only if progression has been documented in the region following therapy.* 8. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. 9. Adequate bone marrow function at screening and baseline: *i. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.* *ii. Platelets ≥ 100 x 10^9/L.* *iii. Hemoglobin ≥ 9.0 g/dL.* *Note Blood transfusions are allowed provided that the subject has not received more than 2 units of red blood cells in the 4 weeks prior to achieve the minimum required hemoglobin level.* 10. Adequate renal function at screening and baseline: *i. Serum creatinine ≤ 1.5x upper limit of normal (ULN) or* *ii. Calculated creatinine clearance (CrCl) ≥ 50 mL/min by Cockroft-Gault formula* 11. Adequate electrolytes at screening and baseline, defined as serum potassium and magnesium levels within institutional normal limits. *Note replacement treatment to achieve adequate electrolytes will be allowed* 12. Adequate hepatic function at screening and baseline: *i. Serum total bilirubin ≤ 1.5 x ULN and < 2 mg/dL. Note Total bilirubin > 1.5 x ULN is allowed if direct (conjugated) bilirubin is ≤ 1.5 x ULN (and indirect (unconjugated) bilirubin is ≤ 4.25 x ULN – Only applicable for France).* *ii. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 2.5 x ULN, or ≤ 5 x ULN in the presence of liver metastases.* 13. Adequate cardiac function at screening: *i. Left ventricular ejection fraction (LVEF) ≥ 50% as determined by MUGA scan or ECHO.* *ii. Mean triplicate QT interval corrected for heart rate according to Fridericia's formula (QTcF) value ≤ 480 msec.* 14. Subject able to take oral medications. 15. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures. 16. Female subjects 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.

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	Notes *(a) Precautions to avoid pregnancy must be conducted from screening through 6 months after the last dose of cetuximab or through 30 days after the last dose of encorafenib or binimetinib, whichever is later if of childbearing potential.* *(b) Permitted methods of contraception as provided (in Section 5.3.1) should be communicated to the subjects and their understanding confirmed. For all females, the pregnancy test must be negative at screening and baseline.* 17. Male subject must agree to take appropriate precautions to avoid fathering a child *Notes* *(a) from screening through 6 months after the last dose of cetuximab or through 90 days after the last dose of encorafenib or binimetinib, whichever is later.* *(b) permitted methods of contraception as provided (in Section 5.3) should be communicated to the subjects and their understanding confirmed.* 18. Subjects under guardianship or partial guardianship will be eligible unless prohibited by local laws or by local/central ethic committees. *Note where allowed, all procedures prescribed by law must be followed.* 19. Affiliated to a social security system, or is a beneficiary (if applicable in the national regulation).
Diagnosis and Criteria for eligibility	**Exclusion Criteria** 1. Prior systemic therapy for metastatic disease. *Note previous adjuvant/neoadjuvant therapy is allowed provided that 1) the interval from the end of chemotherapy to relapse is >6 months OR 2) in the case of neoadjuvant therapy, complete surgical resection was achieved and the interval from the end of chemotherapy to relapse is >12 months. Prior locoregional radiotherapy is allowed.* 2. Prior treatment with any RAF inhibitor, MEK inhibitor, cetuximab or other anti-EGFR treatment. 3. Symptomatic brain metastasis. *Note subjects previously treated or untreated for these conditions who are asymptomatic in the absence of corticosteroid and anti-epileptic therapy are allowed. Brain metastases must be stable for ≥ 4 weeks with imaging (e.g. brain magnetic resonance imaging [MRI] or computed tomography [CT] demonstrating no current evidence of progressive brain metastases at screening).* 4. Leptomeningeal disease. 5. History or current evidence of Retinal Vein Occlusion (RVO) or current risk factors for RVO. *Note Risk factors for RVO are uncontrolled glaucoma or ocular hypertension, history of hyperviscosity syndrome or hypercoagulability syndrome.* 6. Use of any herbal medications/supplements or any medications or foods that are moderate or strong inhibitors or inducers of CYP3A4/5 ≤ 1 week prior to the start of treatment. 7. *Note However, subjects who either discontinue moderate or strong inhibitors or inducers of CYP3A4/5 or switch to another medication at least 7 days prior to starting study treatment are eligible.* Known history of acute or chronic pancreatitis within 6 months prior to the start of the treatment. 8. History of chronic inflammatory bowel disease or Crohn's disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) ≤ 12 months prior to first dose. 9. Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following: *i. 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.* *ii. Symptomatic congestive heart failure (Grade 2 or higher), history or current evidence of clinically significant arrhythmia and/or conduction abnormality ≤ 6 months prior to start of study treatment, except rate controlled atrial fibrillation and paroxysmal supraventricular tachycardia.*

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	10. Uncontrolled hypertension defined as persistent elevation of systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite optimal therapy. 11. Impaired hepatic function, defined as Child-Pugh class B or C. 12. ~~Known history of Gilbert's syndrome or is known to have any of the following genotypes: UDP glucoronosyl transferase (UGT)1A1*6/*6, UGT1A1*28/*28, or UGT1A1*6/*28.~~ No more applicable from Protocol V6.0/Amendment PA03 13. Impaired gastrointestinal function or disease* which may significantly alter the absorption of encorafenib or binimetinib or recent changes in bowel function suggesting current or impending bowel obstruction. **e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection.* 14. Previous or concurrent malignancy* within 5 years of study. **except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix or any other malignancy that has been adequately treated and has not recurred within 3 years prior to study entry.* 15. History of thromboembolic* or cerebrovascular events** ≤ 6 months prior to starting study treatment. **excluding venous thrombosis related to indwelling catheters and treated with low-grade anticoagulants* ***including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis or pulmonary emboli.* 16. Concurrent neuromuscular disorder that is associated with the potential of elevated Creatine Kinase (CK). *Note e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy.* 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 human immunodeficiency virus (HIV) infection. *Note HIV testing will only be conducted in jurisdictions specifically requiring it.* 19. Active hepatitis B or hepatitis C infection. 20. Known contraindication to receive cetuximab at the planned doses. Refer to the most recent cetuximab summary of product characteristics (SPC) or local label as applicable. 21. Subjects who have any medical condition that would, in the Investigator's judgment, prevent the subject's participation in the clinical study due to safety concerns or compliance with study procedures. 22. Any medical or psychiatric condition or laboratory abnormality that may increase the risk with study participation or study drug administration or that may interfere with the interpretation of study. 23. Pregnancy, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test result, or breastfeeding. 24. Is a family member of the Investigator or any associate, colleague, or employee assisting in the conduct of the study (secretary, nurse, technician). 25. Is in a position likely to represent a conflict of interest. 26. Participation in a clinical study with administration of an investigational product within 4 weeks or five times the half-life of the investigational product, whichever is longer, before the first dose of study treatment. Is mentally unable to understand the nature, objectives and possible consequences of the trial; or he/she refuses to its constraints. 27. Is mentally unable to understand the nature, objectives and possible consequences of the trial; or he/she refuses to its constraints.

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Test Product, dose and mode of administration:	Encorafenib: 300 mg PO (oral capsule 4X 75 mg) QD. Binimetinib: 45 mg PO (oral tablet 3X 15 mg) BID. Cetuximab: 400 mg/m^2 intravenous (IV) at Cycle 1 day 1 then 250 mg/m^2 IV every week (QW) for the first 28 weeks. Then, 500mg/m^2 IV every two weeks (Q2W) from week 29 (Cycle 8 day 1). Since implementation of the Urgent Safety Measure (USM) on 26 Mar 2020, to ensure the subjects' safety in the clinical trial by decreasing the number of clinic visits in the context of COVID-19 pandemic, Cetuximab infusions can be given every two weeks at the dose of 500 mg/m^2 administered as a 120-min IV infusion (i.e. on D1 and D15 of each cycle) regardless of the cycle number, after the investigator has evaluated the benefit/risk ratio for the subject with regards to Covid-19 pandemic. If there is a dose modification prior to switching to the biweekly schedule, the total dose per cycle should be maintained (i.e. 200mg/m^2 QW may be changed to a 400mg/m^2 Q2W).Cycle duration: 28 days.
Duration of Treatment:	The treatment will be administered during Main study and Study extension periods until disease progression, unacceptable toxicity, subject's decision, withdrawal of consent, initiation of subsequent anticancer therapy or death. After discontinuation of study treatment, there will be a 30-day safety follow-up period. Subjects will then enter a survival follow-up period. If a subject discontinues the treatment for a reason other than progressive disease, tumor assessment must be performed (as per local and central review) until the start of new anti-cancer therapy, disease progression, death, lost to follow-up, subject decision or withdrawal consent or until the End of the Study.
Statistical Methods:	**<u>Sample Size Determination</u>** The sample size is based on a two-stage design with nominal alpha=2.5% and beta=20%. The null hypothesis that the true response rate is 30% (maximum unacceptable probability of response) will be tested against a one-sided alternative. In the first stage, 40 subjects will be treated. Subjects in whom the presence of *BRAF*^{V600E} is not confirmed by central laboratory will be replaced. If there are 11 or fewer confirmed responses in the 40 treated subjects with a centrally confirmed *BRAF*^{V600E} mutation, inactivity will be declared and the study will be stopped for futility. The time point for the futility analysis will be after all 40 treated subjects of stage 1 with centrally confirmed *BRAF*^{V600E} mutation had the opportunity to complete four post baseline assessments and after subjects with an initial objective response have had an opportunity to have a confirmation scan. However, it will be possible to proceed to Stage 2 as soon as 40 subjects with a centrally confirmed *BRAF*^{V600E} mutation are treated and 12 confirmed responses are observed. Subjects data that will be analyzed during the futility analysis will be reviewed on an ongoing basis in order to determine as soon as possible (even before the inclusion of the 40th subject) whether the criteria for continuing to stage 2 (12 confirmed responses) are satisfied or not. As it may take several treatment cycles for subjects to achieve a confirmed response, a limited number of subjects (maximum 12) from stage 2 may be treated while waiting for all subjects in the initial cohort of 40 subjects in Stage 1 to be evaluable for a confirmed response providing no safety concern was raised by the iDSMC. These additional subjects will not count towards responses in Stage 1 but will be included as part of the Stage 2 cohort, should the study move forward into Stage 2. If at any time it becomes evident that the threshold of 12 responses is unlikely to be met, then additional subjects may not be recruited (eg: 6 or fewer responses among 35 subjects with sufficient follow up [potential for at least 2 assessments]). If the study continues to the second stage, 50 additional subjects will be treated for a total of 90. Subjects in whom the presence of *BRAF*^{V600E} mutation is not confirmed by central laboratory will be replaced. The null hypothesis will be rejected if 37 or more confirmed responses are observed in 90 treated subjects with a centrally confirmed *BRAF*^{V600E} mutation. This design yields a 1-sided type I error rate of 1.6% and power of 80% when the true response rate is 45%. The cut-off for stage 2 analysis will be after all 90 treated subjects of stage 1 and 2 with centrally confirmed *BRAF*^{V600E} mutation had the opportunity to complete four post-baseline tumor assessments, and after subjects with an initial objective response have had an opportunity to have a confirmation scan.

Name of Sponsor:	**Pierre Fabre Médicament represented by the Institut de Recherche Pierre Fabre (IRPF)**
Name of Finished Product:	**Encorafenib, Binimetinib, Cetuximab**
Statistical Methods:	**Data analysis** The Full Analysis Set (FAS) is composed of all included subjects having received at least one dose of study treatment (partial or full). The Efficacy Set (ES) is composed of all FAS subjects with a centrally confirmed *BRAF*^{V600E} mutation.The Per-Protocol Set (PPS) will consist of all subjects from the FAS without any major protocol deviations. The PK Set will consist of all subjects who receive at least 1 dose of encorafenib, binimetinib or cetuximab and who have at least 1 post-dose PK blood collection with associated bioanalytical results. **Efficacy:** The FAS and ES will be used for all efficacy analyses unless otherwise specified. For the main analysis of the primary endpoint, the 95% confidence interval (CI) will be provided on the ES. This analysis will be repeated on the FAS and PPS (supportive analysis). OS will be analyzed using the Kaplan-Meier method that will show median time with accompanying 95% CI and estimates for OS at several time points (including at least 2, 4, 6, 8, 10 and 12 months after start of treatment). Subjects without a death date by the data cut-off date will be censored for OS at their last contact date or the cutoff date, whatever is earlier. Analysis of PFS, DOR and TTR will be performed according to the Kaplan-Meier method. 95% CIs for the median values will be provided. Descriptive methods will be used to present all relevant data: - Continuous data will be summarized with: frequency, median, range, mean, standard deviation and standard error if relevant. - Categorical data will be presented in contingency tables with frequencies and percentages of each modality (including missing data modality). **Safety:** FAS will be used for all safety analyses. Maximum grade or severity will be tabulated, for each Medical Dictionary For Regulatory Activities (MedDRA) System Organ Class and Preferred Term, by cycle and by subject. All analyses will be performed in two different ways: regardless or not of the relationship to treatment as assessed by the investigator. **QoL:** Results of QoL questionnaires (EORTC QLQ-C30, EQ-5D-5L, PGIC) will be summarized for each visit using descriptive statistics on the FAS. Additionally, changes from baseline in the domain scores at the time of each assessment will be summarized for EORTC QLQ-C30 and EQ-5D-5L. Further analysis will be detailed in the Statistical Analysis Plan. **Pharmacokinetic analyses** Plasma concentrations of encorafenib, binimetinib and the active metabolite of binimetinib (AR00426032) and serum concentration of cetuximab will be determined using validated assays. Descriptive statistics of concentrations will be reported. Ad-hoc PK parameters may be generated by compartmental approaches as appropriate.

Name of Sponsor:	Pierre Fabre Médicament represented by the Institut de Recherche Pierre Fabre (IRPF)
Name of Finished Product:	Encorafenib, Binimetinib, Cetuximab
End of study definition:	The end of the study is defined as the time point when all treated subjects will have either progressed or discontinued study treatments (including 30-day Safety Follow-Up visit) for any other reason (unacceptable toxicity, subject's decision, withdrawal of consent, initiation of subsequent anticancer therapy or death).

STUDY FLOW-CHART FOR SCREENING

Cycle/Period		COMMENT
Visit	Screening	
Cycle Days	D-28 to D-1	
Epochs	SCREENING	
Informed consent	**X**	
Inclusion/exclusion criteria	**X**	
Demographics	**X**	
Medical History	**X**	
Prior medications/ therapies/ procedures	**X**	
Height	**X**	
Weight	**X**	
Vital signs	**X**	
Physical examination	**X**	
ECOG PS	**X**	

Cycle/Period		COMMENT
Visit	Screening	
Cycle Days	D-28 to D-1	
Epochs	SCREENING	
ECG	X	
Ophthalmic examination	**X**	Full ophthalmic examination, including best corrected visual acuity for distance testing, OCT, fluorescein angiography if clinically indicated, slit lamp examination, intraocular pressure and dilated fundoscopy with attention to retinal abnormalities
Dermatologic examination	**X**	
ECHO/MUGA	**X**	
Pregnancy test	**X**	For women of childbearing potential: serum pregnancy test
LH, FSH and/or estradiol	**X**	For menopausal women: serum LH,FSH and or estradiol measurement
Hepatitis B surface antigen, Hepatitis C antibody	**X**	
HIV (when required)	**X**	
Hematology	**X**	list of analytes: basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, neutrophils/absolute neutrophil count (ANC), platelets, red blood cells (RBC), white blood cells (WBC)
Clinical chemistry	**X**	list of analytes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total and direct), albumin, alkaline phosphatase, bicarbonate (HCO3) - not mandatory in Japan, blood urea nitrogen (BUN)/urea, calcium, chloride, creatine kinase (CK), creatinine, glucose, lactate dehydrogenase (LDH), magnesium, potassium, sodium, total protein, troponin I or T, uric acid, amylase, lipase. *NOTE:* Direct bilirubin will be measured at screening only if total bilirubin values are abnormal for purposes of determining eligibility to participate in the study. Calculated creatinine clearance(Cockroft-Gault formula) will be measured at screening for purposes of determining eligibility to participate in the study

Cycle/Period		COMMENT
Visit	Screening	
Cycle Days	D-28 to D-1	
Epochs	SCREENING	
Coagulation	**X**	list of analytes: prothrombin time (PT) or International Normalized Ratio (INR), activated partial thromboplastin time (aPTT)
Urinalysis	**X**	Urinalysis – list of analytes: blood, glucose, ketones, leukocytes, hydrogen ion concentration (pH), protein
Blood Sample for CRP	**X**	

Cycle/Period		COMMENT
Visit	Screening	
Cycle Days	D-28 to D-1	
Epochs	SCREENING	
Blood sample for tumor markers (CEA, CA19-9)	**X**	
A tumor sample (archival or fresh) should be sent to central laboratory to test for $BRAF^{V600E}$ and RAS^{wt} status and MSI testing	**X**	
Concomitant medications/therapies	**X**	
Tumor evaluation (CT scan, MRI)	**X**	

Abbreviations: CA19-9 = cancer antigen 19-9; CEA = carcinoembryonic antigen; CT = Computed Tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HIV= Human immuno deficiency virus; MRI = magnetic resonance imaging; MSI = microsatellite instability; MUGA = multi-gated acquisition

STUY FLOW-CHART FOR MAIN STUDY PERIOD (TREATMENT AND FOLLOW-UP PERIOD, UP TO 27 DEC 2020)

Cycle/Period	Cycle 1[a]					Subsequent Cycles[a]						
Visit	C1 D1		C1 D8	C1 D15	C1 D22	Cn D1	Cn D8	Cn D15	Cn D22	End of treatment	Safety Follow-Up[q] (EOS)	Survival (Every 3 Months)
Cycle Days	D1		D8	D15	D22	D1	D8[v]	D15	D22[v]	Dxx	Dxx	Dxx
Epochs	SCREENING	TREATMENT									FOLLOW-UP	LONG-TERM FOLLOW-UP
	Pre-Dose	Post-Dose										
Procedures	± 3-day window for procedures/assessments											
Inclusion/exclusion criteria	X											
Medical History	X											
Prior medications/therapies/procedures	X											
Weight	X[g]					X				X	X	
BSA	X					X						
Vital signs[r]	X		X	X	X	X	X	X	X	X	X	

Cycle/Period	Cycle 1[a]				Subsequent Cycles[a]						
Visit	C1 D1	C1 D8	C1 D15	C1 D22	Cn D1	Cn D8	Cn D15	Cn D22	End of treatment	Safety Follow-Up[q] (EOS)	Survival (Every 3 Months)
Cycle Days	D1	D8	D15	D22	D1	D8[v]	D15	D22[v]	Dxx	Dxx	Dxx
Epochs	SCREENING	TREATMENT								FOLLOW-UP	LONG-TERM FOLLOW-UP
	Pre-Dose	Post-Dose									
Procedures	± 3-day window for procedures/assessments										
Physical examination[r] (D8, D15,D22 if clinically indicated)	X[g]				X				X	X	
ECOG PS[r]	X[g]				X				X	X	
ECG	X[h]	X[h]		X[h]	X[h]				X	X	
Visual assessement (D8, D15,D22 if clinically indicated) / Ophthalmic examination[r]	X[i]				X[i]				X[i]	X[i]	
Dermatologic examination	X[g]				X[j]				X		
ECHO/MUGA					X[k]				X		
Pregnancy test[b]	X[g]				X				X	X	
Hematology[c,r]	X[g]			X	X	X				X	X	
Clinical chemistry[d,r]	X[g]			X		X				X	X	
Coagulation[e,r]	X[g]					X				X	X	
Urinalysis[f,r]	X[g]					X				X	X	

Cycle/Period	Cycle 1[a]				Subsequent Cycles[a]						
Visit	C1 D1	C1 D8	C1 D15	C1 D22	Cn D1	Cn D8	Cn D15	Cn D22	End of treatment	Safety Follow-Up[q] (EOS)	Survival (Every 3 Months)
Cycle Days	D1	D8	D15	D22	D1	D8[v]	D15	D22[v]	Dxx	Dxx	Dxx
Epochs	SCREENING	TREATMENT								FOLLOW-UP	LONG-TERM FOLLOW-UP
	Pre-Dose	Post-Dose									
Procedures	± 3-day window for procedures/assessments										
Blood sample for tumor markers (CEA, CA19-9)[r]	X[g]				X				X		
Concomitant medications/therapies	Assess Continuously										
EORTC QLQ-C30, EQ-5D-5L, PGIC[s]	X				X				X	X	
Healthcare Resource Utilization		Continuous Monitoring[u]									
Tumor evaluation (CT scan, MRI)		Every 6 weeks (±7 days) from first dose (study treatment initiation date) for the first 12 weeks, then every 8 weeks (±7 days); the time-window allowed for first tumor evaluation is day 42 +7 days from first dose[l]								X[m]	
PK blood samples		X[n]			X[n] (cycle2 only)						

Cycle/Period	Cycle 1[a]					Subsequent Cycles[a]						
Visit	C1 D1		C1 D8	C1 D15	C1 D22	Cn D1	Cn D8	Cn D15	Cn D22	End of treatment	Safety Follow-Up[q] (EOS)	Survival (Every 3 Months)
Cycle Days	D1		D8	D15	D22	D1	D8[v]	D15	D22[v]	Dxx	Dxx	Dxx
Epochs	SCREENING	TREATMENT									FOLLOW-UP	LONG-TERM FOLLOW-UP
	Pre-Dose	Post-Dose										
Procedures	± 3-day window for procedures/assessments											
Blood samples for ctDNA analysis (*BRAF*^{V600})	X											
Blood sample for MSI testing (control sample)	X											
Tumor biopsy (optional)										X[o]		
encorafenib/binimetinib dispense (plus dosing diary)	X					X						
Assess encorafenib/binimetinib compliance						X				X		
Cetuximab IV infusion[t]	X		X	X	X	X	X	X	X			
Adverse Events	Assess Continuously											
Survival status											X	Every 3 Months[p]
Documentation of subsequent anticancer therapy											X	Every 3 Months[p]
Documentation of PD after subsequent anticancer therapy												Every 3 Months[p]

a	Except C1D1, if visit is missed. Theoretical cycles dates (7 days ± 3) are kept constant irrespectively of whether the visit is done and/or the product is administered or not. If subject doesn´t come for CnD1 visit, the CnD1 assessments will still need to be performed (and shall be recorded on the unscheduled visit in the e-CRF).
b	Local urine pregnancy test for women of childbearing potential except serum pregnancy test at EOT.
c	Hematology - list of analytes: basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, neutrophils/absolute neutrophil count (ANC), platelets, red blood cells (RBC), white blood cells (WBC)
d	Clinical Chemistry – list of analytes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total and direct),albumin, alkaline phosphatase, bicarbonate (HCO3), blood urea nitrogen (BUN)/ urea, calcium, chloride, creatine kinase (CK), creatinine, glucose, lactate dehydrogenase (LDH), magnesium, potassium, sodium, total protein, troponin I or T, uric acid, amylase, lipase. Calculated creatinine clearance (Cockroft-Gault formula) will be measured at screening Bicarbonates (HCO3): not mandatory in Japan
e	Coagulation – list of analytes: prothrombin time (PT) or International Normalized Ratio (INR);activated partial thromboplastin time (aPTT)
f	Urinalysis – list of analytes: blood, glucose, ketones, leukocytes, hydrogen ion concentration (pH), protein
g	Procedure does not have to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (i.e., first day of dosing).
h	-Electrocardiograms are to be performed in triplicate after 5 minutes rest predose on Cycle 1 Day 1 (conducted within approximately 5 to 10 minutes total time), followed by a single ECG at 2.0 (+/- 0.5) hours after administration of encorafenib and binimetinib and before the start of the cetuximab infusion. -Single ECGs are to be performed on Cycle 2 Day 1 predose and at 2.0 (+/- 0.5) hours after administration of encorafenib and binimetinib and before the start of the cetuximab infusion. -Single ECGs are to be performed predose at remaining time points. Electrocardiograms should be performed prior to PK and PD blood collection at equivalent nominal timepoints.
i	Visual assessment (General inspection of the eyes, examination of motility and alignment, visual disturbance including diminished central vision, blurred vision or loss of vision) to be performed on site by the investigator. Full ophthalmic examination by ophthalmologist to be performed at EOT and, if clinically indicated during treatment, including best corrected visual acuity for distance testing, slit lamp examination, intraocular pressure and dilated fundoscopy with attention to retinal abnormalities, OCT and/or fluorescein angiography as appropriate. A full ophthalmic examination at the 30-day follow up is only required if there was a clinically significant abnormality noted at EOT.
j	Dermatologic examinations are to be performed every 8 weeks from Cycle 1 Day 1 (i.e., on Day 1 of Cycles 3, 5, 7…).
k	ECHO/MUGA scans are to be performed on Cycle 2 Day 1 and Cycle 5 Day 1, then every 12 weeks and EOT
l	Tumor evaluations are to be performed every 6 weeks (±7 days) from first dose for the first 12 weeks, then every 8 weeks (±7 days) until disease progression. The time window allowed for the first tumor assessment (i.e. day 42 from first dose) is +7 days.
m	If a subject discontinue study treatment for reasons other than disease progression, then tumor assessments must be performed (as per local and central review) every 6 weeks (first 12 weeks) then every 8 weeks until the start of new anti-cancer therapy, disease progression, death, lost to follow-up, subject's decision or consent withdrawn.
n	PK samples will be collected during Cycle 1 and Cycle 2 only. On Cycle 1 Day 1 postdose at 2 h (± 10 min) and 6 h (± 30 min). PK samples will be collected on Cycle 2 Day 1 predose (just prior to dosing) and postdoseat 2 h (± 10 min). PK blood samples for encorafenib/binimetinib and potentially relevant metabolites will be processed to plasma. PK blood samples for cetuximab will be processed to serum.
o	Optional tumor sample will be requested only for subjects that discontinue study drug treatment due to disease progression.
p	For subjects who discontinue study treatment due to disease progression, the survival follow up phase will start after the 30-days safety follow up is complete The subject will be contacted by phone for collection of information This may be conducted more frequently as needed. For subjects who discontinue study treatment due to reasons other than disease progression, tumor assessment must be performed until start of new anti cancer therapy,disease progression, death, lost to follow-up, subject's decision or consent withdrawn.
q	To be performed 30-day after end of treatment (EOT) , when clinically appropriate, it is recommended subjects be monitored with physical examinations, dermatological examinations and chest CT scans for cutaneous and non-cutaneous secondary malignancies for up to 6 months after the last encorafenib dose or until initiation of another antineoplastic therapy.

r	To be performed prior to study treatment administration. Only for vital signs: not to be performed at D8 and D22 starting week 29. Complete physical examination to be performed at screening. For all other visits, physical examination should be targeted as clinically indicated
s	The questionnaires should be completed by the subjects at the beginning of the study visit prior to receiving any study treatment, prior to any other study assessment or consultation with the Investigator, and prior to being informed of their current disease status.
t	Cetuximab will be administered as a weekly schedule for the first 28 weeks. Subjects on study will switch to a biweekly schedule starting on week 29 (Cycle 8 day 1). Since implementation of the Urgent Safety Measure on 26 Mar 2020, in order to ensure the subjects' safety in the clinical trial by decreasing the number of clinic visits in the context of COVID-19 pandemic, Cetuximab infusions can be given every two weeks at the dose of 500 mg/m^2 administered as a 120-min IV infusion (i.e.on D1 and D15 of each cycle) regardless of the cycle number, after the investigator has evaluated the benefit/risk ratio for the subject with regards to Covid-19 pandemic. If there was a dose modification prior to switching to the biweekly schedule, the total dose per cycle should be maintained (i.e. 200mg/m^2 QW, may be changed to a 400mg/m^2 Q2W).
u	Information related to the length of stay, hospital facilities used, reasons for hospitalization, and hospital discharge information will be collected
v	From Week 29 (cycle 8), D8 and D22 visits will not be performed (biweekly infusions of cetuximab: no cetuximab infusion on D8 and D22) Since implementation of the Urgent Safety Measure on 26 Mar 2020, in order to ensure the subjects' safety in the clinical trial by decreasing the number of clinic visits in the context of COVID-19 pandemic, Cetuximab infusions can be given every two weeks at the dose of 500 mg/m2 administered as a 120-min IV infusion (i.e. on D1 and D15 of each cycle) regardless of the cycle number, after the investigator has evaluated the benefit/risk ratio for the subject with regards to Covid-19 pandemic. If the investigator implements this change, D8 and D22 visits before C8D1 will be performed by phone calls to ensure subject's safety and will have to be documented in source documents for subjects not having yet reached C8D1 at the time of USM implementation.
Abbreviations: BSA = body surface area; CA19-9 = cancer antigen 19-9; CEA = carcinoembryonic antigen; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = EuroQol-5D-5L; HIV= Human immuno deficiency virus; IV = intravenous(ly); MRI = magnetic resonance imaging; MSI = microsatellite instability; MUGA = multi-gated a cquisition; PD = progressive disease; PGIC = Patient's Global Impression of Change; PK = pharmacokinetic(s).	

STUDY FLOW-CHART FOR STUDY EXTENSION PERIOD (FROM 28 DEC 2020)

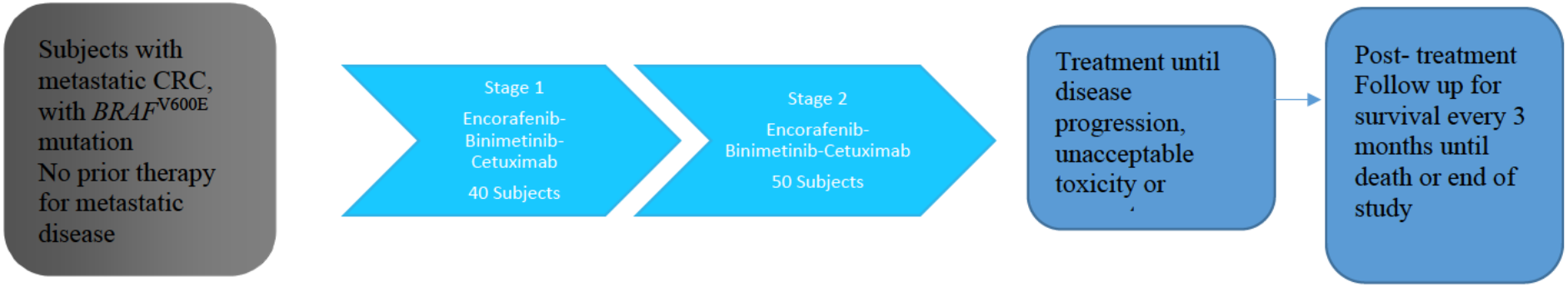
Cycle/Period		*Subsequent Cycles during study extension*[a,b]				
Visit	*Any visit before Study extension period onset*	*CnD1*	*CnD15*	*End of treatment*	*Safety Follow-Up* (EOS)[m]	*Survival (Every 3 Months)*
Cycle Days	*D1/D15*	*D1*	*D15*	*Dxx*	*Dxx*	*Dxx*
Epochs		TREATMENT			*FOLLOW-UP*	LONG-TERM FOLLOW-UP
Procedures						
Informed Consent addendum	X[a]					
Weight		X		X	X	
BSA		X				
Vital signs[n]		X	X	X	X	
Physical examination [n]		X		X	X	
ECOG PS[n]		X		X	X	
ECG		X[h]		X	X	
ECHO/MUGA		X[h]		X		
Visual assessement/ Ophthalmic examination[n]		X[i]		X[i]	X[i]	
Dermatologic examination[n]		X		X		
Pregnancy test[c,n]		X		X	X	
Hematology[d,n]		X		X	X	
Clinical chemistry[e,n]		X		X	X	
Urinalysis[f,n]		X		X	X	
Blood sample for tumor markers (CEA, CA19-9)[g,n]		X		X		

Cycle/Period	*Subsequent Cycles during study extension*[a,b]				
Visit	*CnD1*	*CnD15*	*End of treatment*	*Safety Follow-Up* (EOS)[m]	*Survival (Every 3 Months)*
Cycle Days	*D1*	*D15*	*Dxx*	*Dxx*	*Dxx*
Epochs	TREATMENT			*FOLLOW-UP*	LONG-TERM FOLLOW-UP
Procedures					
Concomitant medications/therapies	X				
Tumor evaluation (CT scan, MRI)	**Every 12 weeks (±7 days)**[j]			X[k]	
encorafenib/binimetinib dispense (plus dosing diary)	X				
Assess **encorafenib/binimetinib** compliance	X		X		
Cetuximab IV infusion	X	X			
Adverse Events	X				
Tumor biopsy (optional)°			X		
Survival status				X	Every 3 Months[l]
Documentation of subsequent anticancer therapy				X	Every 3 Months[l]
Documentation of PD after subsequent anticancer therapy					Every 3 Months[l]

a	From 28 dec 2020 (start of Study extension period), all treated subjects who are still benefiting from study treatments, will continue, if they consent, to receive study treatment in the Study extension period (protocol amendment 6 – protocol V9). After treatment is discontinued (during Main study or Study extension periods), all subjects, if they consent, will be followed for survival until.the End of the Study (defined as the time point when all treated subjects will have either progressed or discontinued study treatments (including 30-day Safety Follow-Up visit) for any other reason (unacceptable toxicity, subject's decision, withdrawal of consent, initiation of subsequent anticancer therapy or death).
b	Theoretical cycles dates (15 ± 3 days) are kept constant irrespectively of whether the visit is done and/or the product is administered or not. If subject doesn´t come for CnD1 visit, the CnD1 assessments will still need to be performed (and shall be recorded on the unscheduled visit in the e-CRF).
c	Local urine pregnancy test for women of childbearing potential except serum pregnancy test at EOT.
d	Hematology - list of analytes: basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, neutrophils/absolute neutrophil count (ANC), platelets, red blood cells (RBC), white blood cells (WBC)
e	Clinical Chemistry – list of analytes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total and direct), albumin, alkaline phosphatase,, calcium, chloride, creatinine, glucose, magnesium, potassium, sodium, total protein,
f	Urinalysis – list of analytes: blood, glucose, ketones, leukocytes, hydrogen ion concentration (pH), protein
g	Blood sample for tumor markers (CEA, CA19-9) should be collected only if performed as per clinical routine practice
h	ECGs scans must be performed every 3 cycles at D1 and at EOT ; and more frequently if clinically indicated during study . ECHO MUGA must be performed every 12 weeks at D1, and at EOT or more frequently if clinically indicated during study
i	Visual assessment (general inspection of the eyes, examination of motility and alignment, visual disturbance including diminished central vision, blurred vision or loss of vision) to be performed on site by the investigator. Full ophthalmic examination by ophthalmologist to be performed at EOT and, if clinically indicated during treatment, including best corrected visual acuity for distance testing, slit lamp examination, intraocular pressure and dilated fundoscopy with attention to retinal abnormalities, OCT and/or fluorescein angiography as appropriate. A full ophthalmic examination at the 30-day FU is only required if there was a clinically significant abnormality noted at EOT
j	Tumor evaluations to be performed every 12 weeks (±7 days) until disease progression
k	If a subject discontinues study treatment for reasons other than disease progression, then tumor assessments should continue to be performed (per local and central review) every 12 weeks until the start of new anti-cancer therapy, disease progression, death, lost to follow-up, patient decision, consent withdrawn or study end
l	For subjects who discontinue study treatment due to disease progression, the survival follow up phase will start after the 30-days safety follow up is complete. The subject will be contacted by phone for collection of information every 3 months. For subjects who discontinue study treatment due to reasons other than disease progression, tumor assessment must be performed until start of new anti cancer therapy,disease progression, death, lost to follow-up, subject's decision, consent withdrawn or study end.

m	To be performed 30-days after end of treatment (EOT). When clinically appropriate,as per standard of care it is recommended that subjects be monitored for physical examinations, dermatological examinations and chest CT scans for cutaneous and non-cutaneous secondary malignancies for up to 6 months after the last encorafenib dose or until initiation of another antineoplastic therapy.
n	To be performed prior to study treatment administration. For Physical examination: examination should be should be targeted as clinically indicated - dermatologic examinations are to be performed every 8 weeks at D1 of the cycle
o	Optional tumor sample will be requested only for subjects that discontinue study due to disease progression.
Abbreviations: BSA = body surface area; CA19-9 = cancer antigen 19-9; CEA = carcinoembryonic antigen; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IV = intravenous(ly); MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; PD = progressive disease.	

STUDY SCHEME



LIST OF ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AMP	Association for Molecular Pathology
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASCP	American Society for Clinical Pathology
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
BP	blood pressure
bpm	beat per minute
BRAF	B-RAF proto-oncogene, serine/threonine kinase
BRAF^{V600E}	B-RAF proto-oncogene, serine/threonine kinase V600E-mutant
BRAFwt	B-RAF proto-oncogene, serine/threonine kinase wild-type
BSA	body surface area
BUN	blood urea nitrogen
CA	competent authority
CA19-9	carbohydrate antigen 19-9
CABG	coronary artery bypass graft
CAP	College of American Pathologists
CEA	carcinoembryonic antigen
CI	confidence interval

CK	creatine kinase
C_{max}	maximum concentration
CR	complete response
CRA	clinical research associate
CRC	colorectal cancer
CrCl	creatinine clearance
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CT DNA	blood circulating tumor DNA
CTFG	Clinical Trials Facilitation Group Guidelines
CYP	cytochrome P450
D	Day
DBP	diastolic blood pressure
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	desoxyribonucleic acid
DOR	duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group performance status
e-CRF	electronic case report form
EDTA	ethylenediaminetetraacetic acid
EGFR	epidermal growth factor receptor
EGFRI	EGFR inhibitor
EMEA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer

EOT	end of treatment
EQ-5D-5L	EuroQol-5D-5L
ERK	extracellular signal-regulated kinase
ESMO	European Society of Medical Oncology
EU	European Union
FA	folinic acid
FAS	full analysis set
FDA	United States Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FOLFIRI	5-fluorouracil/folinic acid/irinotecan
FOLFOX	5-fluorouracil/folinic acid/oxaliplatin
FOLFOXIRI	5-fluorouracil/folinic acid/oxaliplatin/irinotecan
FSH	follicle-stimulating hormone
5-FU	5-fluorouracil
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
H1	histamine receptor
HC03	Bicarbonate
hCG	human chorionic gonadotropin
HDPE	high-density polyethylene
hERG	human ether-a-go-go-related gene
HFSR	hand-foot skin reaction
Hg	Mercury
HIV	human immunodeficiency virus
HR	hazard ratio or heart rate
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
iDSMC	independent Data Safety Monitoring Committee

INR	international normalized ratio
IEC	independent ethics committees
ILD	interstitial lung disease
IRB	institutional review board
IRPF	Institut de Recherche Pierre Fabre
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
KA	Keratoacanthoma
KM	Kaplan-Meier
KRA*S*	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LC/MS-MS	liquid chromatography-tandem mass spectrometry
LDH	lactase dehydrogenase
LFT	liver function tests
LH	luteinizing hormone
LLN	lower limit of the normal reference range
LOQ	limit of quantitation
LVEF	left ventricular ejection fraction
mCRC	metastatic colorectal cancer
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen activated protein kinase kinase
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
NaF PET	sodium fluoride positron emission tomography
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

NGS	next generation sequencing
NRAS	neuroblastoma ras viral oncogene
NSAID	nsaids (non-steroidal anti-inflammatory drugs)
NTI	narrow therapeutic index
OAT	organic anionic transporter
OATP	organic anion-transporting peptide
OCT	optical coherence tomography
OCT	organic cationic transporter
ORR	objective response rate / overall response rate
cORR	confirmed objective response rate
OS	overall survival
PABA	para-aminobenzoic acid
PCR	polymerase chain reaction
pERK	phosphorylated extracellular signal-regulated kinase
PD	progressive disease + pharmacodynamic
PFS	progression-free survival
PGIC	Patient's Global Impression of Change
P-gp	P-glycoprotein
pH	hydrogen ion concentration
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PO	oral(ly) per os
PP	Polypropylene
PPS	per-protocol set
PR	partial response
PRO	patient reported outcome
PT	preferred term or prothrombin time
QD	once daily
QLQ-C30	quality of Life Questionnaire for Cancer Subjects
QoL	quality of life

QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
QW	once weekly
Q2W	every two weeks
RAF	raf rapidly accelerated fibrosarcoma I 3K
RAS	oncogene rat sarcoma
RBC	red blood cells
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RNA Seq	RNA sequencing
RPED	retinal pigment epithelial detachment
RP2D	recommended Phase 2 dose
RR	response rate
RTQPCR	real time quantitative polymerase chain reaction
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	steering committee
SCC	squamous cell carcinoma
SD	stable disease
SLI	safety lead in
SOC	system organ class
SPC	summary of product characteristics
SPF	sun protection factor
SSA	sessile serrated adenoma
$t_{1/2}$	terminal half-life
TEAE	treatment emergent adverse event
Tmax	time of maximum concentration
TdP	torsade de pointes

TSA	traditional serrated adenoma
TTR	time to response
UGT	UDP-glucuronosyl transferase
ULN	upper limit of normal
US	United States
USM	Urgent Safety Measure
V	Version
VEGFi	vascular endothelial growth factor inhibitor
Wt	wild-type
WBC	white blood cells
WHO	World Healh Organization

1. INTRODUCTION AND STUDY RATIONALE

1.1. BACKGROUND INFORMATION ON THE TARGET PATHOLOGY AND THERAPY

Metastatic colorectal cancer (mCRC) continues to be a serious, life-threatening condition. According to GLOBOCAN data, 1.36 million new cases affecting 17.2 individuals per 100000 population (746000 men and 614000 women) are diagnosed in the world each year, and 693000 people (373000 men and 320000 women) die from colorectal cancer (CRC), accounting for a yearly mortality rate of 8.4 per 100000. In the United States, the American Cancer Society's estimate for the number of colorectal cancer cases for 2017 are 95,520 new cases. In the World Health Organisation (WHO) European Region, CRC is the first tumor by incidence, with 471000 new cases each year and a mean mortality rate of 28.2 per 100000 population.

Approximately 25% of subjects present with metastases and 50% eventually develop metastatic disease (**Van Cutsem et al, 2014**).

Standard therapy in subjects with unresectable mCRC includes combination regimens with cytotoxic and targeted agents. In the last decade, substantial advances in the treatment of mCRC have resulted in an improvement in overall survival (OS) from 10 to 12 months to more than 20 months. This improvement is thanks to the addition of irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab to the standard treatment with 5-fluorouracil (5 FU)/folinic acid (FA).

BRAF^{V600E} MUTANT COLORECTAL CANCER

BRAF mutations, which lead to constitutive activation of BRAF kinase and sustained RAS/RAF/MEK/ERK pathway signaling resulting in increased cell proliferation and survival, occur in approximately 10% (range, 5–22%) of the unselected CRC population (**Rozek LS et al, 2010**; **Shaukat A et al, 2010**).

According to the European Society of Medical Oncology (ESMO) Consensus Guidelines for the management of subjects with mCRC (**Van Cutsem E et al, 2016**), *BRAF* mutation status should be assessed alongside *RAS* mutation status for prognostic assessment (and/or potential selection for clinical trials) [level I, B].

In the United States (US), the National Comprehensive Cancer Network panel (NCCN) strongly recommends genotyping of tumor tissue (either primary tumor or metastasis) in all subjects with mCRC, for *RAS* (KRAS exon 2 and non-exon 2; NRAS) and *BRAF* upon diagnosis of stage IV disease (**Benson AB et al, 2017**) Testing for the *BRAF* ^{V600E} mutation (*BRAF*^{V600E}) can be performed on formalin-fixed paraffin-embedded (FFPE) tissues and is usually performed by polymerase chain reaction (PCR) amplification and direct Deoxyribonucleic Acid (DNA) sequence analysis.

The presence of a *BRAF*^{V600E} mutation is considered a marker of poor prognosis in subjects with mCRC and is associated (in the first line setting for metastatic disease) with a median survival of approximately 12 to 14 months compared to 21 to 25 months for subjects with *BRAF* wild-type (*BRAF*wt) tumors (**Van Cutsem E et al, 2011**). Failure to achieve good survival outcomes through standard doublet chemotherapy agents in subjects with *BRAF* ^{V600E} mutant mCRC has ignited efforts to combine multiple target therapies **(Kopetz S el al, 2017**; **Corcoran RB et al, 2016**).

First line treatment options for *BRAF*^{V600E} mutant mCRC patients

Currently, there are no agents specifically indicated for subjects with *BRAF*^{V600E} mutant mCRC. However, since *BRAF* and *KRAS* mutations are almost always mutually exclusive, subjects with *BRAF*^{V600E} mCRC have typically been treated with standard-of-care regimens for *RAS*wt mCRC. Subjects with *RA*Swt mCRC typically receive infusional 5-FU/FA/oxaliplatin (FOLFOX) or (5-FU/FA/irinotecan (FOLFIRI) with or without bevacizumab (anti VEGF antibody) or cetuximab (anti EGFR antibody) as initial therapy. A retrospective study reported no differences in PFS irrespective of whether oxaliplatin- or irinotecan-based chemotherapy was administered in the first-line setting in patients with *BRAF* mutant CRC (6.4 versus 5.4 months; P=0.99). (**Morris V et al, 2014**). There is insufficient evidence to conclude that *BRAF* is a predictive biomarker for irinotecan or oxaliplatin, as patients benefit regardless of their mutational status.

Some authors have proposed more intensive treatment based on the combination of 5-fluoruracil, leucovorin, oxaliplatin, irinotecan and bevacizumab (FOLFOXIRI-Beva) based on a retrospective analysis of a prospective phase II trial evaluating this combination, (**Loupakis F et al, 2014**) which included 15 *BRAF* mutant CRC patients. Results were initially encouraging compared with historical controls with median PFS and OS of 11.8 and 24.1 months and a 72% response rate (RR).

In the follow up phase III trial which randomized a total of 28 patients with *BRAF* mutant mCRC, FOLFOXIRI-Bev had improved results compared with FOLFIRI Bev with respect to OS (median 19.0 versus10.7 months; HR, 0.84; 95% CI, 0.24–1.2), PFS (median 7.5 versus 5.5 months; HR, 0.57; 95% CI, 0.27– 1.23), and ORR (55% versus 42%; Odd Ratio, 1.82; 95% CI, 0.38–8.78).

Use of EGFRi with standard chemotherapy in the first line setting for *BRAF^{V600E}* mutant mCRC patients

Limited data from unplanned retrospective subset analyses of subjects with mCRC treated in the first-line setting suggest that, although a *BRAF^{V600E}* mutation confers a poor prognosis regardless of treatment, subjects with disease characterized by this mutation may receive some benefit from the addition of cetuximab to front-line therapy (**Van Cutsem E et al, 2011**; **Bokemeyer C et al, 2012**). On the other hand, results from the randomized phase III Medical Research Council (MRC) COIN trial suggest that cetuximab may have no effect or even a detrimental one in subjects with *BRAF*-mutated tumors treated with CapeOx (**Douillard JY et al, 2013**; **Maughan TS et al, 2011**).

While data suggest *BRAF* mutation status has clear prognostic value in mCRC, its predictive value for response and benefit from EGFR-directed treatments, such as cetuximab, remain controversial. Retrospective analyses of recent trials have suggested that *BRAF* mutations are not predictive of outcome with EGFR-directed therapies (**Tol J and Punt CJ, 2010**) in certain settings whereas other analyses have suggested that cetuximab and panitumumab are most active in subjects with *BRAF*wt mCRC (**Di Nicolantonio F et al, 2008**; **De Roock W et al, 2010**). In a recent meta-analysis of 7 randomized controlled trials in which subjects received panitumumab or cetuximab in different lines of therapy, and with a range of background chemotherapy, no significant interaction was noted between the benefits of anti-EGFR therapy (measured as OS and PFS) and the presence of *BRAF* mutations. These results suggest that anti-EGFR therapy may have benefit for subjects with

BRAF^{V600E} CRC. Consistent with this recent publication, a joint committee of the American Society for Clinical Pathology (ASCP), the College of American Pathologists (CAP), the Association for Molecular Pathology (AMP), and the American Society of Clinical Oncology (ASCO), issued draft guidelines for the evaluation of molecular markers for CRC which stated that there is insufficient evidence to recommend *BRAF*^{V600E} mutation status as a predictive molecular marker for response to EGFR directed therapies (see **Table 1**).

Table 1: First line Phase II and III clinical trials with EGFR and VEGFi and *BRAF* mutational status for metastatic colorectal cancer subjects

Reference	No of patients	Treatment	BRAFm (%)	OS (months)	PFS (months	RR
NORDIC (Tveit KM et al, 2012)	457	FLOX+C FLOX	20	NA	NA	19.4% 21% NSS
CRYSTAL/OPUS (Bokemeyer C et al, 2012)	1535	FOLFIRI/FOLFOX+C FOLFIRI/FOLFOX	8.2	14.1 9.9 HR, 0.62 P=0.076	7.1 3.7 HR, 0.67 P=0.23	21.3% 13.2% OR,1.6 P=0.46
COIN (Smith CG et al, 2013)	2445	FP + Oxaliplatin + C FP + Oxaliplatin	9	7.2 10 HR 1.18 P=0.46	NA NA HR1.25 P=0.54	NA
PRIME (Douillard JY et al, 2013)	1183	FOLFOX + P FOLFOX	10	10.5 9.2 HR0.9 P=0.76	6.1 5.4 HR0.58 P=0.12	NA
FIRE 3 (Stintzing S et al, 2014)	342	FOLFIRI + C FOLFIRI + Bev	13.7	12.3 13.7 HR0.87 P=0.65	4.9 6 HR0.87 P=0.64	52.2% 40% OR 1.64 P=0.29
TRIBE (Cremolini C et al, 2015)	508	FOLFIRI + Bev FOLFOXIRI+Bev	5.5	10.7 19.0 HR:0.54	5.5 7.5 HR=0.57	42% 56% OR:1.82 (0.38-8.78)

Treatment options after first line for *BRAF*^{V600E} mutant mCRC patients

In a retrospective analysis of subjects with chemo-refractory mCRC treated with chemotherapy and an anti-epidermal growth factor receptor (EGFR) agent, the median progression-free survival (PFS) and OS in subjects with *BRAF* mutant tumors were 2 months and 6.5 months, respectively, compared with a median PFS of 6.5 months and a medianOS of 13,5 months in subjects with *BRAF*wt tumors. In a study evaluating 5-FU/FA/irinotecan (FOLFIRI) plus panitumumab in a pure second-line setting, subjects with *BRAF*^{V600E} mutant mCRC had a median PFS of 2.5 months and a median OS of 4.7 months, compared with a median PFS and a medianOS of 6.9 and 18.7 months, respectively, in subjects with *BRAF*wt tumors. Finally, in 71 subjects with *BRAF*^{V600E} mutant mCRC treated at the MD Anderson Cancer Center between 2003 and 2012, the median PFS with second-line therapy was 10 weeks in the overall group (n=58) and 12 weeks in subjects who were treated with an irinotecan-based regimen (n=39), 28 of whom had received panitumumab or cetuximab concomitantly with irinotecan. The median PFS in subjects receiving second- or third-line therapy corresponded to the timing of the first restaging scan (**Morris V et al, 2014**).

Benefits of combination therapies have been demonstrated in clinical studies of patients with mCRC, including: dual inhibition of BRAF + EGFR such as panitumumab + dabrafenib (**Corcoran RB et al, 2016)** and cetuximab + encorafenib (**Tabernero J et al, 2016**), the ORR reported in these studies were 10% and 22%, respectively; or triplet combinations consisting of BRAF + EGFR inhibition plus MEK inhibition or chemotherapy such as cetuximab +vemurafenib+ irinotecan (**Kopetz S el al, 2017**) or panitumumab + dabrafenib + trametinib (**Corcoran RB et al, 2016**), the ORR reported in these studies were 16% and 21% respectively . In particular, the phase II study of cetuximab + encorafenib demonstrated a median PFS of 4.2 months, and the median overall survival exceeded 1 year, which is substantially improved over the historical standard of care for this population.

Inhibition of BRAF, MEK, and EGFR in BRAF^{V600E} Colorectal Cancer Cells

Cancer cells with *BRAF* mutations are highly dependent on MEK/ERK signaling. As demonstrated in melanoma cells, MEK-dependent activation of MAP Kinase (MAPK) signaling occurs following BRAF inhibition and near-complete inhibition of phospho-ERK is required for tumor responses.

The combination of a BRAF inhibitor and a MEK inhibitor has been shown to be more active than either agent alone, presumably due to delaying or preventing resistance (**Thakur MD and Stuart DD, 2014**). Nonclinical studies in CRC cells has shown that BRAF inhibition causes a rapid feedback activation of EGFR that supports continued proliferation of $BRAF^{V600E}$ CRC tumor cells (**Corcoran RB et al, 2012**; **Prahallad A et al, 2012**). Activation of EGFR can be effectively prevented by the combination of vemurafenib with anti-EGFR agents such as the small-molecule kinase inhibitor, erlotinib, or the monoclonal antibody, cetuximab.

These reports suggest that activation of EGFR may partially explain the limited therapeutic effect of *BRAF* inhibitor monotherapy in subjects with $BRAF^{V600E}$ mutant mCRC and that this can be overcome with concomitant EGFR inhibition. The dependence of *BRAF*-mutant CRC cells on MAPK signaling provides a compelling rationale for inhibiting MEK in addition to *BRAF* and EGFR to achieve more robust inhibition of the pathway.

1.2. INFORMATION ON THE TEST PRODUCT

1.2.1. ENCORAFENIB

Chemical and pharmaceutical characteristics

Encorafenib (LGX818 or W0090), is a novel oral small-molecule kinase inhibitor with potent and selective inhibitory activity against mutant *BRAF* kinase, a member of the RAF/MEK/ERK MAPK pathway, which plays a prominent role in controlling several key cellular functions including growth, proliferation and survival.

For further details, please refer to the current Encorafenib Investigator's Brochure (**Enco IB**).

Non-clinical data

In 1- to 4-week toxicology studies in rats and cynomolgus monkeys, encorafenib was well tolerated at systemic exposures which result in tumor regression in mouse xenograft studies. Findings included hyperplasia and hyperkeratosis in the skin (plantar surface of feet) and non-glandular stomach in the rat. An absence of the later stages of spermatid maturation in male rats was also observed. Significant mortality/morbidity was observed mostly in female rats at the highest dose of 400 mg/kg/day, a dose well above the maximum tolerated dose (MTD) in rats.

In the 13-week toxicology study in monkeys, the only drug-related finding was blister-like lesions identified over the macular region of the retina, observed in 2 monkeys treated at a dose of 60 mg/kg/day. Exposure (maximum area under the concentration–time curve $(AUC)_{0-24}$ achieved in the study at any time point) in the 2 affected monkeys was 5 to 8-fold and 4 to 6-fold greater than that achieved at the 300 and 450 mg once daily (QD) dose levels, respectively, in humans at steady state in Clinical Study CLGX818X2101. One of the animals with this finding showed evidence of recovery after the drug withdrawal. Histopathology examination of the affected eyes suggested that the findings were similar to the retinopathy associated with MEK inhibitors.

Preclinical safety pharmacology data do not indicate a clinical risk for QT interval corrected for heart rate (QTc) prolongation, or adverse effects on the CNS or respiratory system. In Good Laboratory Practice (GLP) 4- and 13-week oral (gavage) toxicity studies in monkeys and a GLP monkey telemetry study, encorafenib had no adverse effect on electrocardiographic (ECG) morphology, rhythm or PR, QRS, QT and QTc duration. Using cloned hERG potassium channels expressed in mammalian cells, the IC_{50} for hERG inhibition by encorafenib was determined to be 73.4 µM indicating that there is unlikely to be an effect of encorafenib on repolarization and QT interval.

The GLP Ames and chromosomal aberration assays as well as a rat micronucleus study indicated that encorafenib is not genotoxic.

Encorafenib was rapidly absorbed in mouse, rat and dog studies. Median Tmax was 2 hours when dosed as a suspension and 0.5 hours when dosed as a solution.

For further details, please refer to the current Encorafenib Investigator's Brochure (**Enco IB**).

Clinical safety

As of the data cutoff date of 11 May 2017, 1431 patients with advanced cancer have received at least one dose of encorafenib, either as a single agent or in combination with other agents in 10 clinical studies.

For further details, please refer to the current Encorafenib Investigator's Brochure (**Enco IB**).

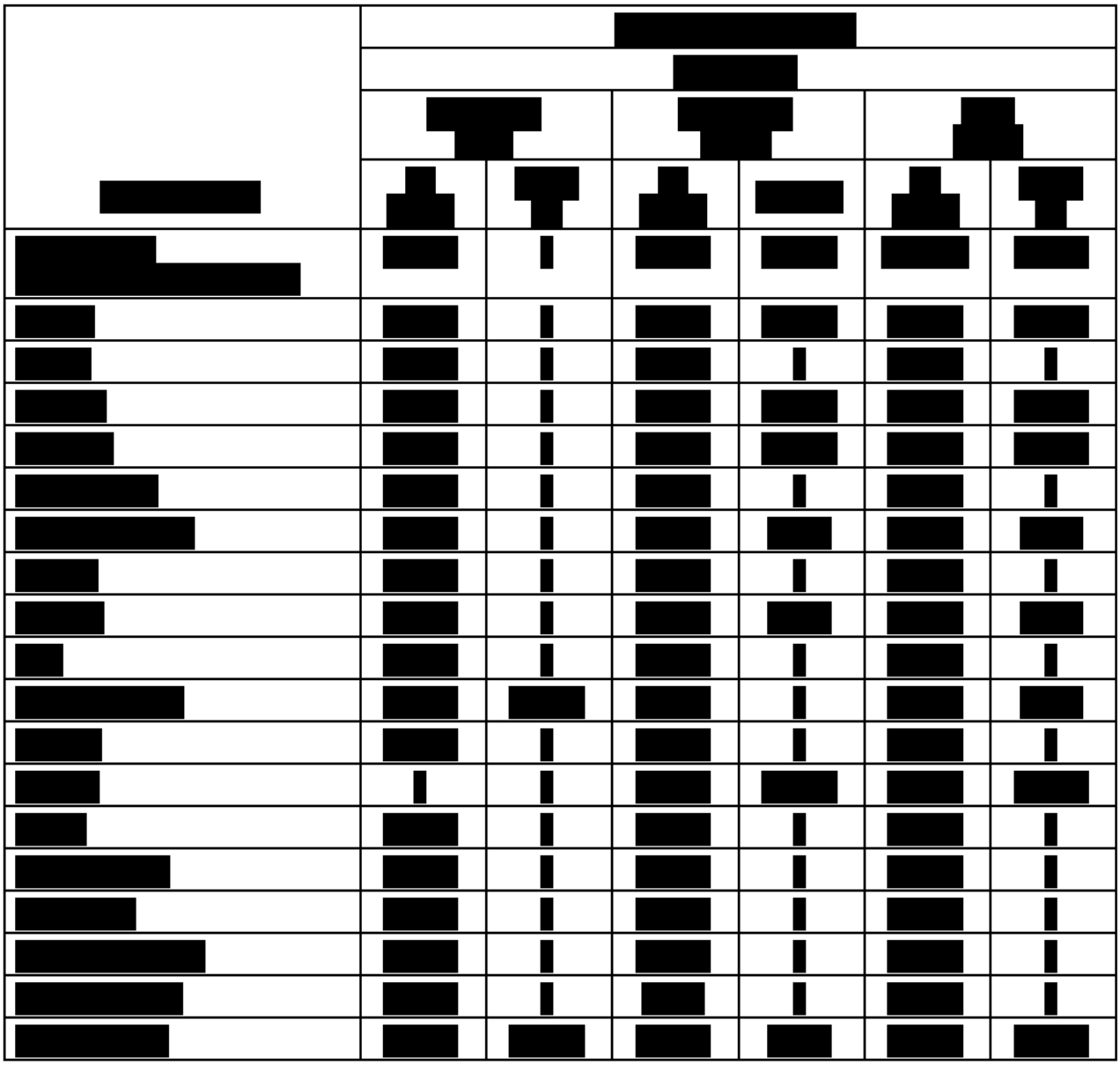
Single-agent encorafenib

Single-agent encorafenib was evaluated in a first-in-human, Phase I dose-escalation/dose-expansion study (Clinical Study CLGX818X2101) in adult patients with *BRAF*^{V600E} mutant locally advanced or metastatic melanoma (dose-escalation and dose-expansion phases) or mCRC (dose-expansion phase only). A total of 107 subjects were treated at doses ranging from 50 mg to 700 mg QD.

In the dose-expansion phase of Study CLGX818X2101, the first 34 patients received encorafenib 450 mg QD (i.e., MTD). Nine of these subjects experienced a dose-limiting toxicity (DLT) during Cycle 1 CCI [redacted] leading to a dose reduction to 300 mg QD in 6 subjects and discontinuation of encorafenib for the remaining 3 subjects. Among the patients who did not have a DLT, the encorafenib dose was reduced to 300 mg QD in 8 subjects, and 1 subject discontinued due to an AE. Based on these findings, 300 mg QD was identified as the recommended Phase 2 dose (RP2D) as single agent.

Eighteen subjects with mCRC received encorafenib in the dose-expansion phase of the study. Twelve subjects received encorafenib 450 mg QD and 6 patients received 300 mg QD. Doselimiting- toxicities were reported in 3 subjects treated at the 450 mg QD dose and in none of the subjects treated at the 300 mg QD dose. The most common (occurring in ≥ 20% of subjects) AEs, regardless of causality, observed at the MTD of 450 mg QD and the RP2D of 300 mg QD in the mCRC subjects in the dose-expansion phase are shown in **Table 2**.

CCI



Encorafenib in combination with an anti EGFR

Study CLGX818X2103

Clinical Study CLGX818X2103 is an ongoing phase Ib/II study evaluating the combination of encorafenib and cetuximab and the triple combination of encorafenib, cetuximab and alpelisib (a PI3Kα inhibitor) in subjects with BRAF-mutant mCRC who experienced disease progression after ≥ 1 prior standard-of-care regimen or who were intolerant to irinotecan-based regimens. Phase Ib has been completed and enrollment to phase II is complete. The aim of the phase Ib portion of the study was to determine the MTD and/or RP2D of the dual combination of encorafenib plus cetuximab and the triple combination.The phase II portion is an ongoing randomized study (N=102) designed to assess the relative clinical efficacy of the dual and triple combinations and to further characterize the safety of the two regimens.

Study CLGX818X2103 Phase Ib

A total of 26 subjects with locally determined *BRAF* mutation status (confirmed using Foundation Medicine) were treated with the dual combination and 28 patients were treated with triple combination. The MTD was not formally reached for either regimen, however, based on general tolerability, the RP2D for the triple combination was determined to be encorafenib 200 mg QD, alpelisib 300 mg QD in combination with standard dose of cetuximab (initial dose 400 mg/m^2 followed by 250 mg/m^2 weekly). The dual combination was studied up to doses of 450 mg QD of encorafenib in combination with cetuximab without reaching MTD and with generally acceptable toxicity. In order to determine the contribution of alpelisib to the efficacy of the triple combination, an equal dose of encorafenib (200 mg QD) in both arms of the phase 2 portion was selected.

In the 26 subjects treated in the dual combination arm, the median age was 63 years (range 43-80 years). At baseline, Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 in 8 (30.8%) subjects, 1 in 16 (61.5%) subjects, and 2 in 2 (7.7%) subjects.

They had received a median of 2 prior therapies (range 1-5) and 11 (42%) patients had received ≥3 prior regimens. Four dose levels of encorafenib QD:100 mg QD (n=2), 200 mg QD (n=7), 400 QD (n=9), and 450 QD (n=8), and cetuximab (400 mg/m^2 initial and 250 mg/m^2 weekly) were evaluated in the dual combination treatment arm. Complete response (CR) was observed in 1 subject and

partial responses (PR) were observed in 5 subjects for an overall response rate (ORR) of 23.1%. All except one of the responses (a PR) was confirmed. The median duration of response was 34.7 weeks (range 4.1-73.3 weeks). Of the 14 patients with stable disease (SD) as best radiological response, tumor regression was observed in 7 (27%). The median PFS was 3.7 months (95% CI, 2.8–10.6 months) and the activity of the dual combination appeared durable with 8 (30.7%) patients with duration of exposure for greater than 1 year with the longest duration being > 88 weeks.

CLGX818X2103 phase II

A total of 50 subjects were randomized to the dual combination arm in phase II. The median age was 60 years (range 29-76) and ECOG PS was 0/1/2 in 45%/56%/2% of patients. The median number of prior treatment regimens was 2 (range 1-6) and 40% had 2 prior regimens and 18% had ≥3 prior regimens. The ORR was 22% (95% CI: 12-36). The median PFS in the subjects treated with encorafenib plus cetuximab was 4.2 months (95% CI, 3.4-5.4). The observed ORR and PFS compare favorably to historical controls, which were normally below 10% ORR and generally 2 months for PFS. The median OS of subjects in the dual combination arm was 12.4 months (95% CI, 7.6, not estimable) which compared favorably to historical controls (**Tabernero J et al, 2016**).

The dual combination was generally well tolerated, as most adverse events observed were Grade 1 or 2 with few Grade 3 or 4 events. Notably, although rash is observed in the majority of patients treated with cetuximab, in the dual combination arm, it was observed in only 7 (14%) patients, all of whom experienced Grade 1/2 rash. Summary of adverse events in the dual combination arm are summarized in **Table 3**.

Table 3: Adverse Events (Regardless of Study Drug Relationship) Reported in ≥ 20% of Dual-Combination Therapy (encorafenib plus cetuximab) (N=50), by Preferred Term — CLGX818X2103, Phase 2

	Encorafenib 200mg / Cetuximab (N=50)	
Preferred Term	**All Grades n (%)**	**Grade 3/4 n (%)**
Any Adverse Event	50 (100)	31 (62.0)
Nausea	23 (46.0)	0
Fatigue	25 (50.0)	2 (4.0)
Vomiting	16 (32.0)	0
Abdominal pain	21 (42.0)	4 (8.0)
Diarrhoea	14 (28.0)	2 (4.0)
Decreased appetite	17 (34.0)	1 (2.0)
Arthralgia	17 (34.0)	0
Headache	16 (32.0)	0
Pyrexia	13 (26.0)	0
Dry skin	9 (18.0)	0
Hyperglycaemia	5 (10.0)	1 (2.0)
Rash	7 (14.0)	0
Lipase increased	15 (30.0)	11 (22.0)
Back pain	12 (24.0)	1 (2.0)
Dermatitis acneiform	9 (18.0)	0
Stomatitis	5 (10.0)	0

1.2.2. BINIMETINIB

Chemical and pharmaceutical characteristics

Binimetinib (MEK162 or W0074) is an orally bioavailable, selective and potent mitogen-activated protein kinase kinase (MEK) 1 and MEK 2 inhibitor that is active in inhibiting phosphorylated extracellular signal-regulated kinase (pERK) and growth of *BRAF*-mutant cancer cells in the low nanomolar range.

Non-clinical data

Acute, sub-chronic, chronic and reproductive toxicity, genotoxicity and phototoxicity studies were completed in rats and monkeys to support chronic administration of binimetinib to adult subjects. There was no evidence of a genotoxic potential in vitro or in vivo. The adverse effects of MEK inhibitors in humans are similar to those observed in rats and monkeys, with the exception of ocular findings. These adverse effects include gastrointestinal intolerance and diarrhea, rash (skin findings in rats only), retinal events (only seen in humans) and retinal vein occlusion (rarely seen in humans). In vitro and in vivo phototoxicity studies conducted in mice indicate that binimetinib has a low risk of weak phototoxic potential at therapeutic doses. Furthermore, there has been no evidence of phototoxicity or photosensitivity in humans treated with binimetinib for cancer or for rheumatoid arthritis.

Given the embryo-lethal effects seen in rats and rabbits and the teratogenic effects seen in rabbits, binimetinib should not be used in pregnant women. Women of child-bearing potential must be advised to use highly effective contraception methods as described in CTFG 2014 (see **Section 5.3.1** in the protocol).

For further details, please refer to the current Binimetinib Investigator's Brochure (**Bini IB**).

Clinical Safety

As of 20 January 2018, a total of 2816 healthy subjects and patients have received at least 1 dose of binimetinib, either as a single agent or in combination with other targeted agents, standard chemotherapy agents or immunomodulating agents. These patients constitute the binimetinib safety population, which includes 229 healthy subjects, 17 subjects with hepatic dysfunction, 6 subjects with renal dysfunction, 164 patients with rheumatoid arthritis and 2400 patients with advanced cancer.

For further details, please refer to the current Binimetinib Investigator's Brochure (**Bini IB**).

Single-agent binimetinib

Based on two phase I studies (one conducted in subjects with advanced solid tumors, advanced or metastatic biliary cancer and *KRAS*- or *BRAF*-mutant metastatic CRC (Clinical Study ARRAY-162-111) and the other conducted in Japanese subjects with advanced solid tumors (Clinical Study CMEK162X1101), the recommended single-agent dose of binimetinib is 45 mg twice daily (BID). This dose was further confirmed in phase II studies: (1) conducted in $BRAF^{V600E}$ or NRAS-mutant melanoma subjects (Clinical Study CMEK162X2201); (2) in advanced solid tumors (Clinical Study CMEK162AUS11); and (3) in Chinese subjects with advanced Neuroblastoma RAS Vital Oncogene *KRAS*/*BRAF/NRAS*-mutant non-small cell lung cancer (Clinical Study CINC280X2205) and in phase III studies: (1) in subjects with *NRAS*-mutant melanoma (Clinical Study CMEK162A2301) and (2) in low grade serous carcinomas of the ovary, fallopian tube or primary peritoneum (Clinical Study ARRAY-162-311).

Available clinical data indicate a predictable safety profile consistent with that reported for other allosteric MEK1/2 inhibitors. Frequently reported treatment-emergent AEs in patients receiving binimetinib include rash, dermatitis acneiform, nausea, vomiting, diarrhea, peripheral edema, fatigue, and creatine kinase (CK) elevation. Other clinically relevant toxicities are retinal events, increased blood pressure, decreased ejection fraction, and noninfectious pneumonitis/interstitial lung disease, all of which should be monitored closely with appropriate diagnostic evaluations.

These observed AEs are generally reversible and manageable by appropriate supportive medical care and/or dose modifications. **Table 4** describes the safety profile of binimetinib as single agent in subjects with NRAS – mutant melanoma (Clinical study CMEK162A2301) [**Dummer R et al, 2017 (NEMO)**].

Table 4: Adverse events regardless of causality in at least 5% (grade 1 or 2) or at least 1% (grade 3 or 4) of patients (Clinical study CMEK162A2301)

	All patients (N=269) binimetinib 45mg BID		
	Grade 1-2 N (%)	**Grade 3 N (%)**	**Grade 4 N (%)**
Diarrhoea	104 (39)	4 (1)	0
Oedema peripheral	96 (36)	1 (<1)	0
Dermatitis acneiform	88(33)	7 (3)	0
Rash	87 (32)	11 (4)	0
Nausea	75 (28)	4 (1)	0
Blood creatine phosphokinase increased	61 (23)	33 (12)	19 (7)
Fatigue	54 (20)	6 (2)	0
Vomiting	51 (19)	6 (2)	0
Asthenia	40 (15)	8 (3)	0
Retinal detachement	39 (14)	0	0
Constipation	35 (13)	2 (1)	0
Pruritus	30 (11)	2 (1)	0
Aspartate aminotransferase increased	29 (11)	6 (2)	0
Decreased appetite	29 (11)	2 (1)	0
Pyrexia	28 (10)	0	0
Skin fissures	28 (10)	0	0
Dyspnoea	26 (10)	3 (1)	0
Ejection fraction decreased	20 (7)	10 (4)	0
Hypertension	17 (6)	20 (7)	0
Alanine aminotransferase increased	15 (6)	7 (3)	0
Anaemia	14 (5)	4 (1)	1 (<1)

Preferred terms are presented by descending order of frequency of grade 1–2 adverse events. A patient with multiple occurrences of an adverse event under a preferred term is counted only once for that preferred term. A patient with multiple adverse events is counted only once in the total row. As per the study protocol, deaths were not graded and therefore were not included in this table; please refer to the (Bini IB) for more detail.

Binimetinib in Combination with Anti-EGFR Agents

The combination of binimetinib and panitumumab was evaluated in patients with mCRC in the Phase 1b/2 Clinical Study CMEK162X2116. Ten patients were treated in the Phase 1b portion of the study with binimetinib (45 mg BID) and the labeled dose of panitumumab (6 mg/kg IV biweekly) which was declared the MTD/RP2D. An additional 40 patients were enrolled in the Phase 2 portion of the study. In the Phase 2 portion, AEs, regardless of causality, reported in ≥ 15% of patients included all grade (%)/Grade 3-4 (%): diarrhea (70.0/12.5), vomiting (55.0/2.5), rash (50.0/12.5), nausea (47.5/5.0), fatigue (35.0/5.0), abdominal pain (32.5/2.5), dermatitis acneiform (32.5/5.0), blood creatine kinase (CK) increased (27.5/7.5), dry skin (25.0/5.0), anemia (20.0/10.0), asthenia (20.0/2.5), constipation (20.0/0), hypokalemia (20.0/12.5), pyrexia (20.0/0), stomatitis (20.0/0), AST increased (17.5/5.0), blood creatinine increased (15.0/2.5), chills (15.0/0) and hypomagnesemia (15.0/0).

Combination of encorafenib and binimetinib

An ongoing Phase 3 (COLUMBUS study - CMEK162B2301), 2-part, randomized, open-label, multicenter study = compared the efficacy and safety of the combination of binimetinib + encorafenib to single-agent vemurafenib and single-agent encorafenib in patients with *BRAF* ^{V600}-mutant locally advanced unresectable or metastatic melanoma (Stage IIIB, IIIC and IV per the American Joint Committee on Cancer [AJCC]) untreated or have progressed on or after first line immunotherapy .

In Part 1 of the study (**Dummer R et al, 2016**), patients were to be randomized in a 1:1:1 ratio to 1 of the 3 treatment arms: binimetinib 45 mg BID + encorafenib 450 mg QD (Combo 450) or single-agent encorafenib 300 mg QD or single-agent vemurafenib 960 mg BID. In Part 2 of the study **Dummer R et al, (part 2)**, patients were to be randomized in a 3:1 ratio to 1 of the 2 treatment arms: (1) binimetinib 45 mg BID + encorafenib 300 mg QD (Combo 300) or (2) single-agent encorafenib 300 mg QD.

Enrollment is complete, with a total of 921 patients (577 in Part 1 [192 Combo 450, 194 encorafenib, 191 vemurafenib] and 344 in Part 2 [258 Combo 300, 86 encorafenib) randomized to treatment. A total of 911 patients (577 in Part 1 [192 Combo 450, 192 encorafenib, 186 vemurafenib] and 344 in Part 2 [257 Combo 300, 84 encorafenib]) received at least 1 dose of study

treatment (Combo 450, Combo 300, encorafenib or vemurafenib). The most frequently reported AEs (≥ 10.0% of patients in either population) are summarized by preferred term and treatment population in **Table 5**.

Table 5: Adverse Events Regardless of Causality Reported in ≥ 10.0% of Patients by Preferred Term (Pooled Data from Studies of Combo 450 and CMEK162B2301 Part 2 Data for Combo 300 in Patients with Melanoma)

	Pooled Data*		Study CMEK162B2301 Part 2	
	Combo 450 N = 274 n (%)		Combo 300 N = 257 n (%)	
Preferred term	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
Any AE	271 (98.9)	168 (61.3)	252 (98.1)	120 (46.7)
Nausea	114 (41.6)	7 (2.6)	70 (27.2)	4 (1.6)
Diarrhoea	104 (38.0)	9 (3.3)	73 (28.4)	4 (1.6)
Fatigue	85 (31.0)	6 (2.2)	57 (22.2)	2 (0.8)
Vomiting	77 (28.1)	6 (2.2)	39 (15.2)	1 (0.4)
Arthralgia	74 (27.0)	2 (0.7)	57 (22.2)	3 (1.2)
Blood CK increased	74 (27.0)	16 (5.8)	51 (19.8)	14 (5.4)
Constipation	66 (24.1)	0	43 (16.7)	0
Headache	57 (20.8)	4 (1.5)	30 (11.7)	1 (0.4)
Anaemia	51 (18.6)	13 (4.7)	24 (9.3)	7 (2.7)
Pyrexia	47 (17.2)	7 (2.6)	43 (16.7)	0
Abdominal pain	47 (17.2)	5 (1.8)	27 (10.5)	3 (1.2)
Asthenia	43 (15.7)	3 (1.1)	38 (14.8)	2 (0.8)
Vision blurred	43 (15.7)	1 (0.4)	26 (10.1)	1 (0.4)
GGT increased	40 (14.6)	23 (8.4)	36 (14.0)	12 (4.7)
Alopecia	38 (13.9)	0	33 (12.8)	0
Myalgia	38 (13.9)	1 (0.4)	35 (13.6)	1 (0.4)
Hyperkeratosis	37 (13.5)	1 (0.4)	25 (9.7)	0
Muscle spasms	37 (13.5)	1 (0.4)	18 (7.0)	1 (0.4)
ALT increased	36 (13.1)	13 (4.7)	29 (11.3)	12 (4.7)
Dry skin	36 (13.1)	0	21 (8.2)	0
Oedema peripheral	35 (12.8)	3 (1.1)	28 (10.9)	0
Dizziness	34 (12.4)	4 (1.5)	21 (8.2)	0
Rash	34 (12.4)	2 (0.7)	18 (7.0)	2 (0.8)

	Pooled Data*		Study CMEK162B2301 Part 2	
	Combo 450 N = 274 n (%)		Combo 300 N = 257 n (%)	
Preferred term	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
Hypertension	31 (11.3)	15 (5.5)	21 (8.2)	9 (3.5)
Back pain	30 (10.9)	2 (0.7)	36 (14.0)	2 (0.8)
Nasopharyngitis	30 (10.9)	0	23 (8.9)	0
Pain in extremity	29 (10.6)	4 (1.5)	27 (10.5)	2 (0.8)
Abdominal pain upper	26 (9.5)	2 (0.7)	32 (12.5)	1 (0.4)

*pooled data from 3 clinical studies of the combination of binimetinib + encorafenib (CMEK162X2110 [Phase 1b/2], CLGX818X2109 [Phase 2] and CMEK162B2301 Part 1 [Phase 3])
Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatinine phosphokinase; Combo = encorafenib plus binimetinib; GGT = gamma-glutamyl transferase; n or N = number
Preferred terms are sorted in descending frequency of the Combo 450 column
Data cutoff date CMEK162B2301 (Parts 1 and 2) 09 Nov 2016; CLGX818X2109 30 Dec 2016; CMEK162X2110 31 Dec 2016

1.2.3. CETUXIMAB

Chemical and pharmaceutical characteristics

Cetuximab is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of human EGFR on both normal and tumor cells, and inhibits receptor activation by competing with the epidermal growth factor and other ligands. In vitro and in vivo assays have shown that binding of cetuximab to the EGFR blocks its dimerization and phosphorylation and its consequent activation, resulting in an inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial factor production. Cetuximab exhibits clinical activity as a monotherapy or in combination with chemotherapy and/or radiation in head and neck cancer and mCRC (**Cunningham D et al, 2004**; **Baselga J et al, 2005**; **Bonner JA, et al 2006**).

Cetuximab is approved in about 100 countries for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer

- in combination with irinotecan-based chemotherapy,
- in first-line in combination with FOLFOX,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan (see the locally applicable cetuximab label).

Nonclinical data

Following the recommended dose regimen (400 mg/m^2 initial dose; 250 mg/m^2 weekly dose), concentrations of cetuximab reach steady-state levels by the third weekly infusion. Cetuximab has a long elimination half-life with values ranging from 70 to 100 hours at the target dose. Although the US label for Erbitux® indicates that US-licensed cetuximab (Erbitux®) provides approximately 22% greater exposure relative to cetuximab which is approved in the European Union (EU), the dosing and administration guidelines are consistent between the regions.

Clinical data

In subjects with mCRC whose disease had progressed during or within 3 months after treatment with an irinotecan-based regimen, treatment with single-agent cetuximab resulted in an objective response rate of 11% and a median time to progression of 1.5 months (**Cunningham D et al, 2004**). In subjects with EGFR-expressing mCRC treated with cetuximab in combination with irinotecan in the second-line setting, the median PFS was 4.0 months (95% confidence interval [CI], 3.24.1 months) and OS was 10.7 months (95% CI, 9.6 -11.3 months) (**Sobrero AF et al, 2008**).

In general, cetuximab is well tolerated and does not exacerbate the side effects of irinotecan or oxaliplatin. The main side effects are skin reactions, particularly an acne-like rash that is characteristic of treatment with many EGFR inhibitors. Such skin reactions are generally manageable. Other less frequently observed side effects associated with cetuximab treatment are diarrhea, fatigue, and hypomagnesemia (**Tabernero J et al, 2008**).

The approved dosing regimen of cetuximab, both as monotherapy and in combination with chemotherapy, is an initial i.v. infusion of 400 mg/m^2 on day 1 with subsequent weekly doses of 250 mg/m2.Regarding the first-line treatment, cetuximab plus FOLFIRI, as compared with FOLFIRI alone, reduced the risk of progression of metastatic colorectal cancer patients with KRAS wild-type tumors (**Van Cutsem E et al, 2009**).

Combination of encorafenib, binimetinib, and cetuximab.

This triple combination is currently being evaluated in the Phase III BEACON CRC study. A total of 30 patients were treated with encorafenib 300 mg QD, binimetinib 45 mg BID and cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 IV weekly in the Safety Lead-in portion of the study. Overall, the observed AEs (**Van Cutsem E et al, 2018 – Table 6**) were consistent with known BRAF, MEK and EGFR inhibitor toxicities. Grade 3/4 adverse events reported in ≥ 10% of patients were fatigue, CK increased, AST increased and urinary tract infection (3 patients [10%] each), all of which were grade 3 events except for a single grade 4 AST elevation. The only grade 3/4 skin-related AE reported was rash (grade 3) in 1 patient (3%).

This rate of severe toxicity is lower than generally observed for cetuximab alone or in combination with standard chemotherapy for mCRC (**Erbitux® USPI**).

Table 6: ARRAY-818-302 (BEACON CRC study) Safety Lead-in: summary of adverse events regardless of causality occurring in ≥15% of patients (N=30)

Event, n (%)	Any grade	Grade 3/4
Any AE	30 (100)	19 (63.3)
Diarrhea	23 (76.7)	1 (3.3)
Dermatitis acneiform	20 (66.7)	0
Fatigue	19 (63.3)	4 (13.3)
Nausea	19 (63.3)	2 (6.7)
Vomiting	15 (50.0)	2 (6.7)
Dry skin	14 (46.7)	0
Anemia	11 (36.7)	2 (6.7)
Blood creatine phosphokinase increased	11 (36.7)	3 (10.0)
Decreased appetite	11 (36.7)	2 (6.7)
Abdominal pain	10 (33.3)	1 (3.3)
Dyspnea	10 (33.3)	2 (6.7)
Constipation	9 (30.0)	0
Pyrexia	9 (30.0)	0
Arthralgia	8 (26.7)	0
Blood creatinine increased	8 (26.7)	0

Event, n (%)	Any grade	Grade 3/4
Vision blurred	8 (26.7)	0
Skin fissures	7 (23.3)	0
Aspartate aminotransferase increased	6 (20.0)	3 (10.0)
Asthenia	6 (20.0)	0
Palmar-plantar erythrodysesthesia syndrome	6 (20.0)	0
Rash maculopapular	6 (20.0)	0
Dizziness	5 (16.7)	0
Malaise	5 (16.7)	1 (3.3)
Myalgia	5 (16.7)	0
Edema peripheral	5 (16.7)	0
Peripheral sensory neuropathy	5 (16.7)	0
Urinary tract infection	5 (16.7)	3 (10.0)

The Triplet combination dose used in the randomized Phase 3 portion of the study for US and EU patients (encorafenib 300 mg QD, binimetinib 45 mg BID and cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 IV weekly) was subsequently administered to 7 patients enrolled in the Japanese Safety Lead-in (JSLI), which was initiated in February 2017. After all patients had completed at least 1 cycle of treatment the DMC reviewed the safety from the JSLI and agreed that Japanese patients may participate in the randomized portion of the study at the same Triplet regimen doses. Ten Japanese sites have been participating in the randomized Phase 3 portion of the study in June 2018.

1.3. STUDY RATIONALE

BRAF mutations, which lead to constitutive activation of BRAF kinase and sustained RAS/RAF/MEK/ERK pathway signaling resulting in increased cell proliferation and survival occur in approximately 10% (range, 5–22%) of the unselected colorectal cancer (CRC) population (**Rozek LS et al, 2010**, **Shaukat A et al, 2010**; **Sorbye et al, 2015**) with lower prevalence in more advanced subject populations.

The presence of a BRAF mutation is considered a marker of poor prognosis in subjects with mCRC and is associated with a median survival of approximately 12 to 14 months relative to 21 to 25

months for subjects with *BRAF*wt tumors (**Van Cutsem E et al, 2011**; **Sorbye et al, 2015**). These data suggest that improved therapies are urgently needed for patients with $BRAF^{V600E}$ mutant mCRC in the first line setting.

Non clinical experiments have provided compelling evidence that combining a BRAF inhibitor with an EGFR inhibitor results in greater anti-tumor effects than either agent alone in $BRAF^{V600E}$ CRC cells (**Corcoran RB et al, 2012**; **Prahallad A et al, 2012**). Consistent with these observations, the combination of the selective *BRAF* inhibitor, encorafenib and cetuximab resulted in a strong synergistic antitumor activity (as shown in **Table 1**).

Clinical data

Consistent with nonclinical data in human CRC cell models (Array data on file), early clinical data suggest that the triple combination BRAF + MEK + EGFR inhibitors may result in greater activity than a dual combination BRAF + EGFR inhibitor in subjects with $BRAF^{V600E}$ mutant mCRC as described below.

Triple combinations in the second or later line of therapy for the metastatic setting

The ongoing multicentric, randomized phase III BEACON CRC study (NCT02928224) is evaluating encorafenib + binimetinib + cetuximab vs encorafenib + cetuximab compared with Investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab in subjects with $BRAF^{V600E}$ mutant mCRC whose disease has progressed after 1 or 2 prior regimens in the metastatic setting. A total of 30 subjects were treated in the SLI, all of whom received encorafenib (300 mg QD) + binimetinib (45 mg BID) + cetuximab (400 mg initial dose then 250 mg/m^2 QW). Among the 29 subjects with $BRAF^{V600E}$ mutated tumors (one patient had a *BRAF* non-V600E mutated tumor) the confirmed overall response rate (ORR) was 48% (14/29) including a complete response in 3/29 patients. The ORR was 62% (including 8 PR and 2 CR) in patients with one previous line of therapy and 31% including 3 PR and 1 CR in those with two prior lines of therapy. Of the 29 patients with a BRAFV600E mutation, the median time on study treatment was 7.9 months (range, 1.0–11.9 months), and 10 (33%) patients remained on study treatment at the time of data cutoff. Preliminary estimate of median PFS is 8.0 months (95% CI, 5.6–8.5 months), with 7 of 29 patients (24%) still in follow-up and progression-free. Progression-free survival was similar between patients who had 1 vs 2 previous regimens (median, 95% CI, 7.6 [4.0–8.3] vs

8.1 [4.1–10.8] months) (**Van Cutsem E et al, 2018**). The confirmed ORR of 48% and median PFS of 8.0 months with the triple combination of encorafenib + binimetinib + cetuximab exceeds historical standard-of-care and exceeds the ORR of 22% in a phase II trial of the doublet of encorafenib + cetuximab (**Tabernero J et al, 2016**). The BEACON CRC SLI results are also improved compared with other recent triple combination including dabrafenib plus trametinib plus panitumumab, in which the ORR was 21% (**Corcoran RB et al, 2016**) and irinotecan, vemurafenib, cetuximab, in which the ORR (confirmed plus unconfirmed) was 16% (**Kopetz S el al, 2017**) in patients with previously treated *BRAF* mutant CRC. In addition, to being better than other triple combinations, the efficacy data from the BEACON CRC SLI is also superior to the ORR of 4% and PFS of 2.0 months in patients treated with the irinotecan plus cetuximab, a combination accepted as current standard-of-care (**Kopetz S el al, 2017**).

The preclinical data and the encouraging preliminary efficacy results observed in the SLI part of the BEACON CRC study justify the evaluation of combination of encorafenib, binimetinib and cetuximab in the first-line setting of this subject population, which represents a high-unmet medical need.

BRAF inhibition as first line treatment for the metastatic disease in BRAFm mCRC subjects

Data from retrospective series and post hoc analyses of randomised trials reveal that standard first-line regimens, including a chemo-doublet and a biologic agent, lead to poor results in terms of PFS, ranging from 4 to 6 months (**Ince WL et al, 2005**).

BRAF mutation status is a strong predictor for overall survival not only in the metastatic setting but also in earlier-stage diagnoses. The *BRAF* mutation is an early event in the CRC disease progression, which is involved in the transformation of epithelia into Traditional Serrated Adenomas (TSAs) or Sessile Serrated Adenomas (SSAs). *BRAF* mutation has also been identified as a potential mechanism of resistance to EGFR blockade. Therefore, it could be hypothesized that the introduction of a treatment combination including a *BRAF* inhibitor as first line might be effective 1) because of the early onset of the *BRAF* mutation and 2) as a strategy to prevent the resistance to EGFR inhibition.

On the other hand, less “targeted’ strategies such as an intensive first-line regimen combining FOLFOXIRI with bevacizumab, seem to be effective in counteracting *BRAF*-mutant tumors’

aggressiveness, as it was shown by Cremolini et al in the TRIBE study. It is important to note that this treatment combination is reserved to "fit" and young patients and not all patients might be eligible to receive such an aggressive treatment. Indeed, (**Loupakis F et al, 2014**) have reported that the treatment combination of FOLFOXIRI and bevacizumab was associated with a significant increase in the rates of grade 3 or 4 neurotoxicity, stomatitis, diarrhea, and neutropenia in comparison to FOLFIRI and bevacizumab. Therefore new treatment combinations are highly awaited for this population in the first line setting.

The current study is designed in light of the promising non-clinical and early clinical data of the combination of encorafenib, binimetinib and cetuximab in subjects with $BRAF^{V600E}$ mCRC who have a poor clinical outcome.

1.4. OVERALL RISK AND BENEFIT ASSESSMENT

An independent data monitoring committee (DMC) regularly reviews the safety of the combination of binimetinib, encorafenib, and cetuximab in the Safety Lead-in and Phase 3 portions of the BEACON CRC trial. The DMC has not identified any unexpected toxicities and has determined that the triple combination data is indicative of an acceptable and manageable tolerability profile.

The safety profiles of each drug were described (in **Section 1.2**). Laboratory assessments as well as clinical procedures will be performed throughout the conduct of the current study to ensure the subjects' safety.

The benefit/risk assessment for this phase II study that will be conducted in compliance with the protocol, Good Clinical Practices (GCP) and the applicable regulatory requirements, appears acceptable for subjects with such an aggressive disease as *BRAF*m mCRC.

2. STUDY OBJECTIVE AND ENDPOINTS

2.1. PRIMARY OBJECTIVE

The primary objective of the study is:

To evaluate the antitumor activity of the combination of encorafenib, binimetinib and cetuximab by assessing the confirmed overall response rate (cORR) by local radiologist/investigator assessment in adult subjects with previously untreated *BRAF*^{V600E}-mutant (*BRAF*^{V600E}) metastatic colorectal cancer (mCRC).

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are:

- To evaluate the cORR by central radiologist assessment.
- To evaluate the ORR (for confirmed + unconfirmed responses) by local radiologist/investigator and central assessment.
- To assess the effect of the combination of encorafenib, binimetinib and cetuximab on the duration of response (DOR).
- To assess the effect of the combination of encorafenib, binimetinib and cetuximab on other time-related efficacy parameters: time to response (TTR), progression-free survival (PFS) and overall survival (OS).
- To characterize the safety and tolerability of the combination of encorafenib, binimetinib and cetuximab.
- To assess the effect on quality of life (QoL).
- To explore health care resource utilization.
- To describe the pharmacokinetics (PK) of encorafenib, binimetinib, a metabolite of binimetinib (AR00426032) and cetuximab.

2.3. EXPLORATORY OBJECTIVES

- To assess the relationship between changes in tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA19-9]) and radiographic response to treatment.
- To assess $BRAF^{V600E}$ status in blood circulating tumor DNA (ctDNA) at baseline.
- To assess the potential predictive significance of the microsatellite instability (MSI) status in subjects with $BRAF^{V600E}$ mutant mCRC.
- To assess blood- and tissue-based predictive biomarkers of activity.

2.4. PRIMARY ENDPOINTS

- cORR as assessed by local radiologist/investigator review as per Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

2.5. SECONDARY ENDPOINTS

- cORR as assessed by central radiologist review as per RECIST 1.1.
- ORR (for confirmed and unconfirmed responses) as per local radiologist/investigator and central assessment.
- DOR assessed based on local radiologist/investigator and central review.
- TTR assessed based on local radiologist/investigator and central review.
- PFS assessed based on local radiologist/investigator and central review.
- OS.
- Type and severity of adverse events (AEs) and serious adverse events (SAEs), changes in hematology and chemistry values, physical examinations, vital signs, electrocardiogram (ECGs) and echocardiogram (ECHO)/ multi-gated acquisition (MUGA) scans and ophthalmological examinations graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 (NCI-CTCAE v4.03).

- Change from baseline in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Cancer subjects (QLQ-C30), EuroQol-5D-5L (EQ-5D-5L), and Patient Global Impression of Change (PGIC).
- Resource utilization focused on hospitalizations occurring during the study treatment phase.
- Plasma concentrations of encorafenib, binimetinib and the active metabolite of binimetinib (AR00426032) and serum concentration of cetuximab.

2.6. EXPLORATORY ENDPOINTS:

- Changes from baseline in blood CEA and CA19-9 at the beginning of each cycle and at the end of treatment.
- *BRAF* ^{V600E} mutation status in ct-DNA at baseline.
- MSI status in formalin-fixed paraffin-embedded (FFPE) samples via established PCR assays in tumor sample versus germline control at screening.
- Genomic and proteomic analysis of tumor tissue at baseline and at end of treatment (optional tumor tissue sample at end of treatment).
- Genomic and proteomic analysis of blood samples at baseline.

3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY

Some of the ethical considerations that lead to an acceptable risk-assessment have already been described in **Section 1.2**, in the encorafenib and binimetinib Investigator's Brochures and in the Cetuximab Summary Of Product Characteristics (**SPC**). The study will be conducted on the basis of appropriate clinical and non-clinical data.

In this study, the treatment will be administered to subjects with mCRC who have received no systemic treatment for metastatic disease. They will be included only after they have received detailed and complete information about the risks and constraints related to their participation and give their written consent for participation in the study.

They will remain under medical control throughout the duration of the study: as described in the assessment and procedures sections. Potential AEs will be reported during all treatment periods,

allowing the Investigator to decide whether the subjects can continue to receive study treatment. In addition, verification of vital signs, as well as ophthalmologic and dermatologic examinations will be performed to detect any safety signals.

The study will be carried out in accordance with the Declaration of Helsinki and its subsequent modifications (the latest in 2013 –Fortaleza), the recommendations for Good Clinical Practice (GCP) (ICH E6, R2), and any applicable local regulatory requirement(s).

The clinical study will start upon receipt of approval from both the relevant independent Ethics Committee (IEC) / Institutional Review Board (IRB) and the Competent Authorities.

4. STUDY DESIGN

4.1. OVERALL DESCRIPTION

This two-stage phase II trial will be conducted as a multinational, multicenter, open-label, single-arm study in 90 subjects. In the first stage 40 subjects will be treated, and an additional 50 subjects will be treated during the second stage. Subjects in whom the presence of $BRAF^{V600E}$ is not confirmed by central laboratory will be replaced. The second stage may be initiated as soon as confirmed responses are observed in at least 12 subjects.

As it may take several treatment cycles for subjects to achieve a confirmed response, if 12 confirmed responses are not observed at the time the 40th subject is treated in Stage 1 a limited number of subjects (maximum 12) from stage 2 may be treated while waiting for all subjects in the initial cohort of 40 subjects in Stage 1 to be evaluable for a confirmed response providing no safety concern was raised by the iDSMC. These additional subjects will not count towards responses in Stage 1 but will be included as part of the Stage 2 cohort, should the study move forward into Stage 2.

If at any time it becomes evident that the threshold of 12 responses is unlikely to be met, then additional subjects may not be recruited (eg: 6 or fewer responses among 35 subjects with sufficient followup [potential for at leat 2 assessments]). If the study continues to the second stage, 50 additional subjects will be treated for a total of 90. Subjects in whom the presence of $BRAF^{V600E}$ is not confirmed by central laboratory will be replaced.

An iDSMC will review the available safety information at regular intervals to ensure that the overall safety remains acceptable during the Main study period (see section 11.5. iDSMC).

For the Main Study period, the treatment will be administered by cycles of 28 days until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy or death. In each 28-day cycle, subjects will receive:

From Day 1 to Day 28: Encorafenib: 300 mg PO (oral capsule 4X 75 mg) once daily (QD).

From Day 1 to Day 28: Binimetinib: 45 mg PO (oral tablet 3X 15 mg) twice daily (BID).

Initial cetuximab dose Cycle 1, Day 1 400 mg/m^2 administered as a 120-min IV infusion followed by a 250 mg/m^2 dose administered as a 60-min IV infusion once weekly (QW) thereafter until week 28. Then, 500mg/m^2 IV Q2W from week 29 (Cycle 8 day 1).

Since implementation of the Urgent Safety Measure on 26 Mar 2020, in order to ensure the subjects' safety in the clinical trial by decreasing the number of clinic visits in the context of COVID-19 pandemic, Cetuximab infusions can be given every two weeks at the dose of 500 mg/m^2 administered as a 120-min IV infusion (i.e. on D1 and D15 of each cycle) regardless of the cycle number, after the investigator has evaluated the benefit/risk ratio for the subject with regards to Covid-19 pandemic.

If there was a dose modification prior to switching to the biweekly schedule, the total dose per cycle should be maintained (i.e. 200mg/m^2 QW, may be changed to a 400mg/m^2 Q2W).

From 28 Dec 2020, access to study treatment will be provided through a Study extension to all subjects whom the investigator considers are continuing to benefit from study treatment (i.e. do not experience unacceptable toxicities and none of the treatment discontinuation criteria are met) until:

- the last ongoing subject will discontinue study treatments (including 30-day Safety Follow-Up visit) for any reason (unacceptable toxicity, progression of disease, subject's decision, withdrawal of consent, initiation of subsequent anticancer therapy or death),
- or binimetinib/encorafenib are commercially available in the first line setting of *BRAF* ^{V600E} mutated mCRC,

- or the binimetinib/encorafenib development program is stopped, whichever comes first.

The same study treatment doses and schedule as for Main study period will be applicable for the Study extension period (including dose modification recommendations).

After discontinuation of study treatment (during Main study or Study extension periods), there will be a 30-day safety follow-up period. Subjects will then enter a survival follow-up period until the End of the Study.

BRAF TESTING:

Because time to treatment initiation is critical for untreated *BRAF*^{V600E} mCRC subjects, will be eligible for the study based on identification of a tumoral *BRAF*^{V600E} mutation as determined by local laboratory result obtained at any time prior to Screening. Only polymerase chain reaction (PCR) and next generation sequencing (NGS)-based local assays results will be acceptable.

The *BRAF* mutation status must be confirmed by the central laboratory no later than 30 days after the first dose of study treatment. In cases where there is discordance between the local assay and central laboratory results, or if the central laboratory is not able to confirm presence of a *BRAF*^{V600E} mutation due to inadequate or poor sample condition or insufficient amount of tumor cells in sample within 30 days of initiating study therapy, subjects may only continue treatment if there is no clinical indication of deterioration or disease progression and the Investigator determines that the subject is deriving benefit. In such instances, subjects must be informed that the *BRAF* mutation status is unconfirmed and must sign a separate informed consent form (ICF) that includes this information and describes alternative treatment options.

Central laboratory *BRAF* mutation tests with a definitive result (positive or negative) cannot be repeated to resolve a discordant result. Subjects whose sample is determined to be inadequate or who have an indeterminate result on central testing should have samples (archival material only) resubmitted for testing until a definite result can be obtained; however, in some cases, the *BRAF* status may remain indeterminate after several attempts to conduct the central test.

If at any time there is lack of confirmation of the *BRAF*^{V600E} mutation in a total of 6 subjects ($\geq$ 6% of the total targeted 90 treated subjects) or discordance between the local assay and the central

laboratory in 3 subjects (≥ 3% of the total targeted 90 treated subjects), all subsequent subjects will be required to have *BRAF*^{V600E} determined by the central laboratory prior to study treatment assignment (i.e., local *BRAF* testing will no longer be accepted for trial eligibility). Information regarding sites and laboratories associated with discordant results will be maintained and results from laboratories with more than 1 prior discordant result will not be accepted for further subject enrollment. It means that further subjects will be treated in this site on the basis of the central laboratory only.

4.2. DISCUSSION OF THE STUDY DESIGN

4.2.1. Choice of the Study Population

Refer to **Section 1**

4.2.2. Choice of the Study Design

In clinical practice, the number of mCRC patients receiving therapy (as well as the treatment efficacy) decreases with subsequent lines of therapy (**Bokemeyer C et al, 2011**; **Maughan TS et al, 2011**). Patients with *BRAF*m mCRC have limited treatment options and currently no targeted therapy blocking *BRAF* has been approved in this patient population. Standard of Care treatment options provide limited number of responses to treatment. As outlined in **Section 1**, the data from retrospective series and post hoc analyses of randomised trials reveal that standard first-line regimens, including a chemo-doublet and a biologic agent, lead to poor results in terms of ORR, PFS, and OS compared to *BRAFwt* patients, even when more aggressive and less "targeted" approaches are used (**Cremolini C et al, 2015**). The available data from the SLI of the BEACON CRC study provides evidence that the triple combination of encorafenib, binimetinib and cetuximab is likely to be at least as effective as the current standard of care in the first line setting.

The objective and advantage of the current study design is to evaluate the antitumor effect while limiting the number of subjects exposed to the triple combination in the frontline setting. The two-stage design allows for this by providing an opportunity to stop the study early due to futility.

4.2.3. Choice of the Dose and Administration Modalities

In order to optimize the potential for benefit while limiting the potential for toxicity, the dose of encorafenib chosen for this study is 300 mg QD, corresponding to its single-agent RP2D.

The proposed 300 mg dose represents an active dose of encorafenib that has been shown in clinical studies to result in tumor regression and clinical responses as a single agent **(Dummer R et al, 2013**; **Gomez-Roca CA et al, 2014**). Non-clinical in vitro and in vivo studies using *BRAF*^{V600E} human melanoma and colon cancer cell lines and xenograft models exploring the relationship between dose and efficacy also provide evidence in support of 300 mg being an appropriate starting dose in subjects. Using the human melanoma xenograft model A375, which expresses *BRAF*^{V600E}, a 20 mg/kg dose was estimated to reduce tumor volume by 85% compared to untreated animals.

Based on relative free fraction exposure, the 20 mg/kg steady-state mouse exposure is equivalent to the average exposure for subjects receiving 300 mg QD dosing. This is also consistent with the observed inhibitory effects of encorafenib in combination with cetuximab using a *BRAF*^{V600E} CRC cell-based system. Inhibition was 70% when studied at a free encorafenib concentration that was equivalent to the average daily concentration in subjects receiving 300 mg QD dosing.

The dose of binimetinib that was chosen corresponds to the single-agent RP2D (45 mg BID).

The dose of cetuximab corresponds to the approved dose in the US Product Information, Summary of the Product Characteristics for Erbitux® and Package Insert respectively in the US, Europe and Japan.

Regarding the use of cetuximab as a biweekly schedule: Tabernero et al. (**Tabernero J et al, 2016** and **Tabernero J et al, 2010**) showed preliminary pharmacokinetic, pharmacodynamic, efficacy, and safety evidence that every-2-weeks administration of cetuximab at a dose of 500 mg/m^2 may be a potentially convenient alternative to the approved weekly dosing regimen of 250 mg/m^2 (following an initial dose of 400 mg/m^2) in the treatment of mCRC. In regards to efficacy, an every-2-weeks dose of 500 mg/m^2 of cetuximab in combination with irinotecan gave a strikingly similar response rate (23%) and median TTP (4.8 months) (**Pfeiffer P et al, 2007**) to those of the approved dosing regimen plus irinotecan (23% and 4.1 months, respectively) (**Cunningham D et al, 2004**), in patients who had progressed on previous chemotherapy. Based on the pharmacokinetic similarities of the two dosing regimens in the first-line setting (**Taberno J et al, 2006**), it is

reasonable to anticipate that the efficacy and safety of the every-2-weeks dosing regimen will also be similar to that observed with the approved dosing regimen (**Tabernero J et al, 2010**).

The justification to switch to a biweekly schedule is to provide a more convenient schedule of administration to subjects who would stay on treatment (and who have not presented any signs of PD) for a period of time equivalent as the median PFS reported with SoC in the first line setting. Although cetuximab has not been approved for a Q2W dosing schedule, there are several key studies supporting the clinical use of this schedule for patients which metastatic CRC in the first line (**Tabernero J et al, 2010**; **Bouchahda M et al, 2011**) as well as the second and third line setting (**Roca JM et al, 2010**; **Martin-Martorell P et al, 2008**; **Pfeiffer P et al, 2008**; **Carneiro BA et al, 2012**; **Mrabti H et al, 2009**; **Shitara K et al, 2012**).

Since implementation of the Urgent Safety Measure on 26 Mar 2020, in order to ensure the subjects' safety in the clinical trial by decreasing the number of clinic visits in the context of COVID-19 pandemic, Cetuximab infusions can be given every two weeks at the dose of 500 mg/m^2 administered as a 120-min IV infusion (i.e. on D1 and D15 of each cycle) regardless of the cycle number, after the investigator has evaluated the benefit/risk ratio for the subject with regards to Covid-19 pandemic.

As described by Tabernero and colleagues, this change in the Cetuximab administration regimen should not impact the pharmacokinetic, pharmacodynamic, efficacy, and safety of Cetuximab in the treatment of mCRC (**Tabernero J et al, 2016** and **Tabernero J et al, 2010**).

In regards to the triple combination, the DMC of BEACON CRC study reviewed the data after the first 88 randomized patients, and these have not indicated any safety concerns. The doses of the study treatment administered in BEACON CRC study were the same as those that will be used in this study. Given that there were no new safety concerns among the 88 subjects randomized, the use of the same doses of study treatment in this study is justified.

4.2.4. Choice of sample size

Taking into consideration the study primary objective, the study sample size with 40 treated subjects with a centrally confirmed *BRAF*^{V600E} mutation in stage 1, and 50 in stage 2 (if study does not stop for futility after stage 1), is considered sufficient to evaluate the antitumor activity of the study treatment (see **Section 13.3** for more details).

5. STUDY POPULATION

Subjects fulfilling all of the inclusion criteria and none of the exclusion criteria will be eligible.

5.1. INCLUSION CRITERIA

1. Provide a signed and dated informed consent document.
2. Male or female ≥ 18 years of age at time of informed consent.
3. Histologically or cytologically confirmed CRC that is metastatic and unresectable at time of study entry (i.e. not suitable for complete surgical resection at screening).
4. Presence of *BRAF*^{V600E} mutation in tumor tissue previously determined by a local assay at any time prior to screening.

Notes:

a. Only PCR and NGS-based local assays results will be acceptable.

b. If at any time there is lack of confirmation of the BRAF^{V600E} mutation in a total of 6 subjects (≥ 6% of the total targeted 90 treated subjects) or discordance between the local assay and the central laboratory in 3 subjects (≥ 3% of the total targeted 90 treated subjects), discordance or impossibility to confirm the BRAF^{V600E} mutation in 3 subjects, all subsequent subjects will be required to have BRAF^{V600E} determined by the central laboratory prior to study treatment assignment.

c. Central testing cannot be repeated to resolve discordances with a local result once the central laboratory delivers a definitive result (positive or negative).

d. If the result from the central laboratory is indeterminate or the sample is deemed inadequate for testing, additional samples should be submitted (archival material only).

e. If more than 1 discordant result from any local laboratory leads to subject enrollment, subsequent results from this local laboratory will not be accepted for further subject enrollment.

5. Eligible to receive cetuximab per locally approved label with regards to tumor RAS status.

   e.g.: In agreement with EU label, evidence of wild type RAS (KRAS and NRAS) in EU countries.

6. Able to provide a sufficient amount of representative tumor specimen (primary or metastatic, archival or newly obtained) for testing of BRAF and RAS mutation status[(a)].

(a) FFPE tumor tissue block or a minimum of 10 slides, optimally up to 15 slides.

7. Evidence of measurable disease, as per RECIST 1.1.

Note: Lesions in areas of prior radiotherapy or other loco-regional therapies are considered measurable only if progression has been documented in the region following therapy.

8. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

9. Adequate bone marrow function at screening and baseline:
    i. *Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.*
    ii. *Platelets ≥ 100 x 10^9/L.*
    iii. *Hemoglobin ≥ 9.0 g/dL.*

Note: Blood transfusions are allowed provided that the subject has not received more than 2 units of red blood cells in the 4 weeks prior to achieve the minimum required hemoglobin level.

10. Adequate renal function at screening and baseline.
    i. *Serum creatinine ≤ 1.5x upper limit of normal (ULN) or*
    ii. *Calculated creatinine clearance (CrCl) ≥ 50 mL/min by Cockroft-Gault formula*

11. Adequate electrolytes at screening and baseline, defined as serum potassium and magnesium levels within institutional normal limits.

Note: replacement treatment to achieve adequate electrolytes will be allowed

12. Adequate hepatic function at screening and baseline:
    i. *Serum total bilirubin ≤ 1.5 x ULN and < 2 mg/dL. Note: Total bilirubin > 1.5 x ULN is allowed if direct (conjugated) bilirubin is ≤ 1.5 x ULN (and indirect (unconjugated) bilirubin is ≤ 4.25 x ULN – Only applicable for France).*
    ii. *Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 2.5 x ULN, or ≤ 5 x ULN in the presence of liver metastases.*
13. Adequate cardiac function at screening:
    i. *Left ventricular ejection fraction (LVEF) ≥ 50% as determined by MUGA scan or ECHO.*
    ii. *Mean triplicate QT interval corrected for heart rate according to Fridericia's formula (QTcF) value ≤ 480 msec.*
14. Subject able to take oral medications.
15. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

16. Female subjects 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.

Notes:
(a) Precautions to avoid pregnancy must be conducted from screening through 6 months after the last dose of cetuximab or through 30 days after the last dose of encorafenib or binimetinib, whichever is later if of childbearing potential.
(b) Permitted methods of contraception as provided (in Section 5.3.1) should be communicated to the subjects and their understanding confirmed. For all females, the pregnancy test must be negative at screening and baseline.

17. Male subject must agree to take appropriate precautions to avoid fathering a child.

Notes:
(a) from screening through 6 months after the last dose of cetuximab or through 90 days after the last dose of encorafenib or binimetinib, whichever is later.
(b) permitted methods of contraception as provided (in Section 5.3.1) should be communicated to the subjects and their understanding confirmed.

18. Subjects under guardianship or partial guardianship will be eligible unless prohibited by local laws or by local/central ethic committees.

Note: where allowed, all procedures prescribed by law must be followed.

19. Affiliated to a social security system, or is a beneficiary (if applicable in the national regulation).

5.2. EXCLUSION CRITERIA

1. Prior systemic therapy for metastatic disease.

Note: previous adjuvant/neoadjuvant therapy is allowed provided that 1) the interval from the end of chemotherapy to relapse is >6 months OR 2) in the case of neoadjuvant therapy, complete surgical resection was achieved and the interval from the end of chemotherapy to relapse is >12 months. Prior locoregional radiotherapy is allowed.

2. Prior treatment with any RAF inhibitor, MEK inhibitor, cetuximab or other anti-EGFR treatment.

3. Symptomatic brain metastasis.

Note: subjects previously treated or untreated for these conditions who are asymptomatic in the absence of corticosteroid and anti-epileptic therapy are allowed. Brain metastases must be stable for ≥ 4 weeks with imaging (e.g. brain magnetic resonance imaging [MRI] or computed

tomography [CT] demonstrating no current evidence of progressive brain metastases at screening).

4. Leptomeningeal disease.

5. History or current evidence of Retinal Vein Occlusion (RVO) or current risk factors for RVO.

Note: Risk factors for RVO are uncontrolled glaucoma or ocular hypertension, history of hyperviscosity syndrome or hypercoagulability syndrome.

6. Use of any herbal medications/supplements or any medications or foods that are moderate or strong inhibitors or inducers of CYP3A4/5 ≤ 1 week prior to the start of treatment.

Note: However, subjects who either discontinue moderate or strong inhibitors or inducers of CYP3A4/5 or switch to another medication at least 7 days prior to starting study treatment are eligible.

7. Known history of acute or chronic pancreatitis within 6 months prior to the start of the treatment.
8. History of chronic inflammatory bowel disease or Crohn's disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) ≤ 12 months prior to first dose.

9. Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:

   i. 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.

   ii. Symptomatic congestive heart failure (Grade 2 or higher), history or current evidence of clinically significant arrhythmia and/or conduction abnormality ≤ 6 months prior to start of study treatment, except rate controlled 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 optimal therapy.

11. Impaired hepatic function, defined as Child-Pugh class B or C.

12. ~~Known history of Gilbert's syndrome or is known to have any of the following genotypes: UDP-glucoronosyl transferase (UGT)1A1*6/*6, UGT1A1*28/*28, or UGT1A1*6/*28.~~ No more applicable from Protocol V6.0/Amendment PA03

13. Impaired gastrointestinal function or disease* which may significantly alter the absorption of encorafenib or binimetinib or recent changes in bowel function suggesting current or impending bowel obstruction.

**eg. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection.*

14. Previous or concurrent malignancy* within 5 years of study.

**except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix or any other malignancy that has been adequately treated and has not recurred within 3 years prior to study entry.*

15. History of thromboembolic* or cerebrovascular events** ≤ 6 months prior to starting study treatment.

**excluding venous thrombosis related to indwelling catheters and treated with low-grade anticoagulants*
***including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis or pulmonary emboli.*

16. Concurrent neuromuscular disorder that is associated with the potential of elevated Creatine Kinase (CK).

Note: e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy.

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 human immunodeficiency virus (HIV) infection.

Note: HIV testing will only be conducted in jurisdictions specifically requiring it.

19. Active hepatitis B or hepatitis C infection.

20. Known contraindication to receive cetuximab at the planned doses. Refer to the most recent cetuximab summary of product characteristics (SPC) or local label as applicable.

21. Subjects who have any medical condition that would, in the Investigator's judgment, prevent the subject's participation in the clinical study due to safety concerns or compliance with study procedures.

22. Any medical or psychiatric condition or laboratory abnormality that may increase the risk with study participation or study drug administration or that may interfere with the interpretation of study.

23. Pregnancy, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test result, or breastfeeding.

24. Is a family member of the Investigator or any associate, colleague, or employee assisting in the conduct of the study (secretary, nurse, technician).

25. Is in a position likely to represent a conflict of interest.

26. Participation in a clinical study with administration of an investigational product within 4 weeks or five times the half-life of the investigational product, whichever is longer, before the first dose of study treatment.

27. Is mentally unable to understand the nature, objectives and possible consequences of the trial; or he/she refuses to its contraints.

5.3. LIFESTYLE GUIDELINES

5.3.1. Contraception

Female subjects who are postmenopausal for at least 1 year or are surgically sterile for at least 6 weeks are considered to be of non-childbearing potential.

Female subjects of childbearing potential must agree to take appropriate precautions to avoid pregnancy from screening through 6 months after the last dose of cetuximab or through 30 days after the last dose of encorafenib or binimetinib, whichever is later.

Male subjects must agree to take appropriate precautions to avoid fathering a child and prevent exposure of seminal fluid to the partner from screening through 6 months after the last dose of cetuximab or through 90 days after the last dose of encorafenib or binimetinib, whichever is later.

The following methods are permitted under this protocol for use by the subject and his/her partner. These methods are listed below and should be communicated to the subjects and their understanding confirmed.

Methods that have been determined to be highly effective (i.e., can achieve a failure rate < 1% per year when used consistently and correctly) according to the CTFG 2014 (**Clinical Trials Facilitation Group**) include:

- Complete abstinence from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner (considered highly effective provided the vasectomized male has received medical assessment of surgical success and that the male is a female subject's sole sexual partner)

Acceptable birth control methods that result in a failure rate of more than 1% per year (CTFG 2014) include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide

NOTE: Due to the potential of encorafenib to induce CYP3A4, hormonal agents (including but not limited to birth control patch, vaginal ring, oral, injectable, or implanted contraceptives) are permissible only when combined with other highly effective or acceptable methods of contraception.

5.3.2. Photosensitivity

Subjects should avoid extended exposure to ultraviolet light and, when outdoors, should wear occlusive clothing, sunscreen and sunglasses while receiving encorafenib or cetuximab and for 2 months following the last dose of each agent.

5.4. NUMBER OF SUBJECTS

The target of 90 subjects with centrally confirmed *BRAF*^{V600E} will be treated in two stages:

- First stage: 40 subjects will be treated
- Second stage: if there are at least 12 confirmed responders in the first stage, 50 additional subjects will be treated in this second stage .

In case of discordance in the results between the local assay and the central laboratory (potential false-positive local result), or lack of *BRAF*^{V600E} confirmation, subject will be replaced.

5.5. RECRUITMENT MODALITIES

Subjects with confirmed *BRAF*^{V600E} mCRC and who have not received any prior systemic therapy for the metastatic disease and who fulfill all inclusion and none of the exclusion criteria will be recruited.

Where authorized by local/national regulation, some specific materials may be used to improve recruitment including: leaflets, advertising in oncology journals, websites, mailing (paper or e-mail) to doctors, subject associations, and subject advocacy groups. Before use of such materials, they will be reviewed and approved by the Sponsor and submitted to and approved by the appropriate IECs/IRBs.

5.6. SUBJECTS IDENTIFICATION

The Subject's code will contain 8 digits, corresponding to the country number, the centre number and the Subject's number according to chronological order (once having signed the written informed consent).

5.7. SUBJECT DISCONTINUATION REASONS

The reasons for a subject's premature discontinuation from the study may be the following (in all cases, available data will be retained for the safety analysis):

5.7.1. Treatment Discontinuation for Individual Subject

Subjects may decide to stop participating in the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. Wherever possible, the tests and evaluations listed for the End of Treatment visit and Safety Follow-up visit should be carried out and an effort should be made to continue follow-up.

If a subject decides to discontinue study treatment, he/she should be asked if he/she is willing to be contacted by telephone for monitoring of survival.

If a subject withdraws consent, the subject's data collected up to the date of consent withdrawal will be included in the analyses. The date, stated reason for and level of consent withdrawal should be documented. Any blood or tissue samples collected up to the date of withdrawal of consent will be analyzed, unless explicitly prohibited by the subject.

The Sponsor should be notified of all subjects' decision to discontinue study treatment and all study withdrawals through the designated e-CRFs in a timely manner.

Subjects meeting any of the following criteria must discontinue study drug treatment:

- **Subject decision to discontinue study treatment** (but request agreement to return for end of treatment assessments, safety follow-up assessments and/or survival follow-up).
- **Withdrawal of consent:** no further participation
- **Lost to follow up:** A subject will be considered as lost to follow up, if he/she did not attend a scheduled visit and for whom no news can be obtained after three documented attempts

with a minimum of 15 days between the first and the last attempt. This status must be dated at the latest as the database lock.

- **Investigator decision** in the subject's interest if an SAE occurs and is considered by the Investigator liable to threaten the health of the subject or if a serious disease occurs and necessitates the prescription of a medication incompatible with the pursuit of the study. The Sponsor should immediately be informed by phone or fax or email and a report explaining the discontinuation will be forwarded to him as soon as possible.
- **Progressive disease:** at any time (to be taken into account only for treatment discontinuation).
- **Unacceptable AE or toxicity** (related or not to the study treatment) or failure to tolerate the study treatment.
- **Dose interruption** of > 28 consecutive days in administration of encorafenib or binimetinib, or noncompliance with study drug administration consisting of > 4 missed consecutive doses of cetuximab due to an AE or clinically significant laboratory abnormality, unless judged by the Investigator and Sponsor Medical Contact or designee to be in the best interest of the subject to continue treatment.
- **Death**.
- **Female subject becomes pregnant, or begins breastfeeding,**
- **Significant protocol deviation** that, in opinion of the investigator and/or sponsor, renders the subject unsuitable for further study drug administration.
- **Termination of the study by the sponsor.**

Subjects meeting any of the following criteria may be discontinued from study drug treatment if, during the course of the study:

- Is found to have a tumor that is *BRAF*wt by the central laboratory.
- Is noncompliant with study procedures or study drug administration in the opinion of the investigator.

5.7.2. Study Discontinuation for individual Subject

The subject may be considered discontinued from the study for the following reasons:

- Withdrawal of consent.
- Lost to follow-up.
- Death.
- Termination of the study by the Sponsor.

5.8. STUDY DISCONTINUATION

This study may be discontinued at any time due to safety concerns, failure to meet expected enrollment goals, administrative reasons or at the discretion of the Sponsor. Should the study be terminated prematurely, the Sponsor will provide written notification to all Investigators and regulatory authorities and will specify the reason(s) for early termination. The Sponsor/Investigator must inform the EC/IRB promptly and provide the reason(s) for the termination.

The Competent Authority (CA) may suspend or prohibit the study if it considers that the conditions of authorisation are not being met or has doubt about the safety or scientific validity of the study.

5.9. REPLACEMENT OF SUBJECTS

Withdrawn subjects will not be replaced.

Subjects with unconfirmed *BRAF*^{V600E} mutation will be replaced.

5.10. POST-STUDY EXCLUSION PERIOD

A post-study exclusion period is not required in this protocol.

5.11. SUBJECT CARD

As soon as consent is signed, the subject will receive from the Investigational Center a personal card to be kept throughout the study duration, which provides the following information: subject's name, Sponsor's name, study code, (if applicable) EudraCT number, complete address of the

Investigating Centre with the name and emergency phone number of the Investigator and a Sponsor 24/7 phone contact number (French and English languages).

The delivery date of the card to the study subject will be documented in the electronic case report form (e-CRF).

The preferred contact for the subject in case of need is in all cases the Investigator or his team. The card includes the name of the Investigator and the phone number which allows direct contact by the subject or the caregiver in case of need.

The card, features an additional phone number which allows, should the need arise, a contact with a Sponsor representative able to address any medical and urgent issues.

The subject is informed that, if a call is necessary, this call will be answered in English / French, which allows the subject to take any appropriate measures.

6. STUDY TREATMENT(S)

In Europe (EU), the Investigational Medicinal Product Management Service of the *Institut de Recherche Pierre Fabre* (*IRPF*) will supply the investigational centers with labeled and packaged encorafenib, binimetinib and cetuximab units necessary for the conduct of the trial.

In the United States (US), labeled and packaged binimetinib and encorafenib will be supplied to investigational centers by Array BioPharma. Cetuximab supply within the US will be supplied either locally or by Array BioPharma. Array BioPharma will employ a licensed company specializing in packaging, labeling, and distribution of investigational medicinal products.

In Japan (JAP), labeled and packaged binimetinib, encorafenib and cetuximab will be supplied to investigational centers by Array BioPharma via a licensed company specializing in packaging, labeling, and distribution of investigational medicinal products via a warehouse facility located in Japan.

6.1. SOURCE, PRESENTATION AND COMPOSITION OF INVESTIGATIONAL PRODUCT(S) AND ASSOCIATED PRODUCT(S)

6.1.1. Encorafenib 75 mg hard capsule

Encorafenib will be prepared in oral hard capsules.

Code and name: W0090-Encorafenib for Europe, LGX818-Encorafenib for US and Japan.

Encorafenib may also be known as ONO-7702 in Japan.

Pharmaceutical presentation: hard capsule of 75 mg

Composition:

- Hard capsule

– **Active ingredient:** Encorafenib
– **List of Excipients:** copovidone, Poloxamer 188, cellulose microcrystalline, succinic acid, crospovidone, silica colloidal anhydrous, magnesium stearate of vegetable origin.

Capsule shell (gelatin, titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172), ink capsule shell (Pharmaceutical Glaze, iron oxide black (E172), Propylene glycol).

6.1.2. Binimetinib 15 mg film-coated tablet

Binimetinib will be prepared in film-coated tablets for oral use.

Code and name: W0074 - Binimetinib for Europe, MEK162 - Binimetinib for US and Japan.

Binimetinib may also be known as ONO-7703 in Japan.

Pharmaceutical presentation: film-coated tablet of 15 mg

Composition:

- Film-coated tablet

- **Active ingredient:** Binimetinib
- **List of excipients:** lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide/silica colloidal anhydrous, OPADRY® yellow 85F92213 (polyvinyl alcohol – part hydrolyzed, macrogol / PEG 3350, titanium dioxide, talc, iron oxide yellow E172, iron oxide black E172)

6.1.3. Cetuximab solution for infusion

Cetuximab is available under different formulations:

- 1 formulation for Europe and Japan
- 1 formulation for US

- **Europe and Japan formulation: ERBITUX® 5 mg/mL solution for infusion**

Cetuximab solution for infusion will be supplied in labelled packages : single-use vial of 500 mg cetuximab (5 mg/mL solution) – vial of 100 mL

Cetuximab is a colorless solution administered intravenously.

Cetuximab is a chimeric monoclonal IgG1 antibody produced in a mammalian cell line (Sp2/0) by recombinant DNA technology.

Composition:

- **Active ingredient:** Cetuximab 5 mg/mL
- **List of excipients:** Sodium chloride, Glycine, Polysorbate 80, Citric acid monohydrate, Sodium hydroxide, Water for injection.

Cetuximab does not contain any antimicrobial preservative or bacteriostatic agents. From a microbiological point of view, the product should be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC, unless opening has taken place in controlled and validated aseptic conditions.

- **US formulation**

Erbitux®(cetuximab) in the US is commercially available and is supplied at a concentration of 2 mg/mL as a 100 mg/50 ML, single-use vial or as a 200 mg/100 mL, single-use vial as a sterile injectable liquid containing no preservatives.

Composition:

Cetuximab is formulated in a solution with no preservatives, which contains:

- **Active ingredient:** Cetuximab 2 mg/mL
- **List of excipients:** sodium chloride, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, and Water for Injection

6.2. PACKAGING AND LABELLING

In Europe, the treatment units will be packed and labelled by the Investigational Medicinal Product Management Service of IRPF according to the European Directive, local requirements and local languages.

In US, the treatment units will be packed and labelled within US by the sponsor designee and comply with the legal requirements of the US.

In Japan, the treatment units will be packed and labelled by sponsor designee and comply with the legal requirements of Japan.

6.2.1. Packaging

6.2.1.1. Encorafenib 75 mg capsule

- **<u>Europe formulation</u>**

  - Primary packaging

  70 hard capsules will be packaged in a bottle 175 cc (HDPE, white, opaque, square) closed with a cap (38 mm, polypropylene (PP), white, child-resistant design, cap with induction seal liner) and containing a 2 grams silica gel desiccant.

  - Secondary packaging (only for Europe)

  The bottle will be packaged in a sealed box.

- **<u>US and Japan formulation</u>**

  - Primary packaging

  70 hard capsules will be packaged in a bottle 175 cc (HDPE, white, opaque, square) closed with a cap (38 mm, PP, white, child-resistant design, cap with induction seal liner and opening seal ring) and containing a desiccant.

  (Tyvek soft packet, 2 gram silica Gel Desiccant).

- Secondary packaging

No secondary packaging.

6.2.1.2. Binimetinib 15 mg film coated tablet

- **Europe formulation**

- Primary packaging

70 film coated tablets will be packaged in a 120 cc bottle (HDPE, without dessicant, white, opaque, square) closed with a cap (38 mm, Polypropylene (PP), white, child-resistant design, cap with induction seal liner).

- Secondary packaging

The bottle will be packaged in a sealed box.

- **US and Japan formulation**

- Primary packaging

70 film coated tablets will be packaged in a 120 cc bottle (HDPE, without desiccant, with induction seal, and child-resistant cap)

- Secondary packaging

No secondary packaging.

6.2.1.3. Cetuximab ERBITUX® 5 mg/mL solution for infusion

- **Europe and Japan formulation: Cetuximab ERBITUX® 5 mg/mL solution for infusion**

- Primary packaging

100 mL of solution in a vial (Type I glass) with a stopper (halobutyl rubber) and a seal (aluminium/polypropylene).

- Secondary packaging

Sealed box of 1 vial: 500 mg.

- **US formulation: Cetuximab ERBITUX® 2 mg/mL solution for infusion**

Erbitux®(cetuximab) in the US is commercially available. Commercially available vials are packed into cartons.

6.2.2. Labelling

- **Labelling for Europe Supply:**

Investigational Products will be labelled in compliance with local requirements, according to the following rules:

I. Treatment unit box labelling:

The secondary packaging box label (green for binimetinib and white for encorafenib and cetuximab) contains the following information:

(a) Name and address of Sponsor
(b) Pharmaceutical dosage form, route of administration, quantity of dosage units, the name/identifier and strength/potency
(c) Packaging batch number
(d) Trial reference code allowing identification of the study (protocol number and EudraCT number)
(e) Treatment number
(f) Name of the Investigator (will be added when preparing to send)
(g) Directions for use (reference may be made to the investigator brochure or other explanatory document intended for the trial subject or person administering the product)
(h) "For clinical trial use only"
(i) Storage conditions
(j) Expiry date as month/year (MM/YYYY)
(k) "Keep out of reach and sight of children" except when the product is for use in trials where the product is not taken home by subjects

The box labelling contains a tear-off flap (also green for binimetinib and white for encorafenib and cetuximab) with the following information:

- Protocol number

- Packaging batch number
- Treatment number
- The name/identifier and strength/potency

Additional mentions will be added according to local authority requirements.

Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings and/or handling instructions may be displayed.

II. Treatment bottle/vial labelling:

The product is supplied in a primary packaging and a secondary packaging which are intended to remain together. The following information is included on the label of the primary package bottle/vial (green for binimetinib and white for encorafenib and cetuximab):

(a) Name of Sponsor
(b) Pharmaceutical dosage form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units, the name/identifier and strength/potency
(c) Packaging batch number
(d) Trial reference code allowing identification of the study (protocol number)
(e) Treatment number
(f) Expiry date as month/year (MM/YYYY)

- **Labelling for US and Japan Supply**

For both encorafenib and binimetinib supplied within the US and Japan, each bottle will be labelled, at a minimum, with a unique identifier (medication number), the lot number, contents (number of tablets), dosage strength, storage conditions and the name and address of the Sponsor designee. Both encorafenib and binimetinib labels will be in the local language and comply with the legal requirements of the US and Japan. Site personnel will add the subject number to the label.

In the US, cetuximab will be supplied either locally or by the Sponsor designee, Array BioPharma.

If the US cetuximab is locally supplied, then the cetuximab does not require specific labelling. Each unit of cetuximab supplied for Japan by the Sponsor designee will be labelled, at a minimum, with a unique identifier (medication number), the lot number, contents (number of tablets), dosage

strength, storage conditions and the name and address of the Sponsor designee. Cetuximab labels will be in local language and comply with the legal requirements of Japan.

6.3. DISTRIBUTION TO CENTERS AND STORAGE

Before the start of the study, the sponsor or designee will supply the Investigational Centre with the necessary treatment units for the study using Interactive Response Technology (IRT).

Additional treatment supplies will be shipped to the Investigational Centre upon request via IRT and according to needs.

Acknowledgement of receipt of all shipments should be managed according to Pharmacy manual process and timelines.

The Clinical Research Associate (CRA) will ensure during the initiation visit that trial medications have been received in good condition and the acknowledgment of receipt has been adequately completed and returned.

In cases of undue delay in study execution, the Pharmacist or Investigator should ensure that the expiry date has not been exceeded. If the date has been exceeded, new treatment units will be supplied to the investigational center.

Labeled, packaged encorafenib, binimetinib and cetuximab will be shipped to each centre by the Sponsor or designee, as described in the Pharmacy Manual.

The Investigator or an approved representative (e.g., registered pharmacist) will ensure that all encorafenib, binimetinib and cetuximab is stored as outlined in the Pharmacy Manual and in accordance with applicable regulatory requirements. The drug storage area at the site must be secure, with access limited to authorized personnel.

Storage conditions will be described on the medication label. Detailed instructions for storage and handling of encorafenib and binimetinib will be provided in the Pharmacy Manual. Cetuximab should be stored according to the locally approved prescribing information.

6.4. ALLOCATION OF TREATMENTS AND DISPENSATION TO SUBJECTS

All subjects who sign an informed consent will be assigned a unique subject number and will be able to start screening. A subject will be assigned for study treatments via the IRT system if he/she meets all eligibility requirements .

According to GCP, all eligibility criteria will be checked during the registration procedure. Assignment of treatment number will be implemented via IRT. All information regarding this process is described in the IRT manual.

Throughout the Treatment Period (Main study and Study extension periods) the Investigator will dispense to the subject the box indicated by IRT (Day 1 of each cycle).

6.5. TREATMENT ADMINISTRATION

6.5.1. Duration of Treatment

During the Main study period, study treatment will be administered until unacceptable toxicity, progression of disease, subject's decision, withdrawal of consent, initiation of subsequent anticancer therapy or death.
During the Study extension period (from 28 Dec 2020), access to study treatment will be provided through a Study extension to all subjects whom the investigator considers are continuing to benefit from study treatment (i.e. do not experience unacceptable toxicities and none of the treatment discontinuation criteria are met) until:

- the last ongoing subject will discontinue study treatments (including 30-day Safety Follow-Up visit) for any reason (unacceptable toxicity, progression of disease, subject's decision, withdrawal of consent, initiation of subsequent anticancer therapy or death),
- or binimetinib/encorafenib are commercially available in the first line setting of *BRAF* ^{V600E} mutated mCRC,
- or the binimetinib/encorafenib development program is stopped, whichever comes first.

Dose Schedule

The investigational products in this study are encorafenib and binimetinib in combination with cetuximab. Dose schedule is described in **Table 7**.

Table 7: Dose and Treatment Schedule

Study treatment	Pharmaceutical form and route of administration	Dose	Frequency
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-minute infusion), then 250 mg/m^2 (60-minutes infusion)	QW for the first 28 weeks
		500 mg/m^2 (120-minute infusion)	Q2W (from week 29 - C8D1) Since implementation of the Urgent Safety Measure on 26 Mar 2020, in order to ensure the subjects' safety in the clinical trial by decreasing the number of clinic visits in the context of COVID-19 pandemic, Cetuximab infusions can be given every two weeks (i.e. on D1 and D15 of each cycle) regardless of the cycle number, after the investigator has evaluated the benefit/risk ratio for the subject with regards to Covid-19 pandemic.

QD: once daily; BID: twice daily; QW, once weekly; Q2W, every 2 weeks

6.5.2. Route and Conditions of Administration of Encorafenib and Binimetinib

Encorafenib will be administered with a QD schedule and binimetinib will be administered with a BID schedule, both PO as a flat-fixed dose, not by body weight or body surface area (BSA).

Binimetinib and encorafenib can be taken without regard to food. Subjects should be instructed to swallow the capsules /tablets whole and not to chew or crush them. Both oral study drugs are to be taken together in the morning and only the BID administered drug (binimetinib) is to be taken in the evening without regard to food.

- QD dosing: subjects should be instructed to take encorafenib capsules daily with a large glass of water (~250 mL) in the morning (together with the morning intake of binimetinib) at approximately the same time every day. Doses of encorafenib that are omitted for AEs or any other reason can be taken up to 12 hours prior to the next dose; if less than 12 hours to the next dose, the regular dosing schedule must continue and subject should be instructed to check with the study doctor. It is forbidden to double the next dose.
- BID dosing: subjects should be instructed to take binimetinib tablets 12 ± 2 hours apart with a large glass of water (~250 mL) in the morning and in the evening at approximately the same times every day. Doses of binimetinib that are omitted for AEs or any other reason should not be made up later in the day, or at the end of the dosing period and it's forbidden to double the next dose.

On days when a blood collection is scheduled at the investigational site, subjects will take the morning dose of encorafenib and binimetinib at the site under the supervision of the Investigator or designee, after any required blood sample collections. The time of dosing and the time of PK samples should be recorded on these clinic visit dates. On all other days, subjects will take encorafenib and binimetinib at home.

If a subject vomits at any time after dosing, the dose of study drug should not be re-administered.

Subjects are prohibited to consume grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of any of these items throughout the entire study and for 7 days before the first dose of study drugs, due to potential CYP3A4 interaction with the study drugs. Orange juice is allowed.

Encorafenib and binimetinib will be administered at least 30 minutes prior to cetuximab without regard to when cetuximab premedications are administered.

The Investigator or responsible site personnel will ensure that the appropriate dose is dispensed and will provide the subject with at least the appropriate number of encorafenib capsules and binimetinib tablets for the number of doses to be taken prior to the next scheduled visit. The site personnel will train the subject and/or the subject's caregiver on dosing procedures for the study drug.

Subjects will receive a diary to document self-administered dosings of encorafenib and binimetinib for each cycle to include the dose of study drug taken, the date of dosing (and times if applicable), and if any doses were missed and the reason for the missed dose. One diary will be provided per cycle. Subjects will be instructed to return unused encorafenib and binimetinib and the subject diary to the center at the end of each cycle. Drug accountability must be performed on a regular basis.

The Investigator or responsible site personnel should instruct the subject to take encorafenib and binimetinib as per protocol (i.e., promote compliance). The dosage prescribed and dispensed to the subject and all dose changes and all missed doses during the study must be recorded in the e-CRF.

6.5.3. Route and Condition of Administration of Cetuximab

Cetuximab will be administered IV weekly on Days 1, 8, 15 and 22 (±3 days) of every 28-day cycle at the study center for the first 28 weeks then every two weeks from week 29 (**Table 7**) according to institutional standards.

The initial cetuximab dose on Day 1 of Cycle 1 is 400 mg/m^2 administered as a 120-minute IV infusion followed thereafter by a 250 mg/m^2 dose administered as a 60-minute IV infusion at each cycle. Subjects who remain on treatment for 28 weeks will be treated with cetuximab 500 mg/m^2 administered as a 120-min IV infusion once every 2 weeks from week 29 (Cycle 8 day 1).

Since implementation of the Urgent Safety Measure on 26 Mar 2020, in order to ensure the subjects' safety in the clinical trial by decreasing the number of clinic visits in the context of COVID-19 pandemic, Cetuximab infusions can be given every two weeks at the dose of 500 mg/m^2 administered as a 120-min IV infusion (i.e. on D1 and D15 of each cycle) regardless of the cycle number, after the investigator has evaluated the benefit/risk ratio for the subject with regards to Covid-19 pandemic.

If there was a dose modification prior to switching to the biweekly schedule, the total dose per cycle should be maintained (i.e. 200mg/m^2 QW, may be changed to a 400mg/m^2 Q2W).

The infusion rate should be consistent with local labelling but should not exceed 10 mg/min (the first infusion rate should not exceed 5mg/min). Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. If an infusion reaction occurs while cetuximab is being administered, the infusion should be stopped immediately, and the subjects should be closely monitored and treated in line with institutional standards. Any re-challenge with cetuximab following an infusion reaction should be first discussed with the Sponsor.

Pre-medication for routine cetuximab infusions may be used in accordance with the label and with the national and/or institutional standards, but should preferably be based on a combination of an H1 antagonist (e.g., diphenhydramine) and dexamethasone (10 mg IV). This combination is mandatory for the first infusion. Pre-medication should be administered no sooner than 1 hour after administration of encorafenib and binimetinib (if applicable) and 30 minutes prior to cetuximab infusion. According to cetuximab labelling instructions, medications such as corticosteroids and antihistamines may be administered at the discretion of the Investigator to treat an existing infusion reaction, or as premedication for a subject who has previously experienced an infusion reaction. Predose PK samples for cetuximab analysis should be collected just prior the beginning of the cetuximab infusion.

Doses of cetuximab that are omitted for AEs or any other reason should not be made up. If cetuximab is discontinued, the frequency of study visits may be decreased after discussion with Sponsor.

6.5.4. Dose Modification

Subjects will be monitored for AEs. The severity of AEs will be evaluated using the NCI-CTCAE v.4.03.

If a subject develops toxicity, the dose should be modified as outlined in **Table 14** and **Table 15**, which include criteria for interruption and reduction of encorafenib, binimetinib and cetuximab. All dose modifications should be based on the worst preceding toxicity. All dosing interruptions and modifications must be recorded in the e-CRF.

If a subject permanently discontinues binimetinib due to an AE or clinically significant laboratory value, they may continue to receive encorafenib in combination with cetuximab.

Due to the lack of efficacy of binimetinib, encorafenib, or cetuximab when used as single agents in subjects with *BRAF*-mutant mCRC, subjects who cannot tolerate these agents in combination with at least one other agent, should discontinue study treatment altogether, complete the end of treatment visit and continue to be followed for survival (and disease progression, if applicable).

Cetuximab may be reduced by 2 dose levels to a minimum of 150 mg/m^2, due to AEs or laboratory abnormalities (**Table 8**). When a dose reduction is required because of an AE, no subsequent dose re-escalation of cetuximab will be permitted for that subject for the duration of study treatment. If after resolution of an AE, treatment is resumed at the same dose, and the same toxicity reoccurs with the same severity, any re-initiation of treatment must be at the next lower dose level irrespective of duration, with some exceptions for skin toxicity.
In addition, a subject must discontinue study treatment if, after treatment is resumed at a lower dose of cetuximab, the same toxicity reoccurs with the same or worse severity.

If a subject misses > 28 consecutive days of encorafenib or binimetinib, or > 4 consecutive cetuximab doses as the result of an AE or clinically significant laboratory abnormality, then the respective agent(s) should be discontinued.

Subjects who discontinue study treatment for a study-related AE or an abnormal laboratory value must complete the end of treatment visit and continue to be followed for survival (and disease progression).

Table 8: Dose Levels for Dose Modification

	Encorafenib (mg QD)	Binimetinib (mg BID)	Cetuximab WEEKLY (mg/m^2)	Cetuximab BI-WEEKLY (mg/m^2) Starting from C8D1 week 29 Or at any cycle since implementation of the Urgent Safety Measure on 26 Mar 2020
Starting Dose	**300**	**45**	**400 mg/m^2 cycle 1 day 1 then 250 mg/m^2 thereafter**	**500**
Dose level -1	225	30	200	400
Dose level -2	150	15	150	300

6.5.4.1. Dose Modification for Encorafenib and/or Binimetinib

Doses of encorafenib and/or binimetinib may be adjusted for AEs throughout the study as described inTable 14. In general, doses should not be reduced or interrupted for Grade 1 AEs other than for specific ocular AEs referred to in **Table 13**, but treatment to control symptoms should be provided as appropriate, if applicable.

An individual subject may have their dose of encorafenib and/or binimetinib reduced to the dose levels specified in **Table 8**.

The lowest permitted dose level of encorafenib is 150 mg QD and the lowest permitted dose level of binimetinib is 15 mg BID.

If the AE causing a dose reduction improves to the subject's Baseline level and remains stable for a minimum of 14 days, the dose can be re-escalated to the next dose level at the discretion of the Investigator, provided there are no other concomitant toxicities that would prevent drug re-escalation. There is no limit to the number of times the subject can have their dose reduced or re escalated (in increments specified in **Table 8**).

- No dose re-escalation of encorafenib is allowed after a dose reduction due to prolonged QTcF ≥ 501 msec
- No dose re-escalation of binimetinib is allowed after a dose reduction due to LVEF dysfunction or prolonged QTcF ≥ 501 msec
- No dose re-escalation of binimetinib or encorafenib is allowed after a dose reduction due to retinal toxicity ≥ Grade 2.

Refer to **Table 14** for recommended dose modifications for encorafenib and/or binimetinib, if applicable, based on the occurrence of treatment-related AEs.

Eye disorders that cannot be specifically graded according to modified NCI-CTCAE, v.4.03, should be graded according to **Table 9**. Serous detachment of the retina should be graded according to **Table 10**.

Uveitis should be graded according to NCI-CTCAE, v.4.03 as described in **Table 11**, Hand-foot skin reactions (HFSR) should be graded according to NCI-CTCAE, v.4.03 as described in **Table 12**. Diarrhea should be graded according to modified NCI-CTCAE, v.4.03 as described in **Table 13**. Furthermore, please refer to **Section 17.1** for additional supportive care recommended guidelines for the management of: cetuximab-induced, encorafenib-induced and/or binimetinib-induced skin reaction (**Section 17.1**), encorafenib-induced HFSR (**Section 17.2**), binimetinib-induced diarrhea (**Section 17.3**) and binimetinib-associated interstitial lung disease/pneumonitis (**Section 17.7**).

Table 9: Modified NCI CTCAE, Version 4.03 Grading of Eye Disorders

Grade	Description
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care activities of daily living
4	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye

Table 10: NCI CTCAE, Version 4.03 Grading of Serous Detachment of the Retina

Grade	Description
1	Asymptomatic (but with findings in ocular coherence tomography, fundoscopy and/or slit lamp biomicroscopy)
2	Symptomatic with moderate decrease in visual acuity (20/40[a] or better); limiting instrumental activities of daily living
3	Symptomatic with marked decrease in visual acuity (worse than 20/40[a]); limiting self-care activities of daily living
4	Blindness (20/200a or worse) in the affected eye

Note: For rhegmatogenous retinal detachment, grade according to NCI-CTCAE v.4.03 Retinal Detachment.
a Please refer to (**Section 17.3**).

Table 11: NCI CTCAE, Version 4.03 Grading of Uveitis

Grade	Description
1	Asymptomatic; clinical or diagnostic observations only
2	Anterior uveitis; medical intervention indicated
3	Posterior or pan-uveitis
4	Blindness (20/200[a] or worse) in the affected eye

a Please refer to (**Section 17.3**).

Table 12: NCI CTCAE, Version 4.03 Grading of Hand-foot Skin Reaction (HFSR)[a]

Grade	Description [b]
1	Minimal skin changes or dermatitis (e.g., erythema, edema, numbness, dysesthesia, paresthesia, tingling or hyperkeratosis) without pain
2	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL
3	Severe skin changes (e.g., peeling, ulceration, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL

Abbreviations: ADL=activities of daily living.

a. HFSR or palmar-plantar erythrodysesthesia syndrome, a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet;

b. More specific examples for Grade 1 and Grade 3 are added to facilitate proper grading (from the sorafenib package insert; West Haven, CT: Bayer Pharmaceuticals Corporation; 2007).

Table 13: Modified NCI CTCAE, Version 4.03 Grading of Diarrhea

Grade	Description
1	Increase of < 4 stools per day over Baseline; mild increase in ostomy output compared to Baseline
2	Increase of 4-6 stools per day over Baseline; moderate increase in ostomy output compared to Baseline
1/2 complicated	Definition as above (Grade 1/2) with the following complicating signs/symptoms: • Moderate to severe cramping • Grade ≥ 2 nausea/vomiting • Decreased performance status • Fever • Sepsis • Neutropenia • Frank bleeding • Dehydration

Grade	Description
	• Unresolved diarrhea after 48 hours of treatment with loperamide (including high-dose administration) and initiation of second-line treatment
3	Increase of ≥ 7 stools per day over Baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to Baseline; limiting self-care activities of daily living
4	Life threatening consequences; urgent intervention indicated

Table 14: Recommended dose modifications for Encorafenib-related and/or Binimetinib related AEs

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	Dose Modification for Encorafenib and for Binimetinib
Eye Disorders - Retinal Events (including serous detachment of the retina), **Note: Results and images of ocular coherence tomography (OCT) must be made available upon request.** **Any visual acuity impairment at screening should be documented and should be considered as baseline.**	
Grade 1	Maintain dose levels of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days. • If subject remains asymptomatic (Grade 1), maintain dose level of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol. • If subject becomes symptomatic (blurred vision, photophobia, etc.) or visual acuity assessment shows Grade 2, follow Grade 2 dose guidelines below.
Grade 2	Interrupt dosing of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days. • If resolved to baseline or Grade ≤ 1, resume treatment at current dose level of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol. • If not resolved to baseline or Grade ≤ 1, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol.
Grade 3	Interrupt dosing of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days: • If resolved to baseline or Grade ≤ 2, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol. • If not resolved to baseline or Grade ≤ 2, continue the interruption and repeat the ophthalmic assessment in 10 days. . If resolved to baseline or Grade ≤ 2, resume treatment at 1 reduced dose levelb of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol . If remains Grade 3, permanently discontinue encorafenib and binimetinib.
Grade 4	Permanently discontinue binimetinib and immediate follow-up with ophthalmic monitoring[c].

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	Dose Modification for Encorafenib and for Binimetinib
Eye Disorders - Posterior Uveitis[c] **Note: Results and images of ocular coherence tomography (OCT) must be made available upon request.** **Any visual acuity impairment at screening should be documented and should be considered as baseline.**	
Grade 1	Maintain dose levels of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days. • If subject remains asymptomatic (Grade 1), maintain dose level of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol. If subject becomes symptomatic (blurred vision, photophobia, etc.) or visual acuity assessment shows Grade 2, follow Grade 2 dose guidelines below.
Grade 2	Interrupt dosing of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days. • If resolved to baseline or Grade ≤ 1, resume treatment at current dose level of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol. • If not resolved to baseline or Grade ≤ 1, resume treatment at 1 reduced dose level[b] of encorafenib and current dose of binimetinib and continue the schedule of visual assessments established per protocol. If posterior uveitis lasts > 6 weeks, permanently discontinue binimetinib and encorafenib.
Grade 3	Interrupt dosing of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days: • If resolved to baseline or Grade ≤ 2, resume treatment at 1 reduced dose level[b] of encorafenib and current dose of binimetinib and continue the schedule of visual assessments established per protocol. • If not resolved to baseline or Grade ≤ 2, continue the interruption and repeat the ophthalmic assessment in 10 days. • If remains Grade 3, permanently discontinue encorafenib and binimetinib.
Grade 4	Permanently discontinue encorafenib and binimetinib and immediate follow-up with ophthalmic monitoring[c].
Eye Disorder - RVO[c](Retinal Vein Occlusion) **Note: Results and images of ophthalmic examinations should be made available upon request. This includes scans/images of fluorescein angiography should a subject be assessed using this technique.**	
RVO of any grade	Permanently discontinue binimetinib and immediately follow-up with ophthalmic monitoring[c].
Other Eye Disorders (i.e., Non-Retinal Events)	
Grade 1 – 2	Maintain dose level of encorafenib and binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution.
Grade 3	Interrupt dosing of encorafenib and binimetinib and refer subject to ophthalmologist within 7 days[c]: • If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib. • If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue encorafenib and binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution[c].
Grade 4	Permanently discontinue encorafenib and binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution[c]

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	Dose Modification for Encorafenib and for Binimetinib
Liver-Related Adverse Events	
Grade 1 AST or ALT > ULN to 3 × ULN	Maintain dose level of encorafenib and binimetinib.
Grade 2 AST or ALT > 3 to 5.0 × ULN or 3 × baseline value[d] **AND** **blood bilirubin[g]** **≤ 2.0 × ULN**	Maintain dose level of encorafenib and interrupt dosing of binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: • If resolved in ≤ 14 days, maintain dose level of encorafenib and binimetinib. • If not resolved in ≤ 14 days, interrupt dose of encorafenib (in addition to prior binimetinib) until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then resume treatment at current dose level of encorafenib and 1 reduced dose level[b] of binimetinib. If additional occurrence: • Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib. Treatment with encorafenib and binimetinib may be resumed sequentially at the Investigator's discretion, with encorafenib being resumed alone for one week before resuming binimetinib treatment.
AST or ALT > 3.0 to 5.0 × ULN AND blood bilirubin[g] > 2.0 × ULN	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1, then: • If resolved in ≤ 7 days, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib. • If not resolved in ≤ 7 days, permanently discontinue encorafenib and binimetinib. Treatment with encorafenib and binimetinib may be resumed sequentially at the Investigator's discretion, with encorafenib being resumed alone for one week before resuming binimetinib treatment.
Grade 3 AST or ALT > 5.0 to 8.0 × ULN) **AND** **blood bilirubin[g]** **≤ 2.0 × ULN**	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: • If resolved in ≤ 14 days, resume treatment at current dose level of encorafenib and binimetinib. • If not resolved in ≤ 14 days, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib. Treatment with encorafenib and binimetinib may be resumed sequentially at the Investigator's discretion, with encorafenib being resumed alone for one week before resuming binimetinib treatment. If additional occurrence: • Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib.
AST or ALT >8 × ULN AND blood bilirubin[g] ≤ 2.0 × ULN	Permanently discontinue encorafenib and binimetinib.
AST or ALT > 5.0 × ULN **AND** **blood bilirubin[g]** **> 2.0 × ULN**	Permanently discontinue encorafenib and binimetinib.

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	Dose Modification for Encorafenib and for Binimetinib
Grade 4 AST or ALT > 20.0 × ULN	Permanently discontinue encorafenib and binimetinib.
Cardiac Disorders - Left Ventricular Systolic Dysfunction[a] (Dose Adjustment for Binimetinib ONLY).	
Asymptomatic absolute decrease of > 10% in LVEF compared to baseline and the LVEF is below the institution's LLN (e.g., a decrease of 60% to 48% is an absolute decrease of 12%)	Interrupt dosing of binimetinib and repeat evaluation of LVEF within 2 weeks. • If the LVEF recovers (defined as LVEF ≥ 50% or ≥ lower limit of normal (LLN) and absolute decrease ≤ 10% compared to baseline) ≤ 21 days, resume treatment at 1 reduced dose level[b] of binimetinib after approval of the Sponsor's Medical Monitor. Monitor LVEF 2 weeks after resuming binimetinib, every 4 weeks for 12 weeks and subsequently as per protocol. • If LVEF does not recover in ≤ 21 days, permanently discontinue binimetinib. Closely monitor LVEF until resolution or for up to 16 weeks.
Grade 3 – 4	Permanently discontinue binimetinib. Closely monitor LVEF until resolution or up to 16 weeks. Note: Copies of ECHO and/or MUGA scans could be requested for subjects to be available to the Sponsor for subjects with absolute decrease of >10% in LVEF compared to baseline and LVEF < 50% or LLN.
CK Elevation	
Grade 1-2	Maintain dose of encorafenib and binimetinib. Ensure subject is adequately hydrated. Closely monitor CK and serum creatinine. • If total CK ≥ 3 × ULN, measure CK isoenzymes and myoglobin in blood or urine.
Grade 3 > 5.0 - 10.0 x ULN **without** renal impairment (i.e., serum creatinine < 1.5 × ULN or 1.5 × baseline)	If asymptomatic, maintain dosing of encorafenib and binimetinib. Ensure subject is adequately hydrated. Monitor and measure isoenzymes and myoglobin in blood or urine and serum creatinine. If symptomatic (muscle pain/spasms/muscle weakness), maintain dosing of encorafenib and interrupt dosing of binimetinib until resolved to CTCAE Grade ≤ 1 and monitor closely, then: • If resolved in ≤ 21 days, maintain dose of encorafenib and resume treatment at 1 reduced dose level[b] of binimetinib. • If not resolved in ≤ 21 days, maintain dose of encorafenib and permanently discontinue binimetinib.
Grade 4 **without** renal impairment (i.e., serum creatinine < 1.5 × ULN or 1.5 × baseline)	If asymptomatic, maintain dose of encorafenib and interrupt dosing of binimetinib. Ensure subject is adequately hydrated. Monitor and measure isoenzymes and myoglobin in blood or urine and serum creatinine. • If resolved in ≤ 21 days, maintain dose of encorafenib and resume treatment at 1 reduced dose level[b] of binimetinib. • If not resolved in ≤ 21 days, maintain dose of encorafenib and permanently discontinue binimetinib. If symptomatic (muscle pain/spasms/muscle weakness), maintain dose of encorafenib and permanently discontinue binimetinib.
Grade 3 or 4 **with** renal impairment (i.e., serum creatinine ≥ 1.5 × ULN or 1.5 × baseline)	Interrupt dosing of encorafenib and binimetinib until resolved to CTCAE Grade < 1 or baseline level. Ensure subject is adequately hydrated. Monitor closely and measure isoenzymes and myoglobin in blood or urine and serum creatinine, then: • If resolved in ≤ 21 days, consider resuming treatment at 1 reduced dose level[b] of encorafenib and binimetinib. • If not resolved in ≤ 21 days, permanently discontinue encorafenib and binimetinib. 2nd occurrence: • Permanently discontinue encorafenib and binimetinib.

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	Dose Modification for Encorafenib and for Binimetinib
Cardiac Investigation – Prolongation of QT interval QTcF value	
QTcF > 500 ms during treatment and change from pre-treatment value remains ≤ 60 ms	Subjects should have regular ECG monitoring (continuous where appropriate) until an adequately trained physician (such as a cardiologist or internist) has reviewed the data. Electrolyte abnormalities including magnesium should be corrected and cardiac risk factors for QT prolongation (e.g., congestive heart failure, bradyarrhythmias) should be controlled. 1st occurrence: • Temporarily interrupt dosing of encorafenib and binimetinib until QTcF < 500 ms. Then resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib. 2nd occurrence: • Temporarily interrupt dosing of encorafenib and binimetinib treatment until QTcF < 500 ms. Then resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib. If a subject restarts binimetinib and encorafenib following resolution of Grade 3 QTcF prolongation event, the subject should be evaluated with triplicate predose ECGs on Day 1 of the next cycle, followed by a single postdose ECG and a single predose ECG on Day 15, as well as single predose ECG and a single postdose ECG on Day 1 of the subsequent cycle (2nd cycle after the Grade 3 QT prolongation event). 3rd occurrence: • Permanently discontinue encorafenib and binimetinib.
QTcF increase during treatment is both > 500 ms and > 60 ms change from -pretreatment values	Subjects should have regular ECG monitoring (continuous where appropriate) until an adequately trained physician (such as a cardiologist or internist) has reviewed the data. Electrolyte abnormalities including magnesium should be corrected and cardiac risk factors for QT prolongation (e.g., congestive heart failure, bradyarrhythmias) should be controlled. • Permanently discontinue encorafenib and binimetinib.
Rash [see cetuximab dose modifications (Table 15) and (Section 17.1).	
Grade 1	Maintain dose level of encorafenib and binimetinib. Initiate Initial Rash Treatment Regimen (see **Section 17.1.** if it was not already started and rash should be closely monitored).
Grade 2	1st occurrence: • Maintain dose level of encorafenib and binimetinib • Initiate Initial Rash Treatment Regimen if it was not already started and rash should be closely monitored • Reassess within ≤ 14 days. If rash worsens or does not improve, interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level of encorafenib and binimetinib. For dermatitis acneiform, treatment with encorafenib may be maintained if, in the judgment of the Investigator, the rash is considered to be unrelated to encorafenib. If treatment with encorafenib was maintained and no improvement within 8 days, interrupt dosing of encorafenib. 2nd occurrence: • Reassess within ≤ 14 days. If rash worsens or does not improve, interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level of encorafenib and 1 reduced dose level[b] of binimetinib. For dermatitis acneiform rash, treatment with encorafenib may be maintained if, in the judgment of the Investigator, the rash is considered to be unrelated to encorafenib. If treatment with encorafenib was maintained and no improvement within 8 days, interrupt dosing of encorafenib.

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	Dose Modification for Encorafenib and for Binimetinib
Grade 3	1st occurrence: • Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Reassess weekly. Then resume treatment at current dose level of encorafenib and binimetinib. • Consider referral to dermatologist and manage rash per dermatologist's recommendation. 2nd occurrence: • Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib. Resume treatment with encorafenib at the same dose level if, in the judgment of the Investigator, the rash is considered to be unrelated to encorafenib. • Consider referral to dermatologist and manage rash per dermatologist's recommendation.
Grade 4	Permanently discontinue encorafenib and binimetinib[f]
Hand-foot Skin Reaction (HFSR)/Palmar-plantar Erythrodysesthesia Syndromee (Dose Adjustment for Encorafenib ONLY) (See Section 17.2 and Table 12)	
Grade 1	Maintain dose of encorafenib. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications.
Grade 2	1st occurrence: • Maintain dose of encorafenib and HFSR should be closely monitored. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. • If no improvement ≤ 14 days, interrupt dosing of encorafenib until resolved to Grade ≤ 1. Resume treatment with encorafenib at current dose level. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. Additional occurrence: • Treatment with encorafenib may be maintained or interrupted based upon the Investigator's discretion. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. • If interrupted dosing of encorafenib per Investigator's judgment, interrupt until resolved to Grade ≤ 1. Resume treatment with encorafenib at the same dose level or 1 reduced dose level[b] based upon the Investigator's discretion.
Grade 3	1st or additional occurrence: • Interrupt dosing of encorafenib until resolved to Grade ≤ 1. Promptly initiate supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. Reassess the subject weekly. Then resume treatment at one reduced dose level[b] of encorafenib • Consider referral to dermatologist and manage HFSR per dermatologist's recommendation. > 3nd occurrence: • Interrupt dosing of encorafenib until resolved to Grade ≤ 1, decision to resume treatment with encorafenib at one reduced dose level[b] or permanently discontinue encorafenib should be based upon the Investigator's discretion.
SCC, KA and any Other Suspicious Skin Lesion (Dose Adjustment for Encorafenib ONLY)	
Grade ≤ 3	Maintain dose of encorafenib (dose interruptions or modifications are not required). Treatment of SCC, KA, and any other suspicious skin lesion (eg, new primary melanoma) should occur based upon institutional practice.

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	Dose Modification for Encorafenib and for Binimetinib
Diarrhea (See Section 17.3).	
Uncomplicated Grade 1-2	Maintain dose of encorafenib. Consider temporary interruption of binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level of binimetinib.
Complicated Grade 1-2	Consider temporary interruption of encorafenib until resolved to Grade ≤ 1. Then resume treatment at current dose level of encorafenib Interrupt dosing of binimetinib until resolved to Grade ≤ 1. Then resume treatment at 1 reduced dose level[b] of binimetinib.
Grade 3-4	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level of encorafenib if, in the judgment of the Investigator, the toxicity is considered to be unrelated to encorafenib, or at one reduced dose level[b]. Resume treatment at 1 reduced dose level[b] of binimetinib.
Nausea/Vomiting	
Grade 1-2	Maintain dose level of encorafenib and binimetinib. Promptly institute antiemetic measure.
Grade 3	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at 1 reduced dose level[b] of encorafenib. Resume treatment with binimetinib at the current dose if, in the judgment of the Investigator, the toxicity is considered to be unrelated to binimetinib, or at 1 reduced dose level[b]. Note: Interrupt dosing of encorafenib and binimetinib for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).
Grade 4	Permanently discontinue encorafenib and binimetinib[f].
Interstitial lung disease/pneumonitis - Section 17.7	
Grade 1	Maintain dose level of encorafenib and binimetinib. Monitor weekly.
Grade 2	Maintain dose of encorafenib. Withhold binimetinib for up to 3 weeks. If improved to Grade 0 or 1, resume treatment at 1 reduced dose level of binimetinib. If not resolved within 3 weeks, permanently discontinue binimetinib.
Grade 3-4	Permanently discontinue binimetinib.
All Other Adverse Events (Suspected To Be Related To Encorafenib and/or Binimetinib)	
Grade 1-2	If the event is a persistent Grade 2 AE not responsive to a specific therapy, consider interruption or reduction of encorafenib and binimetinib, as applicable
Grade 3	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤1 or to pretreatment/baseline level. If the event resolves ≤ 21 days, then study drug may be resumed at 1 reduced dose level[b] based upon the Investigator's discretion.
Grade 4	Permanently discontinue encorafenib and binimetinib[f]

a : Not according to NCI-CTCAE
b : Dose reduction below 150 mg QD for encorafenib, and below 15 mg BID for binimetinib is not allowed.
c : Ophthalmic monitoring mandated for retinal events, posterior uveitis, RVO: further evaluation with specialized retinal imaging (e.g. ocular coherence tomography, fluorescein angiography). Any diagnosis of retinal events must be supported by presence or absence of symptoms, visual acuity assessment and findings in OCT.
d : For subjects enrolled with liver metastases and baseline LFT elevations.
e : Disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.
f : A subject with a Grade 4 AE may resume treatment at the lower dose level if the AE recovers to Grade ≤ 1 within 28 days of discontinuing drug and, if in the opinion of the Investigator and Sponsor Medical Monitor, the event is not life-threatening and the subject can be managed and monitored for recurrence of AE. Any subjects requiring a treatment interruption of duration > 28 days must discontinue study drug permanently.
g : Refers to total bilirubin.

6.5.4.2. Dose Modifications for Cetuximab

Recommended dose modifications for cetuximab based on the occurrence of cetuximab treatment-related AEs are summarized in **Table 15**. **Section 17.1** contains recommended guidelines for prophylactic and symptomatic treatment of cetuximab-induced rash.

Table 15: Recommended dose modifications for Cetuximab during a cycle of therapy

Worst toxicity CTCAE, v.4.03 Grade	**Dose Modification for Cetuximab During a Cycle of Therapy**
Infusion Reaction	If an infusion reaction occurs while cetuximab is being infused, the infusion should be stopped immediately and the subject should be evaluated.
Grade 1 or 2	Restart and complete the disrupted infusion at the discretion of the Investigator. The infusion must be restarted at a reduced rate. Additional pre-medications such as antihistamines or low-dose systemic corticosteroids may be administered when the infusion is restarted per institutional standards. All subsequent infusions must also be administered at the reduced rate.
Grade 3 or 4	Permanently discontinue cetuximab
Rash: see encorafenib and/or binimetinib dose modifications (**Table 14**)]	
Grade 1 or 2	Maintain dose level; consider initiating appropriate therapy (such as antihistamines, topical corticosteroids, and low-dose systemic corticosteroids)
Grade 3, despite therapy	Omit dose until resolved to ≤ Grade 2, then: • If resolved in ≤ 7 days (or ≤ 14 days for acneiform rash), then maintain dose level • If not resolved in ≤ 7 days despite appropriate skin toxicity therapy (or ≤ 14 days for acneiform rash), then permanently discontinue cetuximab
Grade 3 recurrent	Omit dose until resolved to ≤ Grade 2, then: • If resolved in ≤ 7 days (or ≤ 14 days for acneiform rash), then decrease 1 dose level • If not resolved in ≤ 7 days despite appropriate skin toxicity therapy (or ≤ 14 days for acneiform rash), then permanently discontinue cetuximab • Permanently discontinue cetuximab after 3rd recurrence (i.e., upon 4th occurrence)
Grade 4, despite skin toxicity therapy	Permanently discontinue cetuximab
Interstitial lung disease - **Section 17.7**: in case of ILD, for all grades, cetuximab must be discontinued	

6.6. REPLACEMENT PROCEDURE

Not Applicable

6.7. BLIND BREAKING PROCESS

Not Applicable

6.8. ACCOUNTABILITY ON SITE AND RETURN/DESTRUCTION OF INVESTIGATIONAL PRODUCT(S) AND ASSOCIATED PRODUCT(S)

The Investigator should maintain accurate written records of treatment received, dispensed, returned and any remaining treatment units, on the treatment accountability form. These records should be made available for CRA monitoring. The packaging of the medication should remain intact until just before the dispensation.

At each visit, the Investigator will record the number of capsules and tablets returned by each subject.

At the end of the study, all used and unused treatments including packaging should be noted, and will be destroyed at the center (or local warehouse if not possible at the center). A copy of the treatment accountability form should be provided by the Investigator to the CRA and a destruction certificate should be received by Sponsor.

6.9. RECALL OF INVESTIGATIONAL PRODUCT(S) AND RESCUE MEDICATION

In cases of recall of investigational products (decided by the Competent Authorities or the Sponsor), the Investigator will be immediately informed by the Sponsor.

The Investigator, in collaboration with the Sponsor representatives (Study Manager, CRA) must urgently:

- stop the delivery of the concerned investigational products to the subjects,

- inform the concerned subjects that they must immediately stop taking these investigational products and return them to the center.

The Study Manager/CRA will organize the return of the recalled products to the sponsor or designee, or will insure the destruction of the recall products at site under the investigator's responsibility (destruction certificate to be obtained).

7. CONCOMITANT THERAPY AND THERAPEUTIC / DIAGNOSTIC PROCEDURES

Any existing concomitant therapies (at screening), any new concomitant therapies or change in the dosage of an existing concomitant therapy during the course of the study must be recorded on the e-CRF (as describe in the e-CRF completion guideline). All non-essential therapies must be stopped at screening.

All medications, whether prescription or nonprescription, and non-drug therapies (e.g., blood transfusions) taken within 4 weeks prior to the first administration of study treatment, and all concomitant therapy administered during the study must be recorded on the Prior/Concomitant Therapies e-CRF page up to 30 days after the last study treatment administration.

All medications (other than study treatment) and significant non-drug therapies (including physical therapy, and blood transfusions) administered during the study must be listed on the concomitant therapies e-CRF page.

For all concomitant therapies taken during the study, the following information must be noted in the relevant section(s) of the e-CRF:

- The name of the treatment / therapy
- The reason for prescription
- The route of administration
- The dose
- The frequency
- The duration (start date and end date)

Any therapeutic and diagnostic procedures such as endoscopic examinations, diagnostics tests, ablation, surgical procedures etc. not planned by the study protocol must also be noted in the e-CRF. These procedures may be associated with events, in which case the condition that leads to the procedure must be reported in the appropriate section of the e-CRF (AEs, medical history).

For all such procedures that occur during the study, the following information must be noted in the relevant section(s) of the e-CRF:

- The name of the procedure
- The indication
- The duration (start date and end date)

7.1. PROHIBITED THERAPY AND THERAPEUTIC/DIAGNOSTIC PROCEDURES

None of the concomitant therapies and therapeutic/diagnostic procedures listed below are allowed during the study period (except those listed **in Section 7.2**):

- Anticancer agents such as cytotoxic chemotherapy small-molecule targeted agents, biological agents, immune response modifiers or hormonal therapy,
- Local therapies which could interfere with treatment (e.g. surgical excision or ablation of lesions are not permitted without Sponsor approval while subjects are receiving study treatment),
- Investigational drugs (other than study drugs) and devices,
- Radiation therapy (not including palliative radiotherapy at focal sites that covers ≤ 10% of the bone marrow reserve),
- Herbal preparations/medications. Subjects should stop using herbal medications 7 days prior to first dose of study treatment,
- Concomitant moderate or strong systemic CYP3A4 inhibitors or inducers which are likely to significantly increase or decrease respectively encorafenib exposure and thus should not be used during this study (see **Section 17.5**).

If another therapy and/or therapeutic / diagnostic procedure has to be prescribed in the interests of the subject's health, the decision to discontinue the subject from the study should be taken by the Investigator.

7.2. AUTHORIZED THERAPY, THERAPEUTIC AND DIAGNOSTIC PROCEDURES

In general, the use of any concomitant medication/therapies deemed necessary for the care of the subject is permitted, unless otherwise specified. Additional information regarding concomitant medications/therapies is provided in the Investigator's Brochures for encorafenib and binimetinib and the cetuximab locally approved labelling.

Subjects receiving any of the medications listed in **Section 17.5** must be used with caution carefully monitored for potentiation of toxicity due to any individual concomitant medication and may require dose titration of the drug substance. Investigators should use caution when prescribing concomitant medications, as clinical experience with these compounds in subjects with cancer is often limited. Investigators should contact the Sponsor or designee when they are unsure whether a drug should be prescribed to a subject in the clinical study. All concomitant medications/therapies, transfusions, procedures and dietary supplements must be documented in the e-CRF.

7.2.1. Skin Toxicity Treatments

Subjects should be treated for cetuximab-induced, encorafenib-induced and/or binimetinib-induced skin toxicity following the supportive care recommended guidelines for the management of these toxicities and prophylaxis measures referred to in **Section 17.1**.

7.2.2. Hand-Foot Skin Reaction Treatment

HFSR has been reported for encorafenib, so it is recommended that subjects are informed prior to starting study treatment to avoid activities that can cause friction to the hands and/or feet. In addition, supportive measures for prevention and/or management of HFSR should be instituted. Clinical judgment and experience of the treating physician should guide the management plan of each subject. Subjects receiving encorafenib should be treated for encorafenib-induced HFSR

following the supportive care recommended guidelines for the management of these toxicities (**Section 17.3**).

7.2.3. Anti-Diarrheal

Subjects should be treated for diarrhea as per institutional guidelines, and/or as indicated in the locally approved prescribing information, or for subjects receiving binimetinib, per the supportive care recommended guidelines for the management of binimetinib-induced diarrhea (**Section 17.3**).

7.2.4. Antiemetics

Prophylactic antiemetics should only be administered if the subject experiences nausea or vomiting and at the discretion of the Investigator. It is recommended that subjects use drugs that do not cause QT prolongation. Note that some antiemetics have a known risk for Torsade de Pointes (TdP) (**Section 17.5**).

7.2.5. Permitted Concomitant Therapy requiring Caution and/or Action

7.2.5.1. CYP and UGT Substrates and Inhibitors

Encorafenib is a reversible inhibitor of CYP2B6, CYP2C9, CYP3A4 and UGT1A1. It is also a time-dependent inhibitor of CYP3A4. Likewise, binimetinib is also a reversible inhibitor of CYP2B6. Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, and UGT1A1 or those substrates that have a narrow therapeutic index (**Section 17.5**).

There is a potential for encorafenib to induce CYP3A4, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least one form of non-hormonal contraception is required during participation in this study (See **Section 5.3** for use of contraception methods required for this study). Caution should be used in subjects receiving concomitant treatment with other drugs that are substrates of CYP3A4 as the efficacy of these drugs could be reduced when administered with encorafenib.

Encorafenib has been identified in vitro to be metabolized by CYP3A4 and to a lesser extent by CYP2C19. The use of strong inhibitors of CYP3A4 is prohibited. Concomitant use of moderate

CYP3A4 inhibitors while on study should be avoided. If use of moderate CYP3A4 inhibitors is unavoidable and no alternatives are available, short-term use (≤ 30 days) following discussion with the Sponsor may be permitted with accompanying dose reduction to one-half of the encorafenib dose prior to use of moderate CYP3A4 inhibitors (or as close as can be achieved without exceeding the target dose). The encorafenib dose that was taken prior to initiating the CYP3A4 inhibitor may be resumed after the inhibitor has been discontinued for 3 to 5 elimination half lives. Strong inhibitors of CYP2C19 should be used with caution when co-administered with encorafenib.

Binimetinib has been identified to be primarily metabolized by glucuronidation. It is advised that strong inhibitors of UGT1A1 should be used with caution when co-administered with binimetinib (**Section 17.5**).

Subjects should be closely monitored for the occurrence of AEs.

7.2.5.2. Transporter Substrate and Inhibitors

In vitro data showed that both encorafenib and binimetinib are substrates of the transporter P-glycoprotein (P-gp). Binimetinib is also a substrate of BCRP. Encorafenib is a BCRP inhibitor. Thus, the use of drugs that are known to inhibit or induce P-gp or BCRP should be used with caution. Encorafenib is also a potent inhibitor of the renal transporters, organic anionic transporter OAT1, OAT3 and organic cationic transporter (OCT) 2, and the hepatic transporter organic anion-transporting peptide (OATP1)B1 and OATP1B3. The co-administration of drugs that are known to be sensitive or narrow therapeutic index substrates of BCRP, P-gp, OAT1, OAT3, OCT 2, OATP1B1 and OATP1B3 should be used with caution (**Section 17.5**).

7.2.5.3. Drugs with a Conditional or Possible Risk to Prolong the QT Interval and/or Induce Torsade de Pointes

Investigators should use caution when administering encorafenib or binimetinib with concomitant medications with a known, conditional or possible risk to prolong the QT interval and/or induce TdP (**Section 17.5**). Subjects receiving such medications must be carefully monitored for potentiation of toxicity due to any individual concomitant medication, and may require dose titration of the concomitant medication.

8. ASSESSMENTS

8.1. EFFICACY ASSESSMENTS

Tumor response will be evaluated locally by the Investigator according to RECIST, v1.1 (**Section 17.6**).

All potential sites of tumor lesions will be assessed at screening, the following should be performed:

- A CT scan with IV contrast of chest, abdomen and pelvis is the preferred technique. If there is concern about radiation exposure, an MRI may be used instead of a CT.
- In subjects with a history of asymptomatic brain metastases, a brain MRI or CT scan
- If clinically indicated, a whole-body bone scan (i.e., if bone metastases are suspected or known at baseline). A whole-body bone imaging method may be used per local standard of care (e.g., Tc99m bone scan, fluorodeoxyglucose-positron emission tomography [FDG-PET], sodium fluoride-positron emission tomography [NaF PET] scan or whole-body bone MRI).

Skeletal lesions identified on a whole-body bone scan at baseline, which are not visible on the chest, abdomen, or pelvis CT (or MRI) scan should be imaged at baseline using localized CT, MRI, or X-ray.

As far as possible, the same method of assessment of each lesion should be used at screening and for all visits, for consistent comparison.

During the Main study period, all post-screening assessments should be performed every 6 weeks (±7 days) from the first dose for the first 12 weeks of treatment; except for first tumor evaluation for which the time-window allowed is day 42 +7 days from first dose. Then, every 8 weeks thereafter until disease progression, subject decision, withdrawal of consent, initiation of subsequent anticancer therapy, subject is lost to follow-up, death or defined end of study as described in **Section 5.7**.

During the Study extension period, all assessments should be performed every 12 weeks (±7 days), until disease progression, subject decision, withdrawal of consent, initiation of subsequent

anticancer therapy, subject is lost to follow-up, death or defined end of study as described in **Section 5.7.**

If a subject discontinues study treatment for reasons other than disease progression, tumor assessments must continue to be performed (as per local and central review) every 6 weeks (first 12 weeks) then every 8 weeks during the Main study period and every 12 weeks during the Study extension period (as per local review), until the start of new anti-cancer therapy, disease progression, death, lost to follow-up, subject decision or withdrawal consent.

Regardless of whether study treatment is discontinued, the following should be performed:

- Chest, abdomen, and pelvis CT (or MRI) scans
- Brain MRI or CT scan, if metastases were documented at baseline
- Skeletal lesions identified at baseline should continue to be imaged at subsequent scheduled visits using localized CT, MRI, or X-ray (using the same method used at baseline for all visits for any given lesion). After baseline, whole body bone scans need not be repeated, unless clinically indicated.
- Additional imaging evaluations may be performed if there is symptomatic evidence suggesting the possibility of disease progression based on clinical symptoms or physical examination at any time.

If off-schedule imaging evaluations are performed or if progression is suspected, every effort should be made to perform subsequent imaging evaluations in accordance with the original imaging schedule.

All CT scans should be performed with IV contrast. If a subject is known to have a medical contraindication to the contrast agent or develops a contraindication during the study, a CT scan without IV contrast of the chest and MRI with IV contrast, if possible, of the abdomen and pelvis may be performed. A CT scan of the brain, preferably with IV contrast, may be performed if MRI is contra-indicated.

Chest X-ray or ultrasound should not be used for tumor response assessments in this study.

Any lesions that have been subjected to loco-regional therapies (e.g., radiotherapy, ablation, etc.) should not be considered measurable, unless they have clearly progressed since that therapy. Previously treated lesions that have not progressed should be considered non-measurable and therefore, assessed as non-target lesions.

While FDG-PET scans are not required for this study, sites may perform combined PET/CT scans per their local standard of care, provided the CT is of similar diagnostic quality as a CT scan performed without PET, including the use of oral and IV contrast media. If acquired according to local standard of care, FDG-PET may be relied upon to document progressive disease (PD) in accordance with RECIST.

When possible, each center should have a designated radiologist responsible for the interpretation of scans and response evaluations for study subjects. At a minimum, a single radiologist should perform all evaluations for an individual subject.

Transmission for central review

All imaging data acquired for efficacy purposes during the Main study period will be transmitted to an imaging vendor for central review. Image transmission to the imaging vendor should be accomplished according to the imaging vendor manual. Full details of the central reading process are included in the Independent Review Charter.

8.2. PHARMACOKINETICS ASSESSMENT

8.2.1. Blood Samples Collection

8.2.1.1. Collection Schedule

Blood samples (4 mL/time point) for determination of encorafenib, binimetinib and the active metabolite of binimetinib (AR00426032) plasma levels will be collected, during Cycle 1 and Cycle 2, at the following times.

Cycle 1:

- Day 1: T2h (±10 min) and T6h (±30 min) post encorafenib/ binimetinib dose.

Dosing and sampling information will consist of the date and time of the first encorafenib and binimetinib dose, the encorafenib and binimetinib dose amount administered, and exact date and time of the PK samples;

Cycle 2:

- Day 1: predose (T0) (just prior to the dose of encorafenib/ binimetinib), T2h (±10min) post encorafenib/ binimetinib dose.

Dosing and sampling information will consist of:

- For predose sample:
  - date and time of the last two previous binimetinib doses (morning/evening) and the current day's binimetinib dose, including the dose amounts taken and exact date and time of the PK samples.
  - date and time of the last previous encorafenib dose and the current day's encorafenib dose, including the dose amounts taken and exact date and time of the PK samples

- For T2h sample:
  - date and time of the current day's first encorafenib and binimetinib dose, including the dose amounts administered, and exact date and time of the PK samples.

Blood samples (4 mL per time point) for determination of cetuximab serum levels will be collected, during Cycle 1 and Cycle 2, only at the following times:

Cycle 1:

- Day 1: T2h (± 10 min) and T6h (± 30 min) after the beginning of cetuximab infusion.
- Post dose infusion information should include date, dose, start time, and infusion duration. Any eventual infusion interruptions should also be documented.

Cycle 2:

- Day 1: predose (T0) (just prior the infusion), T2h (± 10 min) after the start of cetuximab infusion.

Dosing and sampling information will consist of:

- Predose sample: collection should occur before the beginning of cetuximab infusion. Information should include date, dose, start time, and infusion duration of the last previous dose of cetuximab and exact date and time of the PK sample.
- For T2h: include the current day's date, dose, start time, and infusion duration of the infusion and exact date and time of the PK sample. Any eventual infusion interruptions should also be documented.

Blood sample collection times are presented in (**Table 16**) and **(Table 17**):

Table 16: Pharmacokinetic sampling times for Encorafenib, Binimetinib and AR0042603

	Cycle 1 Day 1		Cycle 2 Day 1	
Time after encorafenib/ binimetinib dosing on designated dosing days (h)	2	6	0 (Pre-dose)	2
PK sample for encorafenib, binimetinib and AR00426032 (4 mL per time point)	x	x	x	x

Abbreviations: h = hours; PK = pharmacokinetic
PK samples will be collected on Cycle 1 Day 1 postdose (encorafenib/binimetinib) 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 postdose at 2 h (± 10 min). Blood samples for encorafenib/binimetinib PK will be processed to collect plasma.

Table 17: Pharmacokinetic sampling times for Cetuximab

	Cycle 1 Day 1		Cycle 2 Day 1	
Time after the start of cetuximab infusion on designated dosing days (h)	2	6	0 (Pre-infusion)	2
PK sample for cetuximab (4 mL per time point)	x	X	x	X

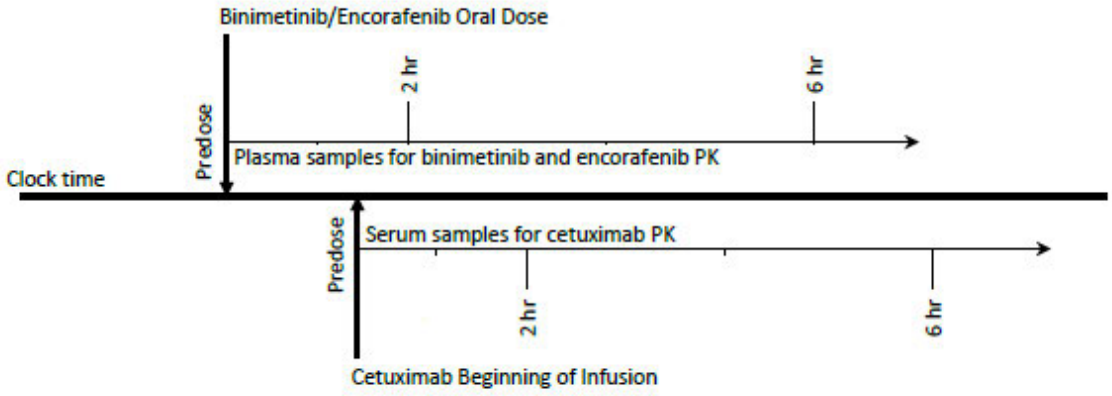
Abbreviations: h = hours; PK = pharmacokinetic
PK samples will be collected on Cycle 1 Day 1 post-infusion (cetuximab) at 2 h (± 10 min) and 6 h (± 30 min). PK samples will be collected on Cycle 2 Day 1 pre-infusion (just prior to infusion of cetuximab) and post-infusion at 2 h (± 10 min). Blood samples for cetuximab PK will be processed to obtain serum. Time points are based on the start of infusion.

The total number of blood samples for analytical determination will be 8 *per* subject, making the total volume of collected blood for pharmacokinetics approximately 32 mL *per* subject.

If a subject receiving any of the treatments defined in this protocol experiences an AE that results in an unscheduled visit or meets the criteria for an SAE, a blood sample for measurement of concentrations of drug-related analytes should be collected, if feasible, if less than 24 hours have elapsed since the last dose of study drug.

Study visits for PK sampling should be scheduled in the morning so that correct predose and postdose PK blood samples can be collected. On the PK visit days, the morning doses of encorafenib and binimetinib, if applicable, **should be taken at the study site, only after collecting the predose PK sample** (for cycle 2). A graphic representation of blood PK sampling for plasma and serum is provided in **Figure 1**.

Figure 1: Graphic representation for pharmacokinetic sampling plan*



**Predose PK samples for cetuximab analysis should be collected just prior the beginning of the cetuximab infusion, regardless of the pre-medication that may be used prior to cetuximab infusion.*

If a vomiting episode occurs within the first 4 hours post-dosing of binimetinib and encorafenib during the day of the last dose prior to collection of PK samples, the exact time (whenever possible) must be noted in the e-CRF. In addition, on Day 1 of cycles 1 and 2 when postdose PK samples are collected, if vomiting occurs, the exact time of the first vomiting episode within the first 4 hours post-dosing on that day must be noted.

8.2.1.2. Technical Handling

Complete instructions for sample processing, handling and shipment will be provided in a separate Laboratory Manual.

Each blood sample will be drawn by direct venipuncture or via an indwelling catheter. Each sample will be 4 mL (according to the Collection Schedule **Table 16**, **Table 17**).

Important points for blood collection:

- Blood sampling from a central venous line is not allowed if this line was used to infuse cetuximab,
- If an indwelling catheter is used for blood collection, approximately 1 mL will be drawn and discarded before sampling,
- Blood samples must be collected from the body side contralateral to the site of the cetuximab infusion,

- Care must be taken to collect blood slowly without causing hemolysis

8.2.2. Samples Handling and shipping

Complete instructions for sample labelling, handling, storage and shipping to the central laboratory will be provided in a separate Laboratory Manual. The samples will be stored in the central laboratory until transfer to the bioanalytical center for analytical determination.

8.2.3. Analytical determination

Analytical determination of encorafenib, binimetinib and the active metabolite of binimetinib (AR00426032) in plasma will be carried out at a designated CRO laboratory using validated LC/MS-MS methods.

Analytical determination of cetuximab in serum will be carried out at a designated CRO laboratory using a validated method.

8.2.4. Sample Storage

Biological samples dedicated to analytical determination will not be discarded before the final clinical study report (CSR) is released and without prior notification to the study manager and authorization of the head of the PK/PD Department of IRPF.

8.3. SAFETY ASSESSMENT

8.3.1. Adverse Events

At screening, any concomitant diseases will be reported as medical history in the e-CRF. At each subsequent visit, the occurrence of AEs since the last visit will be determined by the subject's spontaneous reporting, the Investigator's non-leading questioning and his/her clinical evaluation. The severity of AEs will be evaluated using the NCI-CTCAE, v.4.03.

All AEs that occur after signature of informed consent through 30 days after the last dose of study drug must be recorded on the AE e-CRF, irrespective of their etiology and relationship to study treatment. Assessment and reporting of AEs is described in detail in **Section10** and will be

completed at the time points specified in the study flow chart (Main study period and Study extension period flow charts).

8.3.2. Clinical Safety Laboratory Assessments

The local clinical center's laboratory will analyze and report all laboratory safety tests performed at the center to the Investigator who will ensure they are entered in the e-CRF. Clinical laboratory tests will be performed according to the laboratory procedures and the latest updated references. Ranges from the laboratory will be used to identify abnormal values.

Assessments including clinical chemistry, hematology, urinalysis, coagulation, and pregnancy tests do not have to be repeated if performed within 72 hours prior to the first dose on Cycle 1 Day 1.

Additional clinical laboratory tests may be obtained at any time during the study at the Investigator's discretion.

8.3.2.1. Schedule

The laboratory investigations will be carried out as described in **Table 18** for Main study period.

For the Study extension period, the laboratory investigations will be carried out as described in **Table 19**

Table 18: Laboratory schedule_ Main study period

Visit	Screening	C1 D1		C1 D8	C1 D15	C1 D22	Cn D1	Cn D8	Cn D15	Cn D22	End of treatment	Safety Follow-Up[g] (EOS)
Cycle Days	D-28 to D-1	D1		D8	D15	D22	D1	D8[h]	D15	D22[h]	Dxx	Dxx
Epochs	SCREENING	TREATMENT										FOLLOW-UP
		Pre-Dose	Post-Dose									
Pregnancy test[a]	X	X[f]					X				X	X
LH, FSH and/or estradiol[a]	X											
Hepatitis B surface antigen, Hepatitis C antibody	X											
HIV (when required)	X											
Hematology[b]	X	X[f]			X	X	X				X	X
Clinical chemistry[c]	X	X[f]			X		X				X	X
Coagulation[d]	X	X[f]					X				X	X
Urinalysis[e]	X	X[f]					X				X	X
Blood Sample for CRP	X											

a local urine pregnancy test for women of childbearing potential except serum pregnancy test at screening and EOT. For menopausal women only: serum LH,FSH and or estradiol measurement if applicable

b Hematology - list of analytes: basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, neutrophils/absolute neutrophil count (ANC), platelets, red blood cells (RBC), white blood cells (WBC)

c Clinical Chemistry – list of analytes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin [total and direct (*and indirect – only applicable for France)]* ,albumin, alkaline phosphatase, bicarbonate (HCO3)- not mandatory in Japan, blood urea nitrogen (BUN)/urea, calcium, chloride, creatine kinase (CK), creatinine, glucose, lactate dehydrogenase (LDH), magnesium, potassium, sodium, total protein, troponin I or T, uric acid, amylase, lipase.

NOTE: Direct bilirubin *(and indirect – only applicable for France)* will be measured at screening only if total bilirubin values are abnormal; for purposes of determining eligibility to participate in the study.Calculated creatinine clearance (Cockroft-Gault formula) will be measured at screening

d Coagulation – list of analytes: prothrombin time (PT) or International Normalized Ratio (INR);activated partial thromboplastin time (aPTT)

e Urinalysis – list of analytes: blood, glucose, ketones, leukocytes, hydrogen ion concentration (pH), protein

f Procedure does not have to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (i.e., first day of dosing).

g To be performed 30-day after end of treatment (EOT) , when clinically appropriate, it is recommended subjects be monitored with physical examinations, dermatological examinations and chest CT scans for cutaneous and non-cutaneous secondary malignancies for up to 6 months after the last encorafenib dose or until initiation of another antineoplastic therapy.

h From Week 29 (cycle 8), D8 and D22 visits will not be performed (biweekly infusions of cetuximab: no infusions on D8 and D22)

Table 19: Laboratory schedule_Study extension period

Visit	*Cn D1*	*Cn D15*	*End of treatment*	*Safety Follow-U*[e] (EOS)
Cycle Days	D1	D15	Dxx	Dxx
Epochs	TREATMENT			FOLLOW-UP
Pregnancy test[a]	X		X	X
Hematology[b]	X		X	X
Clinical chemistry[c]	X		X	X
Urinalysis[d]	X		X	X

a local urine pregnancy test for women of childbearing potential except serum pregnancy test at EOT.

b Hematology - list of analytes: basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, neutrophils/absolute neutrophil count (ANC), platelets, red blood cells (RBC), white blood cells (WBC)

c Clinical Chemistry – list of analytes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total and direct), albumin, alkaline phosphatase,, calcium, chloride, creatinine, glucose, magnesium, potassium, sodium, total protein, Calculated creatinine clearance (Cockroft-Gault formula)

d Urinalysis – list of analytes: blood, glucose, ketones, leukocytes, hydrogen ion concentration (pH), protein

e To be performed 30-day after end of treatment (EOT) , when clinically appropriate., it is recommended that subjects be monitored for physical examinations, dermatological examinations and chest CT scans for cutaneous and non cutaneous secondary malignancies for up to 6 months after the last encorafenib dose or until initiation of another antineoplastic therapy.

8.3.2.2. Parameters

Table 20: Summary of Clinical Laboratory Tests_Main study period

Hematology	**Chemistry**	**Urinalysis**	**Coagulation**
Basophils Eosinophils Hematocrit Hemoglobin Lymphocytes Monocytes Neutrophils/ANC Platelets RBC WBC	ALT AST Bilirubin [total and direct (and indirect – only applicable for France)][a] Albumin Alkaline phosphatase Bicarbonate (HCO_3) BUN/urea Calcium Chloride CK[b] Creatinine Glucose LDH Magnesium Potassium Sodium Total protein Troponin I or T Uric acid Lipase Amylase Serum CK isoenzymes [b] Myoglobin[b]	Blood Glucose Ketones Leukocytes pH Protein Myoglobin[b]	PT or INR aPTT Other At Screening only: • Hepatitis B surface antigen • Hepatitis C antibody • CRP • Calculated creatinine clearance (Cockroft-Gault formula) • LH, FSH and/or estradiol (if applicable) • HIV (if required) • At Screening and EOT • Serum pregnancy test (if applicable)

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; CRP = C-reactive protein; FSH = follicle-stimulating hormone; INR = International Normalized Ratio; LDH = lactate dehydrogenase; LH = luteinizing hormone; pH = hydrogen ion concentration; PT = prothrombin time; aPPT = activated partial thromboplastin time; RBC = red blood cell(s); WBC = white blood cell(s); HIV = Human Immuno deficiency Virus.

[a] Direct bilirubin (*and indirect – only applicable for France)* will be measured at screening only if total bilirubin values are abnormal; for the purposes of determining eligibility to participate in the study.

[b] For Grade 2 total CK that is also $\geq 3 \times$ ULN or asymptomatic Grade 3 total CK: measure CK, CK isoenzymes and myoglobin in blood or urine weekly for 3 weeks. If total CK remains above the grade that led to the increased monitoring, continue to assess CK, CK isoenzymes and myoglobin, along with regularly scheduled clinical chemistry assessments, until normalization or improvement to Grade 1. When CK is elevated, ensure the subject is adequately hydrated.

Table 21: Summary of Clinical Laboratory Tests_Study extension period

Hematology	Chemistry	Urinalysis	Other
Basophils Eosinophils Hematocrit Hemoglobin Lymphocytes Monocytes Neutrophils/ANC Platelets RBC WBC	**ALT** **AST** **Bilirubin [total and direct (*and indirect – only applicable for France*)]** **Albumin** **Alkaline phosphatase** **Calcium** **Chloride** **Creatinine** **Glucose** **Magnesium** **Potassium** **Sodium** **Total protein**	**Blood** **Glucose** **Ketones** **Leukocytes** **pH** **Protein**	**At EOT** **Serum pregnancy test (if applicable)**

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = pH = hydrogen ion concentration; RBC = red blood cell(s); WBC = white blood cell(s)

Hematology, Coagulation and Clinical Chemistry:

Blood samples for the hematology, coagulation and chemistry laboratory tests listed in Table Summary of Clinical Laboratory Tests (**Table 20**) will be collected at the time points specified in Table Laboratory Schedule (**Table 18**) for Main study period.

For the Study extension period, blood samples for the hematology and chemistry laboratory tests listed in Table Summary of Clinical Laboratory Tests (**Table 21**) will be collected at the time points specified in Table Laboratory Schedule (**Table 19**).

Blood sample collections occurring on dosing days must be performed prior to study drug administration. Laboratory test results required to make decisions regarding potential dose modifications (as specified in **Section 6.5.4**) should be reviewed prior to study treatment administration.
Additional tests may be done at the Investigator's discretion, in the subjects' best interest.

Urinalysis

Urine samples for the laboratory tests listed in Summary of Clinical Laboratory Tests (**Table 20**) for Main study period will be collected at the time points specified in Table Laboratory Schedule **(Table 18**).

Urine samples for the laboratory tests for the Study extension period listed in Summary of Clinical Laboratory Tests (**Table 21**) will be collected at the time points specified in Table Laboratory Schedule (**Table 19**).

All urine collections occurring on dosing days must be performed prior to study treatment administration.

Pregnancy and Assessment of Fertility

For Main study and Study extension periods, all females of childbearing potential are required to undergo a local serum pregnancy assessment at Screening and end of treatment (EOT) and local urine pregnancy assessments at time points specified in Table Laboratory Schedule **(Table 18 and Table 19**)
Any positive pregnancy tests will result in immediate cessation of study treatment administration.Female subjects of non-childbearing potential (as defined in **Section 5.3**) do not require pregnancy tests.

8.3.3. Physical Examination

A physical examination will be carried out for each body system at the screening visit and on Day 1 of every cycle (for Main study and Study extension periods).

At Screening, the physical examination should include general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast and pelvic examinations will be performed; body weight will be measured as part of the physical examination. Height will only be measured at Screening.

For subsequent visits, the physical examinations should be targeted as clinically indicated.

The physical examination will be globally evaluated prior to study drug administration as "normal/abnormal". Further target inspection will be undertaken for any abnormal finding and will be recorded as AEs.

8.3.4. Vital Signs

8.3.4.1. Schedule

Vital signs include Heart Rate (HR), systolic and diastolic blood pressure (SBP, DBP), respiration rate, and temperature. They will be assessed at the time points indicated in the study flow chart (please refer to the flow-chart corresponding to the current period: Main study or Study extension).

8.3.4.2. Technical Procedure and Parameters

SBP and DBP, expressed in mmHg,and HR expressed in beat per minute (bpm) will be measured per institutional standards.

Limits for abnormal values for SBP and DBP should be graded according to NCI-CTCAE, v.4.03 as described in tables below (Table 22 and Table 23).

Table 22: Modified NCI CTCAE, Version 4.03 Grading for Hypertension

Grade	Description
Grade 1	Prehypertension (systolic BP 120-139 mm Hg or diastolic BP 80-89 mm Hg)
Grade 2	Stage 1 hypertension (systolicBP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (>=24hrs); symptomatic increase by>20 mm Hg (diastolic) or to>140/90 mm Hg if previously WNL; monotherapy indicated
Grade 3	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); Medical intervention indicated; more than one drug or more intensive therapy than previously used indicated
Grade 4	Life-threatening consequences (e.g., malignant hypertension, Transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated

Definition: A disorder characterized by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure exceeding 140 over 90 mm Hg.

Table 23: Modified NCI CTCAE, Version 4.03 Grading for Hypotension

Grade	Description
Grade 1	Asymptomatic, intervention not indicated
Grade 2	Non-urgent medical intervention indicated
Grade 3	Medical intervention or hospitalization indicated
Grade 4	Life-threatening and urgent intervention indicated

Definition: A disorder characterized by a blood pressure that is below the normal expected for an individual in a given environment.

An institutional thermometer will be used to measure body temperature.

All vital sign measurements occurring on dosing days must be performed prior to study treatment administration.

Any treatment-emergent abnormal findings will be recorded as AEs.

8.3.5. Electrocardiogram (ECG) and Echocardiogram/Multi-gated Acquisition Scans (ECHO/MUGA)

8.3.5.1. Schedule

ECG and ECHO/MUGA will be assessed as indicated in the study flow chart (please refer to the flow-chart corresponding to the current period: Main study or Study extension).
ECGs for which abnormal results are collected after study treatment initiation should be repeated until the values return to normal or to a stable status. The frequency with which such checks should be made will be defined by the Investigator according to the degree of abnormality.

8.3.5.2. Technical Procedure and Parameters

- **Electrocardiogram**

An ECG will be recorded as described on the flowchart (please refer to the flow-chart corresponding to the current period: Main study or Study extension) using the internationally recognized 12-lead cardiograph. An institutional cardiograph will be used.

Prior to performing the 12-lead ECG, subjects should rest in the supine position for at least 5 minutes. The ECG measurement performed at the Screening Visit will be used to determine eligibility. The mean of the triplicate ECG measurements recorded pre-dose on Cycle 1 Day 1 will serve as the subject's Baseline value for all postdose comparisons. The ECG measurement at any time point should be used for AE grading and recommended dose modifications.
When an ECG is to be performed at the same time point as a blood collection, the ECG is to be performed first.

Interpretation of the tracing, Heart Rate (HR), QTcF interval (Fridericia's correction formula), PR and QRS complex should be made by a qualified physician and evaluated as normal or abnormal . All data should be documented in the e-CRF.

Clinically significant abnormalities present when the subject signed the Screening informed consent should be reported in the e-CRF. New or worsened clinically significant findings occurring after the informed consent must be recorded in the e-CRF.

- **Echocardiogram/Multi-gated Acquisition Scans**

Cardiac ejection fraction will be assessed by transthoracic ECHO or MUGA scans as described on the flowchart (please refer to the flow-chart corresponding to the current period: Main study or Study extension). The same method should be used throughout the study.

Subjects who develop signs/symptoms of congestive heart failure at any point during the study are required to have an evaluation of LVEF measurement by ECHO or MUGA.

8.3.6. Ophthalmic Assessments

During the Main study period, visual assessment must be performed by investigator, to assess general inspection of the eyes, examination of motility and alignment, visual disturbance including diminished central vision, blurred vision or loss of vision at each Day 1, if clinically indicated at D8, D15, D22 during treatment and at 30-days follow-up visit.

During the Study extension period, visual assessment must be performed by investigator, to assess general inspection of the eyes, examination of motility and alignment, visual disturbance including diminished central vision, blurred vision or loss of vision at each Day 1, if clinically indicated at D15 during treatment and at 30-days follow-up visit.

At screening, EOT, if clinically indicated, during treatment, and at safety 30 day-follow-up visit in case of ocular clinical event at EOT visit, a full ophthalmic examination will be performed by an ophthalmologist (during Main study and Study extension periods).

The full ophthalmic examination includes:

- Best corrected visual acuity for distance testing, slit lamp examination, intraocular pressure and dilated fundoscopy (with attention to retinal abnormalities, especially retinal pigment epithelial detachment (RPED), serous detachment of the retina and RVO).
- OCT will be performed systematically at screening and if clinically indicated during treatment and at EOT.
- Fluorescein angiography will be performed only if clinically indicated from screening to EOT.

For all subjects, ophthalmic assessments may be performed more frequently per standard of care or if clinically indicated for evaluation of any visual signs or symptoms. Subjects with clinical suspicion of retinal abnormalities (i.e., RPED, posterior uveitis, serous detachment of the retina, RVO, photopsia, metamorphopsia, impairment of visual acuity, etc.), must complete at least one of the following additional assessments:

- For non-vascular abnormalities: OCT of the macula (spectral domain OCT recommended).
- For vascular abnormalities: fluorescein angiography of the central 30 degrees.

Images/results of the ophthalmic examinations (at a minimum, OCT and/or fluorescein angiography) should be sent to the study site and be maintained in the subject's source document file. These images/results may be requested to be sent to the Sponsor or designee.

8.3.7. Dermatologic Evaluations

Dermatologic evaluations will be performed at the site by the Investigator to monitor for the possible development of keratoacanthoma (KA) and/or squamous cell carcinoma (SCC), as these have been reported to occur with selective BRAF inhibitor treatment. This assessment can be done predose or postdose and will be performed at the time points specified in the Flowchart (please refer to the flow-chart corresponding to the current period: Main study or Study extension).

In case of occurrence of KA or SCC, subjects will undergo complete surgical excision of the skin lesion following institutional standards. The evaluation can be done by the dermatologist if clinically indicated.

It is recommened that dermatological examination should be performed every two months for up to 6 months following discontinuation of encorafenib.

8.3.8. ECOG Performance Status

Assessment of ECOG PS will be performed at the time points specified in the Flow Chart (please refer to the flow-chart corresponding to the current period: Main study or Study extension). ECOG PS should be obtained on the scheduled day, even if study treatment is being held (see **Table 24**).

Table 24: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

8.4. TISSUE AND BLOOD BIOMARKER ASSESSMENTS

All tissue and blood biomarker assessments are described in **Table 25** for the Main study period.

All tissue and blood biomarker assessments are described in **Table 26** for the Study extension period

8.4.1. Tumor Biomarker Assessments

- **BRAF testing**

Subjects will be eligible for the study based on identification of a $BRAF^{V600E}$ mutation in the tumor as determined by local laboratory result obtained any time prior to Screening. Only PCR and NGS-based local assays results will be acceptable. The *BRAF* mutation status must be confirmed by the central laboratory no later than 30 days from first dose of study treatment.

In cases where there is discordance between the local assay and central laboratory results, or if the central laboratory is not able to confirm presence of a $BRAF^{V600E}$ mutation due to inadequate or poor sample condition or absence of available material within 30 days of initiating study therapy, subjects may only continue treatment if there is no clinical indication of deterioration or disease

progression and the Investigator determines that the subject is deriving benefit. In such instances, subjects must be informed that the *BRAF* mutation status is unconfirmed (negative or indeterminate) and must sign a separate informed consent form (ICF) that includes this information and describes alternative treatment options.

If the result from the central laboratory is indeterminate or the sample is deemed inadequate for testing, additional samples should be submitted (archival material only).

This analysis will be performed on an archival FFPE tumor sample or fresh biopsy provided at screening and may also be performed on an optional biopsy obtained at End of Treatment.

- **Other assessments in tumor tissue samples**

The tissue source submitted to the central laboratory will also be used for retrospective testing of MSI status and *RAS* mutation status. Information regarding tissue specimen requirements, sample handling and shipment will be provided in the Laboratory Manual.

This test will analyze tumor mutations representative of the mutational load. Germline DNA obtained via a blood sample (MSI germline control) will also be required (10mL) for the Main study period (see **Table 25**).
These biomarker analysis will be exploratory and will not be part of the CSR.

8.4.2. Blood Biomarker Assessments

8.4.2.1. C-reactive protein

A blood sample (3.5 mL*) for* analysis of C-reactive protein (CRP), a biomarker of inflammation, will be collected during Screening. Complete instructions for sample collection, processing, handling and shipment to the central laboratory will be provided in the Laboratory Manual.

8.4.2.2. Tumor markers

Blood samples (10 mL of each) for analysis of tumor markers CEA and CA 19-9 will be collected at screening, predose on day 1 of cycle 1 if more than 72 hours after screening and pre-dose on day 1 of each subsequent cycles,and at the EOT visit (Main study period). This measurement will provide a surrogate marker of response to treatment.

During the Study extension period, blood samples (10 mL of each) for analysis of tumor markers (CEA and CA 19-9) will be collected at pre-dose on day 1 of each cycle,and at the EOT visit, only if as per routine clinical practice.

The analysis of these blood samples will be performed by the local laboratory.

8.4.2.3. Circulating DNA (ct-DNA)

ctDNA will be analyzed at baseline in a plasma sample (2 blood samples of 10 mL). *BRAF*^{V600E} mutational status will be explored and compared to the *BRAF*^{V600E} mutational status observed in the local test used for inclusion and for retrospective tumor mutation analysis. In addition to *BRAF*^{V600E}, other cancer genes may be explored in order to identify biomarkers for sensitivity or resistance to treatment.

All blood biomarker analysis will be exploratory and will not be part of the CSR.

8.4.3. Predictive Biomarkers of Activity

Further exploratory biomarker research may be conducted on collected blood and tumor samples. These studies would extend the search for other potential biomarkers relevant to the effects of the drugs given in combination in this study, and/or prediction of these effects, and/or resistance to the treatment, and/or safety, and these additional investigations would be dependent upon clinical outcome, reagent and sample availability. Samples used for these analyses will be:

- Remaining tumor tissue (**Section 8.4.1**): retrospective analyses may include and not limited to: expression of proteins by immunohistochemistry or gene expression by RNA analysis (RNAseq, nanostring, RT-Q PCR, etc).
- Remaining blood samples (**Section 8.4.2.3**): remaining blood samples collected at baseline may be analyzed for potential genomic or proteomic predictive markers of activity.

Complete instructions for sample collection, processing, handling and shipment to the central laboratory will be provided in the Laboratory Manual.

These analyses will be exploratory and will not be part of the CSR.

8.4.4. Optional tumor biopsy

If the subject consents, optional fresh tumor samples may be collected at the time of progression in subjects with accessible lesions. Accessible lesions are defined as tumor lesions which are easily biopsied with minimum risk to the subject. Lesions with the greatest change in dimensional size are the recommended lesions to be excised at the time of PD. Whenever possible, biopsies at progression should be performed within 3 days of study drug discontinuation (during the Main study or Study extension periods). The tissue from these biopsies will be used to determine possible mechanisms of resistance. Subjects will be asked (in a specific section of the main ICF) if they agree to provide this tumor sample.

All blood biomarker analysis will be exploratory and will not be part of the CSR.

Table 25: Biomarker samples_Main study period

Cycle/Period		Cycle 1				Subsequent Cycles						
Visit	Screening	C1 D1	C1 D8	C1 D15	C1 D22	Cn D1	Cn D8	Cn D15	Cn D22	End of treatment	Safety Follow-Up[q] (EOS)	Survival (Every x Months)
Cycle Days	D-28 to D-1	D1	D8	D15	D22	D1	D8	D15	D22	Dxx	Dxx	Dxx
Epochs	SCREENING	TREATMENT									FOLLOW-UP	LONG-TERM FOLLOW-UP
		Pre-Dose	Post-Dose									
Procedures		± 3-day window for procedures/assessments										
Blood sample for tumor markers (CEA, CA19-9)	X	X					X				X		
A tumour sample (archival or fresh) should be send to central laboratory to test for BRAFV600E and RASwt status and MSI testing	X												
Blood samples for ctDNA analysis (i.e. BRAFV600)		X											
Blood sample for MSI testing (control)		X											
Tumor biopsy (optional)											X[a]		

(a) Optional tumor sample will be requested only for subjects that discontinue study due to disease progression.

Table 26: Biomarker samples_Study extension period

Cycle/Period	*Subsequent Cycles during study extension*[a,b]				
Visit	*CnD1*	*CnD15*	*End of treatment*	*Safety Follow-Up* (EOS)[m]	*Survival (Every 3 Months)*
Cycle Days	*D1*	*D15*	*Dxx*	*Dxx*	*Dxx*
Epochs	TREATMENT			*FOLLOW-UP*	LONG-TERM FOLLOW-UP
Procedures					
Blood sample for tumor markers (CEA, CA19-9)[a]	X		X		
Tumor biopsy (optional) [b]			X		

(a) Blood sample for tumor markers (CEA, CA19-9) should be collected only if performed as per routine clinical practice
(b) Optional tumor sample will be requested only for subjects who discontinue study due to disease progression.

8.4.5. Retention of Samples for Future Analysis

If the subject agrees, and in accordance with local laws, any tumor (archival or fresh), blood and plasma samples remaining after determination of *BRAF*^{V600E} status may be stored for up to 10 years after the final CSR of the study is released. The samples may be further analyzed to address scientific questions and/or development of biological tests related to administration of encorafenib + cetuximab + binimetinib and/or cancer. The decision to perform such exploratory biomarker research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

The Sponsor will be the exclusive owner of any data and discoveries resulting from this study.

8.5. CONCOMITANT THERAPY AND THERAPEUTIC / DIAGNOSTIC PROCEDURE ASSESSMENT

Concomitant therapies and therapeutic / diagnostic procedures will be evaluated at each cycle at D1, D8, D15, D22 and starting Cycle 8, at D1 and D15 and at EOT/30-day Safety Follow Up (Main study period).

Since implementation of the Urgent Safety Measure on 26 Mar 2020, in order to ensure the subjects' safety in the clinical trial by decreasing the number of clinic visits in the context of COVID-19 pandemic, Cetuximab infusions can be given every two weeks at the dose of 500 mg/m^2 administered as a 120-min IV infusion (i.e. on D1 and D15 of each cycle) regardless of the cycle number, after the investigator has evaluated the benefit/risk ratio for the subject with regards to Covid-19 pandemic.

For the subjects moving to this every two weeks regimen before C8D1, concomitant therapies and therapeutic / diagnostic procedures will be evaluated at each cycle at D1 and D15 and at EOT/30-day Safety Follow Up.

During the Study extension period, concomitant therapies and therapeutic / diagnostic procedures will be evaluated at each cycle at D1 and D15 and at EOT/30-day Safety Follow Up.

Requirements relating to subject's concomitant therapies and therapeutic / diagnostic procedures before entry or throughout the trial can be found in **Section 7**.

8.6. QUALITY OF LIFE ASSESSMENT

Patient reported outcome (PRO) assessments will be collected during Main study period using the QoL questionnaires EORTC QLQ-C30 ,EQ-5D-5L and Patient Global Impression of Change (PGIC) at the time points specified in Study Flow Chart (Main study period Flow Chart).

These questionnaires will be used to explore PRO measures of health-related QoL, functioning, cancer symptoms, and treatment-related side effects.

The QLQ-C30 EQ-5D-5L and PGIC are recognized reliable and valid measures in the treatment of cancer subjects.

The questionnaires should be administered to subjects in the subjects' local language at the beginning of the study visit prior to receiving any study treatment, prior to any other study assessment or consultation with the Investigator, and prior to being informed of their current disease status.

Attempts should be made to collect all questionnaires for all subjects, including those who discontinue prior to the EOT visit. However, if the subject refuses to complete the questionnaires, this should be documented in study source records. Subject refusal to complete study questionnaires is not a protocol deviation.

Subjects should be given sufficient space and time to complete all study questionnaires, and all administered questionnaires should be reviewed for completeness. If missing responses are noted, subjects should be encouraged to complete any missing responses.

Completed questionnaires, including both responses to the questions and any unsolicited comments written by the subject, should be reviewed by the Investigator or designee to ensure every question has been answered and that there is only one response for each question. If omissions or double responses occur, they should be brought to the attention of the subject. Investigators must not encourage the subject to change responses reported in questionnaires.

In addition, the completed questionnaires should be reviewed and assessed by the Investigator for responses which may indicate potential AEs or SAEs. This review should be documented in study source records.

8.7. HEALTHCARE RESOURCE UTILIZATION

Hospitalization data of interest will focus on those hospitalizations reported as Serious Adverse Events as required in **Section 10.2.1**

Healthcare resource utilization data regarding hospitalizations should be captured continuously through-out the Main study period treatment phase starting on the date of first study treatment administration until 30 days after the last administration dose, as described in the Study Flow Chart (during the Main study period only).

Information related to the length of stay, hospital facilities used, reasons for hospitalization, and hospital discharge information will be evaluated.

8.8. COMPLIANCE

The subject will be reminded regularly to bring back to the site at each study visit any remaining encorafenib and binimetinib blisters and boxes (used or unused).

Compliance will be evaluated at each cycle on Day 1 and at EOT by reviewing subject diary entries, accounting of returned study drug and subject interviews (Main study and Study extension periods).

Cetuximab will be administered intravenously per protocol in the clinic by study personnel. Information regarding individual study drug infusions is to be documented as described in **Section 6.5**

9. STUDY PROCEDURES

Details of schedule, technical procedures and parameters per assessment/exam are described in **Section 8**.

Starting Cycle 1 Day 1 and during the whole treatment period, (during the Main study and the Study extension periods), all procedures/assessments should take place in a ± 3 day-window from the corresponding visit, unless otherwise specified.

Except C1D1, the visit can be missed. Theoretical cycles dates (7 days ± 3) are kept constant irrespectively of whether the visit is done and/or the product is administered or not. If subject doesn´t come for CnD1 visit, the CnD1 assessments will still need to be performed (and shall be recorded on the unscheduled visit in the e-CRF).

Study procedures section is divided in 2 main sub-sections:

-1 for the study visits and procedures during the Main Study period (until 27 Dec 2020)

-1 for the study visits and procedures during the Study extenstion period (from 28 Dec 2020)

9.1. **MAIN** STUDY PERIOD (FROM FIRST SUBJECT SCREENED TO 27 DEC 2020)

9.1.1. VISIT 1 – Screening visit (Day -28 to -1 prior to Cycle 1 Day 1)_ Main study period

The subject considered eligible for screening by the Investigator will be informed of the characteristics and the consequences of the trial both verbally and by reviewing the subject's information sheet and ICF (see **Section 14.3**). If he/she accepts to participate in the study, he/she will sign the informed consent and will keep a copy.

All screening procedures to determine eligibility must be performed within specific time windows prior to the first dose of protocol treatment.

The subject will be assessed for the following:

- Demographic characteristics (gender, age, race, ethnicity)
- Medical history
- Prior medications/therapies/procedures

- Physical examination (incl. height, weight)
- Vital signs
- ECOG PS
- Concomitant medications/therapies (authorized, disallowed)
- Twelve-lead single ECG (after 5-min rest in supine position)
- Full ophthalmic examination
- Dermatologic examination
- ECHO/MUGA
- Serum pregnancy test (for females of childbearing potential only)
- LH, FSH and/or estradiol measurements (for females who are post-menopausal)
- Hepatitis B surface antigen, hepatitis C antibody
- HIV (if required)
- Hematology
- Clinical chemistry
- Coagulation
- Urinalysis
- Blood sample for CRP
- Blood sample for tumor markers (CEA, CA19-9)
- A tumor sample (archival or fresh) should be sent to central laboratory to test for *BRAF*^{V600E} and *RAS*^{wt} status and for MSI testing
- Tumor assessments (CT scan, MRI) as defined by RECIST
- The Investigator will inform the Sponsor of the screening using IRT.

9.1.2. Cycle 1 - Day 1 _ Main studyperiod

If the subject still fulfills the eligibility criteria during the screening period and/or the results of additional examinations, the Investigator will dispense to the Subject the box number indicated by the IRT. Eligibility is determined using results of screening assessments performed before the first dose of study treatment and up to and including Cycle 1 Day 1.

If the following study procedures were not performed within 72 hours before Day 1, they must be repeated on Cycle 1 Day 1 (i.e., first day of dosing):

- Physical examination, including measurement of body weight
- Dermatologic examination
- Obtain blood samples for hematology, coagulation, clinical chemistry
- Obtain blood samples for tumor markers (CEA and CA19-9)
- Obtain urine sample for urinalysis and for pregnancy test for females of childbearing potential
- Assess ECOG PS

All of the following study procedures are to be performed on Cycle 1 Day 1:

- Visual assessment by investigator: general inspection of the eyes, examination of motility and alignment, visual disturbance including diminished central vision, blurred vision or loss of vision
- QOL questionnaires (EORTC QLQ-C30, EQ-5D-5L, PGIC)
- Assess vital signs (blood pressure, pulse, temperature and respiratory rate)
- Calculate BSA predose
- Obtain 3 serial, resting and supine 12-lead ECGs conducted within approximately 5 to 10 minutes total time and prior to the first dose, followed by a single ECG 2.0 (+/- 0.5) hours following administration of encorafenib + binimetinib and before the start of the cetuximab infusion. ECGs should be performed prior to the 2-hour post-dose PK blood collection.

- Verify inclusion/exclusion criteria
- Collect blood samples for:

– MSI germline control
– ctDNA for BRAF testing
– PK plasma level determination of encorafenib, binimetinib and AR00426032: 2h (± 10 min) and 6 hours (± 30 min) after administration of encorafenib and binimetinib.
– PK serum level determination of cetuximab: 2h (± 10 min) and 6 hours (± 30 min) after the start of cetuximab infusion

- Administer dose of encorafenib and binimetinib with water
- Administer cetuximab premedication according to SPC (antihistaminic and corticosteroïd pretreatment are mandatory for the the first infusion)
- Administer cetuximab as an IV infusion
- Document prior (pre-dose) and concomitant medications/therapies
- Assess AEs
- Dispense the treatment number using IRT
- Dispense a 4-week supply of encorafenib and binimetinib along with a monthly dosing diary. Review dosing instructions with the subject.

9.1.3. Cycle 1 - Day 8 _ Main study period

The subject will be assessed for the following:

- Physical examination if clinically indicated
- Visual assessment by investigator if clinically indicated (in case of any abnormalities a full ophthalmic examination must be performed by an ophthalmologist)
- Assess vital signs (blood pressure, pulse, temperature and respiratory rate)
- Administer cetuximab premedication according to institutional standards
- Administer cetuximab as an IV infusion
- Review concomitant medications/therapies

- Assess AEs since previous visit
- Obtain information on Healthcare Resource Utilization in case of hospitalization since previous visit (see **Section 8.7**)

9.1.4. Cycle 1 - Day 15 _ Main study period

- Physical examination if clinically indicated
- Visual assessment by investigator if clinically indicated (in case of any abnormalities a full ophthalmic examination must be performed by an ophthalmologist)
- Assess vital signs (blood pressure, pulse temperature and respiratory rate)
- Obtain blood samples for hematology and clinical chemistry
- Obtain single ECG (predose)
- Administer cetuximab premedication according to institutional standards
- Administer cetuximab as an IV infusion
- Review concomitant medications/therapies
- Assess AEs since previous visit
- Obtain information on Healthcare Resource Utilization in case of hospitalization since previous visit (see **Section 8.7**)

9.1.5. Cycle 1 - Day 22 _ Main study period

- Physical examination if clinically indicated
- Visual assessment by investigator if clinically indicated (in case of any abnormalities a full ophthalmic examination must be performed by an ophthalmologist)
- Assess vital signs (blood pressure, pulse temperature, and respiratory rate)
- Obtain a blood sample for hematology
- Administer cetuximab premedication according to institutional standards
- Administer cetuximab as an IV infusion

- Review concomitant medications/therapies
- Assess AEs since previous visit
- Obtain information on Healthcare Resource Utilization in case of hospitalization since previous visit (see section 8.7)

9.1.6. Subsequent Cycles _ Main study period

Tumor assessments (i.e., appropriate radiological scans to document all suspected sites of disease) are to be performed every 6 weeks (±7 days) from the first dose for the first 12 weeks, then every 8 weeks (±7 days) thereafter until disease progression, subject decision, withdrawal of consent, initiation of subsequent anticancer therapy, subject is lost to follow-up, or death, regardless of whether study treatment is discontinued.

The time-window allowed for the first tumor assessment (i.e. day 42 from first dose) is +7 days.

Information on Healthcare Resource Utilization will be obtain in case of hospitalization and during the whole treatment period until 30 days after the last administration of study treatment. (see **Section 8.7)**

9.1.7. Subsequent Cycles Day 1 _ Main study period

- QOL questionnaires (EORTC QLQ-C30, EQ-5D-5L, PGIC)
- Weight
- Calculate BSA
- Physical examination
- Assess vital signs (blood pressure, pulse temperature, and respiratory rate)
- Assess ECOG PS
- Single ECG are to be performed pre-dose at D1 of each subsequent cycle. **At Cycle 2 only:** obtain a single ECG predose and 2.0 hours (+/- 0.5 hour) after administration of encorafenib + binimetinib and before the start of the cetuximab infusion. ECGs should be performed prior to the 2-hour post-dose PK blood collection.

- Visual assessment by investigator (in case of any abnormalities a full ophthalmic examination must be performed by an ophthalmologist)
- Dermatologic examination every 8 weeks from Cycle 1 Day 1 (i.e., Day 1 of Cycles 3, 5, 7, etc.)
- ECHO/MUGA scans Cycle 2 Day 1 and Cycle 5 Day 1, then every 12 weeks
- Collection of blood samples for:

– PK: Cycle 2 only:
  . Plasma level determination of encorafenib, binimetinib and AR00426032: predose (just prior to encorafenib/binimetinib dose) and 2 hours (± 10 min) following administration of encorafenib and/or binimetinib
  . Serum level determination of cetuximab: predose (just prior to cetuximab infusion) and 2 hours (± 10 min) after the start of cetuximab infusion

– Hematology, coagulation and clinical chemistry
– Tumor markers (CEA and CA19-9)

- Obtain a urine sample for urinalysis and urine pregnancy testing for women of childbearing potential
- Administer dose of encorafenib and binimetinib with water
- Administer cetuximab premedication according to institutional standards
- Administer cetuximab as an IV infusion
- Assess compliance of encorafenib and/or binimetinib dosing and use of dosing diary.
- Review concomitant medications/therapies
- Assess AEs since previous visit
- Dispense a 4-week supply of encorafenib and binimetinib along with a monthly dosing diary. Review dosing instructions with the subject.

9.1.8. Subsequent Cycles - Day 8, Day 15 and Day 22 _ Main study period

- Physical examination if clinically indicated

- Visual assessment by investigator if clinically indicated (in case of any abnormalities a full ophthalmic examination must be performed by an ophthalmologist)
- Assess vital signs (blood pressure, pulse, temperature, and respiratory rate). Vitals signs do not need to be done at D8 and 22 starting week 29 (when the Q2W schedule is in place)
- Administer cetuximab premedication according to institutional standards
- Administer cetuximab as an IV infusion
- Review concomitant medications/therapies
- Assess AEs since previous visit

From week 29 the D8 and D22 visits will not be performed (biweekly infusion of cetuximab: no cetuximab infusion on D8 and D22).

Since implementation of the Urgent Safety Measure on 26 Mar 2020, if the investigator implements this change, each D8 and D22 visit (before C8D1) for subjects having not yet reached C8D1 at the time of USM implementation will be performed by phone calls and will have to be documented in source documents to ensure subject's safety.

9.1.9. End-of-Treatment Visit _ Main study period

At the time of study treatment discontinuation, the EOT visit should be completed for all subjects as soon as possible after the last dose of study drug, and every effort should be made to perform the procedures listed below. This visit should take place as soon as possible and ≤ 14 days after the last dose of study treatment. An e-CRF should be completed, giving the date and reason for stopping the study treatment. All subjects will enter the follow-up period

If a subject withdrawal occurs or if the subject fails to return for visits, the Investigator must determine the primary reason for a subject's discontinuation from the study and record this information on the relevant page of the e-CRF.

Subjects will be assessed for the following:

- QOL questionnaires (EORTC QLQ-C30, EQ-5D-5L, PGIC)

- Physical examination including weight
- Full ophthalmic examination
- Vital signs (blood pressure, pulse, temperature and respiratory rate)
- ECOG PS
- Single ECG
- Dermatologic examination
- ECHO/MUGA
- Serum pregnancy test (for females of childbearing potential only)
- Collection of blood samples for:

– Hematology, coagulation and clinical chemistry
– Tumor markers (CEA and CA19-9)

- Obtain a urine sample for urinalysis
- Optional tumor biopsy sample (only if discontinuation due to disease progression)
- Assess compliance of encorafenib and/or binimetinib dosing and use of the dosing diary. Collect all remaining bottles of study drugs.
- Review concomitant medications/therapies
- Assess AEs since previous visit
- Obtain information on Healthcare Resource Utilization in case of hospitalization since previous visit (see **Section 8.7**)

9.1.10. Safety Follow-up Visit and Survival Visits _ Main study period

Tumor assessments (i.e., appropriate radiological scans to document all suspected sites of disease) should continue to be performed every 6 weeks (±7 days) for the first 12 weeks, then every 8 weeks (±7 days) thereafter until disease progression, initiation of subsequent anticancer therapy, subject is lost to follow-up, subject decision, withdrawal of consent or death.

When clinically appropriate, it is recommended that subjects be monitored with physical examinations, dermatological examinations and CT scans for cutaneous and non-cutaneous secondary malignancies for up to 6 months after the last encorafenib dose or until initiation of another antineoplastic therapy.

9.1.10.1. Safety 30 Day-Follow-up Visit _ Main study period

All subjects will return for a Safety Follow-up visit approximately 30 days after the last dose of study drug, or prior to the initiation of subsequent anticancer therapy, whichever occurs first.

Information related to AEs (including concomitant medication taken for ongoing AEs) and ongoing antineoplastic treatments will be collected for 30 days after the last dose of study drug.
The following study procedures will be performed, completed or reported:

- QOL questionnaires (EORTC QLQ-C30, EQ-5D-5L, PGIC)
- Physical examination including weight
- Vital signs (blood pressure, pulse, temperature and respiratory rate)
- ECOG PS
- Single ECG
- Visual assessment by investigator (full ophthalmic examination by an ophthalmologist only in case of ocular clinical event at the EOT visit)
- Urine pregnancy test
- Hematology, coagulation and clinical chemistry
- Urinalysis
- Survival Status
- Documentation of subsequent anticancer therapy
- Obtain information on Healthcare Resource Utilization in case of hospitalization since previous visit (see **Section 8.7**)

9.1.10.2. Survival Visit (every 3 months) _ Main study period

The Survival follow-up period will start after the completed 30 days safety follow up, until the End of Study.

If a subject discontinues the treatment for a reason other than progressive disease, tumor assessment must be performed (as per local and central review) until the start of a new anti-cancer therapy, disease progression, death, lost to follow-up, subject decision or withdrawal of consent. Subjects who discontinue the treatment will be contacted by phone every 3 months (or more frequently as needed) for collection of information during the survival follow-up period:

- Survival status
- Documentation of subsequent anticancer therapy
- Documentation of the date of progressive disease following the initiation of subsequent anticancer therapies

9.2. STUDY EXTENSION PERIOD (FROM 28 DEC 2020)

9.2.1. Subsequent Cycles_Study extension period

Written information and consent form addendum related to Study extension period must be submitted to the subject with an oral explanation. It must be agreed and signed by the subject before any Study extension-related procedure starts.

Tumor assessments (i.e., appropriate radiological scans to document all suspected sites of disease) are to be performed every 12 weeks (±7 days) until disease progression, subject decision, withdrawal of consent, initiation of subsequent anticancer therapy, subject is lost to follow-up, or death, regardless of whether study treatment is discontinued.

9.2.2. Subsequent Cycles Day 1 _ Study extension period

- Weight
- Calculate BSA
- Physical examination
- Assess vital signs (blood pressure, pulse, temperature, and respiratory rate)
- Assess ECOG PS
- ECGs scans must be performed every 3 cycles at D1 D1 or more frequently if clinically indicated
- Visual assessment by investigator (in case of any abnormalities a full ophthalmic examination must be performed by an ophthalmologist)
- Dermatologic examination every 8 weeks
- ECHO/MUGA scans every 12 weeks or more frequently if clinically indicated
- Collection of blood samples for:
    - Hematology and clinical chemistry
    - Tumor markers (CEA and CA19-9) – only if as per routine clinical practice
- Obtain a urine sample for urinalysis and urine pregnancy testing for women of childbearing potential
- Administer dose of encorafenib and binimetinib with water
- Administer cetuximab premedication according to institutional standards
- Administer cetuximab as an IV infusion
- Assess compliance of encorafenib and/or binimetinib dosing and use of dosing diary.
- Review concomitant medications/therapies

- Assess AEs since previous visit
- Dispense a 4-week supply of encorafenib and binimetinib along with a monthly dosing diary. Review dosing instructions with the subject.

9.2.3. Subsequent Cycles - Day 15 _ Study extension period

- Physical examination if clinically indicated
- Visual assessment by investigator if clinically indicated (in case of any abnormalities a full ophthalmic examination must be performed by an ophthalmologist)
- Assess vital signs (blood pressure, pulse, temperature, and respiratory rate).
- Administer cetuximab premedication according to institutional standards
- Administer cetuximab as an IV infusion
- Review concomitant medications/therapies
- Assess AEs since previous visit

9.2.4. End-of-Treatment Visit _ Study extension period

At the time of study treatment discontinuation, the EOT visit should be completed for all subjects as soon as possible after the last dose of study drug, and every effort should be made to perform the procedures listed below. This visit should take place as soon as possible and ≤ 14 days after the last dose of study treatment. The e-CRF should be completed, giving the date and reason for stopping the study treatment. The e-CRF should be completed, giving the date and reason for stopping the study treatment. All subjects will then enter the follow-up period until the End of Study.

If a subject withdrawal occurs or if the subject fails to return for visits, the Investigator must determine the primary reason for a subject's discontinuation from the study and record this information on the relevant page of the e-CRF.

Subjects will be assessed for the following:

- Physical examination including weight
- Full ophthalmic examination

- Vital signs (blood pressure, pulse, temperature and respiratory rate)
- ECOG PS
- Single ECG
- Dermatologic examination
- ECHO/MUGA
- Serum pregnancy test (for females of childbearing potential only)
- Collection of blood samples for:
    - Hematology and clinical chemistry
    - Tumor markers (CEA and CA19-9) if as per routine clinical practice
- Obtain a urine sample for urinalysis
- Optional tumor biopsy sample (only if discontinuation due to disease progression)
- Assess compliance of encorafenib and/or binimetinib dosing and use of the dosing diary. Collect all remaining bottles of study drugs.
- Review concomitant medications/therapies
- Assess AEs since previous visit

9.2.5. Safety Follow-up Visit and Survival Visits _ Study extension period

Tumor assessments (i.e., appropriate radiological scans to document all suspected sites of disease) should continue to be performed every 12 weeks (±7 days) thereafter until disease progression, initiation of subsequent anticancer therapy, subject is lost to follow-up, subject decision, withdrawal of consent or death.

When clinically appropriate, it is recommended that subjects be monitored for physical examinations, dermatological examinations and CT scans for cutaneous and non-cutaneous secondary malignancies for up to 6 months after the last encorafenib dose or until initiation of another antineoplastic therapy.

9.2.5.1. Safety 30 Day-Follow-up Visit _ Study extension period

All subjects will return for a Safety Follow-up visit approximately 30 days after the last dose of study drug, or prior to the initiation of subsequent anticancer therapy, whichever occurs first.

Information related to AEs (including concomitant medication taken for ongoing AEs) and ongoing antineoplastic treatments will be collected for 30 days after the last dose of study drug.

The following study procedures will be performed, completed or reported:

- Physical examination including weight
- Vital signs (blood pressure, pulse, temperature and respiratory rate)
- ECOG PS
- Single ECG
- Visual assessment by investigator (full ophthalmic examination by an ophthalmologist only in case of ocular clinical event at the EOT visit)
- Urine pregnancy test
- Hematology and clinical chemistry
- Urinalysis
- Survival Status
- Documentation of subsequent anticancer therapy

9.2.5.2. Survival Visit (every 3 months) _ Study extension period

The Survival follow-up period will start after completion of the 30 days safety follow up visit, and all subjects will be followed until the End of the study, i.e. until the last subject will have either progressed or discontinued study treatments (including 30-day Safety Follow-Up visit) for any other reason (unacceptable toxicity, subject's decision, withdrawal of consent, initiation of subsequent anticancer therapy or death).

If a subject discontinues the treatment for a reason other than progressive disease, tumor assessment must be performed (as per local review) until the start of a new anti-cancer therapy, disease progression, death, lost to follow-up, subject decision or withdrawal of consent. Subjects who discontinue the treatment will be contacted by phone every 3 months (or more frequently as needed) for collection of information during the survival follow-up period:

- Survival status
- Documentation of subsequent anticancer therapy

- Documentation of the date of progressive disease following the initiation of subsequent anticancer therapies

10. ADVERSE EVENTS: DEFINITION, NOTIFICATION AND REPORTING

10.1. ADVERSE EVENTS

10.1.1. Definition

An AE is any untoward medical occurrence, including the exacerbation of a pre-existing condition, in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH-Guideline for GCP).

Any new or worsening adverse event that is assessed by the investigator as related to the disease progression must be reported as an AE.

The relationship to disease progression must be captured as specified in e-CRF.

If the AE meets the seriousness definition and thus becomes SAE, it should be notified to the Sponsor Pharmacovigilance Department by the investigator as soon as he/she is informed of the event and no later than 24 hours after knowledge.

Note: Disease progression documented solely by medical imaging techniques with no new or worsening symptoms will not require to be reported as an AE nor notified as SAE to the Sponsor Pharmacovigilance Department but documented as progression of disease in the tumor assessments (RECIST) e-CRF forms.

All laboratory tests, vital signs, ECGs collected after study treatment initiation for which abnormal results meet the criteria for AE are collected after study treatment initiation should be repeated until the values return to normal or to a stable status and recorded into the e-CRF.

The frequency with which such checks should be made will be defined by the investigator according to the degree of abnormality.

For any of the following reasons, an abnormal result should be considered as clinically significant and reported as an AE. :

- A symptomatic value.
- A value or a change that requires active management (e.g., study treatment dose modification, discontinuation of study treatment, more frequent follow-up assessments, corrective treatment …).
- Any value judged by the investigator as clinically significant.

Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or baseline, or per Investigator discretion.

10.1.2. Severity of Adverse Events

The severity rating of an AE refers to its intensity. The severity of each AE will be determined by the Investigator using the NCI-CTCAE, v4.03. For any term that is not specifically listed in the CTCAE scale, intensity should be assigned a Grade of 1 through 5 using the following CTCAE guidelines:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Fatal

To avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided:

- - “Severe” is used to describe the intensity of a specific AE, which may be of relatively minor medical significance.
- - “Seriousness” is based on the regulatory definition supplied below (see **Section 10.2.1**)

10.2. SERIOUS ADVERSE EVENTS

10.2.1. Definition

A serious adverse event (SAE) includes but is not necessarily restricted to any event which:

- results in death (whatever may be the cause)

Death is an outcome of an SAE and not an SAE in itself. Death should only be reported as an SAE term when no additional information is known about a fatal event. When death is an outcome, the event(s) resulting in death should be reported (e.g., "pulmonary embolism" with a fatal outcome) and assigned severity Grade 5.

- is life-threatening
- results in persistent or significant disability/incapacity
- requires the subject's in-patient hospitalisation or prolongation of current hospitalisation*
- is a congenital anomaly or birth defect
- is serious for other reason: medical and scientific judgment should be exercised in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the outcomes described in the definition above. These should also usually be considered serious.

In addition, for all subjects with COVID-19 (with critical symptoms and/or hospitalization), a Serious Adverse Event should be declared.

*Note that any hospitalisation, or prolongation of hospitalisation due to the circumstances listed below will not be notified as an SAE to the Sponsor by the Investigator:

- a visit to the emergency room, or outpatient observation that does not result in admission,
- preparation for routine health assessment/procedure (e.g. routine colonoscopy),
- planned medical/surgical admission (planned prior to entry into study trial, appropriate documentation required),
- administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances).

10.2.2. Reporting of Serious and non-serious AEs

All AEs, serious and non-serious and regardless of causality to study drug (including the exacerbation of a pre-existing condition), will be fully recorded on the appropriate e-CRF. For each AE, the Investigator must provide its duration (start and end dates or ongoing), severity (intensity), assessment of causality and seriousness and whether corrective action or therapy was required and whether action was taken with regard to study drug treatment.

Any AE that occurs after the signing of the ICF should be recorded on the AE e-CRF page regardless the relationship with the study procedure. All AEs occurring from the first dose of study drug including the 30 days after the last dose of study (30-day follow-up period) drug must be recorded on the AE e-CRF regardless of the relationship with the study drug.

If an AE occurs more than once in the same subject during the study, each occurrence must be recorded as a separate AE.

Any SAE occuring from the signing of the ICF should be reported as an SAE regardless of the relationship with the protocol procedure or with study drug.

The investigator must notify the sponsor of this event by sending within 24 hours the "SAE Form", with all the available information about the event, to the sponsor's Corporate Vigilances e-mail dedicated box :

HQ.pharmacovigilance@pierre-fabre.com

In case it is not possible to send the report by e-mail it can be sent by fax to:

+ 33 1 49 10 80 90

In addition, all SAEs must be recorded into the e-CRF.

Study disease progression (including malignant disease progression with fatal outcome), if documented by the use of appropriate method (as per protocol) will be reported as progression of study disease in the e-CRF (study end-point) and should NOT be reported as an SAE unless a causal relationship to study treatment is suspected.

10.2.3. Follow-up of SAEs

The Investigator will provide follow-up information regarding a reported SAE using the SAE form providing the results of relevant examinations, laboratory and diagnosic tests, and hospitalisation records as needed.

Investigators must follow subjects with AEs/SAEs until the event has resolved, the condition has stabilized, withdrawal of consent, subject is lost to follow-up or death OR until 30 days after the last dose of study drug, whichever occurs first. Ongoing treatment-related AEs/SAEs may be followed beyond the 30-day follow-up period if clinically indicated.

10.2.4. SAEs occurring after the 30-day safety follow-up period

After the 30 day follow-up period, any SAEs that are considered related to any study drug or protocol procedures will be captured in the e-CRF and reported to the Sponsor using the SAE form.

10.3. REPORTING OF STUDY TREATMENT OVERDOSE TO THE SPONSOR

An overdose of study drug (whether symptomatic or asymptomatic) is to be reported as an AE in the e-CRF.

For the purpose of this trial, an overdose will be defined as any study drug dose administration exceeding the subject's assigned dose of study drug (s) as per protocol recommendations.

In the absence of associated AE seriousness criteria, the overdose and associated non-serious AE, are reported only on the AE page of the e-CRF. **If the definition** of seriousness criteria **is met for any associated AE**, the SAE form must be also completed and transmitted to the Sponsor.

10.4. REPORTING OF PREGNANCY TO THE SPONSOR

Pregnancy occurring during the period between signing of the ICF but before any study treatment exposure is not to be reported to the Sponsor unless associated to an AE.

If pregnancy is suspected while the female subject is receiving study treatment, the study treatment(s) should be discontinued immediately until the result of the pregnancy testing is known. If pregnancy is confirmed, administration of study drug is to be discontinued immediately and the subject must be withdrawn from the study.

The Investigators must report to the Sponsor any on-treatment pregnancy of a female subject or a female partner of a male subject which occurs during study treatment and within the 30 days after the last dose administration of binimetinib or encorafenib and within the 6 months after the last dose administration of cetuximab.

On-treatment pregnancy (of female subject and female partner of male subject) must be reported to the Sponsor within 24 hours of the Investigator's knowledge using the investigational product pregnancy form.

Any pregnancy will be followed through to outcome, and the outcome must be reported to the Sponsor, including the infant's health status, using the pregnancy outcome report form.

10.5. SPONSOR'S RESPONSIBILITIES FOR SAFETY REGULATORY REPORTING PURPOSES

The Sponsor and/or designee will submit expedited and periodic reports to both Competent Authorities and Ethics Committees as regards to the Directive 2001/20/EC EU regulations or as per local specific regulatory requirements in participating countries.

11. DATA COLLECTION AND STUDY MONITORING

11.1. DATA COLLECTION

11.1.1. Case Report Forms

An e-CRF will be provided by the CRO. It will contain fields for all the data required to be obtained based on the protocol, except any computerized data which will be directly transferred to the database.

The Investigator is responsible for ensuring that all required data are properly recorded in each subject's e-CRF and related documents. Prior to the start of the study, the Investigator will complete a delegation form. The signature and initials of all persons in charge of e-CRF completion should be recorded on this form.

The e-CRFs are to be completed in a timely manner and preferably within 3 days of the study visit, allowing extraction of appropriate e-CRF data available for Sponsor review. All the information will be recorded from source documents into the e-CRF by an authorized person.
All answer fields in the e-CRF pages must be filled in for all visits, otherwise an explanation should be given.

The completed e-CRF, including any paper SAE/pregnancy/pregnancy outcome forms, must be promptly reviewed, signed and dated by a qualified person, who is an Investigator.
Each subject who will have received the study treatment must be entered into the e-CRF.
For all other subjects having signed an ICF, the subject's summary page of the e-CRF, along with all applicable information documenting the screen failure/discontinuation reason must be completed.
The Investigator is responsible for the management, completeness and accuracy of the information in the e-CRF. The CRAs will be trained about the e-CRF and have access to the e-CRF module for monitoring purposes.
A copy of the e-CRF with all related documentation will be stored by the Sponsor at the end of the study. Another copy of the e-CRF data will be stored by the Investigator for at least 25 years or according to the local requirements.

11.1.2. Source Documents

A source document is an original record or certified copy of an original record of clinical findings, observations or any other medical or paramedical activities performed during the clinical trial, necessary for the transcription and the verification of the collected data.

Source documents along with all other trial-related documents (copies of all ICFs, e-CRFs, treatment inventories and any correspondence related to the study) must be kept in the Investigator's file throughout the study, and then must be stored in the study center's archives for a period of at least 25 years or as per local legal requirements.
For further details see **Section 15.2**

11.2. STUDY MONITORING

11.2.1. Monitoring visits

On-site visits will be carried out by a representative of the Sponsor's staff (Study Manager or CRA) prior to study initiation and at regular intervals to closely monitor the study throughout its duration. Additional visits and communication by telephone, mail, email, fax or meeting may be performed if necessary. Any site visit performed by the Sponsor's representatives will be recorded in the Investigator's site file.

11.2.1.1. Site Preselection Visit

Before selecting a center for the study, a visit will be carried out by the CRA and/or the Study Manager to ensure that the Investigator has the necessary capacities (availability subject, recruitment, environment), technical means and staff to carry out the study.

11.2.1.2. Initiation Visit

Before the start of the study at all investigational sites, an initiation visit will be carried out by the CRA to check at a minimum that:

- The Investigator:
  - has received the technical protocol, administrative and financial agreement signed by all parties
  - has received the written statement of the IEC/IRB approval and the list of its members and their functions
  - has received the written statement of Competent Authority approval
- The original dated and signed *curriculum vitae* of the Investigator(s) has been collected
- Laboratory normal ranges have been collected
- All study materials are available on the study site
- All participants agree with the monitoring procedures and know the study procedures
- All participants are aware of a possible audit or inspection

The CRA also has to provide training on the study protocol requirements and study specific procedures.

11.2.1.3. Follow-up Visits

Throughout the study, regular follow-up visits will be carried out by the CRA to check compliance with GCP, strict application of the protocol, subject's informed consents, proper retention, storage and management of the study treatment, as well as the source and other trial-related documents. It is the CRA's responsibility to inspect e-CRFs at regular intervals throughout the study to verify the completeness, accuracy and consistency of the data, to verify the conformity of the data entered into the e-CRF with the source documents and to ensure its correct completion, and AE reporting.

11.2.1.4. Closing Visit

At the end of the study, a final visit will be carried out by the CRA to:

- Verify that the copies of e-CRFs are correctly stored
- Control the accountability of intact and used treatment units before destruction
- Obtain the last data clarifications and/or solutions if any
- Make an on-site review of all study documentation and complete it if necessary
- Remind the Investigator of his/her regulatory obligations, study document archiving process and duration.

11.2.2. Direct Access to Source Documents

In accordance to the requirements of GCP, all Sponsor representatives (Study Manager, CRA and Auditors) must be given direct access to all source and study data to perform quality monitoring/audit, thus ensuring accuracy and completeness of data.

Investigators are reminded that all Sponsor representatives maintain professional confidentiality with regards to the subject data.

11.3. PERIODIC SAFETY DATA REVIEW

All safety data collected from the study (SAEs, AEs, clinical laboratory data, vital signs, physical examinations, ophthalmic examinations, dermatologic examinations, tumor assessments, ECG, ECHO/MUGA scans, etc.) are periodically reviewed by the medical monitor or designee to detect any potential safety signals during the study and to review safety critical data. The modalities of this safety signal detection review is described in a separate document.

11.4. STEERING COMMITTEE

A steering committee (SC) will be established comprising Investigators participating in the trial and Sponsors' representatives from the Clinical Study Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will be responsible for reviewing the safety data of the subjects treated in the study as well as reviewing efficacy results for ORR from the interim and final analyses.

The SC will review protocol amendments as appropriate. The details of the role of the Steering Committee will be defined in a SC charter.

11.5. IDSMC

An Independent Data Safety Monitoring Committee (iDSMC) will be established to perform additional review of available safety data at regular intervals to ensure that the overall safety of the trial remains acceptable. The iDSMC will also have the opportunity to review toxicities observed over time, in cycles of treatment beyond the first cycle. Following each meeting, the iDSMC will provide in writing, recommendations to the Sponsor whether to continue, modify, or stop the study in compliance with the iDSMC Charter.

The iDSMC membership, data to be reviewed, timing of the planned reviews as well as the operating procedures will be described in the iDSMC charter.

12. DATA MANAGEMENT

Data management will be subcontracted to a CRO brafunder the supervision of the Sponsor's Data Manager of the IRPF Biometry Department.

All clinical data related to the study will be collected and saved in a computerized database according to the following procedures.

12.1. DATA COLLECTION

12.1.1. Electronic Case Report Form (e-CRF)

An e-CRF will be developed for this study. The electronic Case Report Form (e-CRF) will be used to record all subject data required by the protocol.

The e-CRF should be compliant with FDA regulations (Guidance for industry: Computerized systems used in clinical investigations 2007), European regulations (GCP guidelines – ICH E6 R2), compliant with 21CFR part 11 (electronic records and electronic signatures) and Japanese regulations, fully validated, and should include an access control and a traceability system for data corrections (audit trail).

Prior to the start of the study, the Investigator will complete a delegation form. The signature and initials of all persons in charge of e-CRF completion should be recorded on this form. Each person involved in e-CRF completion, review, correction and/or validation will be trained and will then have an individual login and access code to the e-CRF. An e-CRF user guide will be available for Investigators/on-site personnel involved in e-CRF completion and for CRAs.

All information entered into the e-CRF will be recorded from source documents by authorized personnel. The Investigator is responsible for the management and accuracy of the information entered into the e-CRF.

Each local assessment or examination (ECG, Laboratory samples, Questionnaires, …) will be entered into the appropriate e-CRF forms by the designated investigational site staff at each site.
An e-CRF must be completed for each subject enrolled in the study (i.e. signed ICF).

12.1.2. Pharmacokinetics data

Actual dates and times of blood collections for study treatments dosing will be entered in both the e-CRF and the requisition form. Appropriate dates and times of study treatment intake will be entered in the e-CRF. The samples will be sent to a designated CRO for analysis.

Validated results from bioanalysis of treatments concentrations in plasma or serum will be transmitted by the bioanalytical center to the sponsor or designated CRO. The study treatment

concentrations will be uploaded in the final database from an electronic data file provided by the bioanalytical laboratory.

12.1.3. Biomarkers

Dates and actual times of biomarker samples will be entered in both the e-CRF and the requisition form.

***BRAF^{V600E}* mutation status:** is assessed by local laboratory and/or by central laboratory. Results from central laboratory will be sent to each site for validation of local result. The result from local laboratory will be entered by the designated investigational site staff at each site into the e-CRF as well as the confirmation provided by the central laboratory. The result from the central laboratory will be provided with an electronic data file.

Other biomarkers: The samples will be sent to sponsor or a designated CRO for analysis. If any of the biomarker analyses are intended to form part of the CSR, they will be transferred to the data management CRO for validation and integration into the study database.

CEA, CA 19-9: are assessed by local laboratory, and data will be entered into the appropriate e-CRF forms by the designated investigational site staff at each site.

12.1.4. Imaging

Local assessment (Main study and Study extension periods): scans will be assessed by local radiologists at the sites and RECIST measurements will be entered into the appropriate e-CRF forms by the designated investigational site staff at each site.

Central assessment (Main study period only): scans will then be submitted for a centralized review. The central imaging reader will review the scans and results will be provided with an electronic data file to the CRO.

12.2. DATA CLEANING

The Data Manager will define descriptions of manual and electronic edit checks in the study Data Validation Plan for reviewing and querying data. Upon approval, the edit checks and listings will be programmed.

The Data Manager will follow the cleaning of the data over the course of the study. The Investigator will be asked to resolve queries by making changes directly into the e-CRF. The system's automatic audit trail will record the date, time and author of the changes.

12.3. DATA CODING

AEs, concomitant diseases, medical/surgical histories will be coded using MedDRA dictionary (latest version in use).

Prior and concomitant medications will be coded using WHO-DRUG dictionary (latest version in use).

The coding will be validated by a physician.

12.4. DATABASE LOCK

The validated database will be locked upon request of the Sponsor's Data Manager following the completion of all required steps, i.e.: entry, reception and check of all data, resolution of all queries, validation of the coding, Clinical and Pharmacovigilance database reconciliation, and data review / validation committee meeting performed.

12.5. DATA STORAGE

Data and any modifications will be saved and kept available upon request of the Sponsor. The Sponsor's Data Manager will assume storage of the locked clinical database in SAS format on a secured server.

Electronic capture of all e-CRFs will be sent in PDF format to the Sponsor, and then stored on a dedicated secured server by the Sponsor.

A CD-ROM containing the PDF version of all e-CRFs of the site (including audit-trail) will be archived by the investigational site.

13. STATISTICAL ANALYSIS

13.1. GENERAL CONSIDERATIONS

A detailed statistical analysis plan (SAP) will be prepared by the Sponsor. This plan may modify the statistical methods outlined in the protocol; however, any major modifications related to the primary outcome measure definition or analysis will also be described in a protocol amendment.

The statistical analysis will be done under the supervision of the study statistician at the Biometry Department, IRPF. Analyses will be programmed in accordance with the SAP.

The CSR is planned to be written at the time of the primary outcome measure analysis (after Stage 1 if the study is stopped for futility, otherwise after Stage 2).

The cut-off date for futility analysis and Stage 2 analysis is estimated to occur approximately when all treated subjects with a centrally confirmed *BRAF*^{V600E} mutation of the concerned stage have either discontinued or have four post-baseline tumor assessments. And in case the last subject required for the concerned stage has an objective response, it should be confirmed in the following tumor assessment before the analysis is being performed. However, it will be possible to proceed to Stage 2 as soon as 40 subjects with a centrally confirmed *BRAF*^{V600E} mutation are treated and 12 confirmed responses are observed.

All available data will be included at the time of the cut-off date for secondary time-to-event endpoints and safety assessments. Unless the study is stopped at an earlier point in time, any further CSR update (or addendum) will be written at the end of study.

After the primary outcome measure analysis (after Stage 1 if the study is stopped for futility, otherwise after Stage 2), an analysis will be performed at the end of the Main study period, and at the end of the Study extension period).

Descriptive methods will be used to present all relevant data:

- Continuous data will be summarized with: frequency, median, range, mean, standard deviation and standard error if relevant.
- Categorical data will be presented in contingency tables with frequencies and percentages of each modality.

13.2. OUTCOME MEASURES

13.2.1. Primary outcome measure

The best overall confirmed response assessed per RECIST v1.1 will be used to evaluate the tumor response in terms of cORR for the combination of encorafenib, binimetinib and cetuximab. This will be based on local radiologist/investigator-assessed tumor evaluations.

The cORR is defined as the number of subjects achieving an overall best confirmed response of CR or PR divided by the total number of subjects. This may also refer to as confirmed 'objective response rate' in some protocols or publications.

13.2.2. Secondary outcome measures

The following secondary outcome measures will be determined:

- The cORR assessed by central radiologist review.
- The ORR (for confirmed + unconfirmed responses) based on local radiologist/investigator-assessed tumor evaluations, and ORR assessed by central radiologist review.
- Overall survival defined as the time from first dose to death due to any cause. If a subject is not known to have died, survival will be censored at the date of last known date the subject was alive or at the cutoff date, whatever is earlier. OS will be calculated for FAS (**see Section 13.5**).

- Progression-free survival, defined as the time from first dose to the earliest documented date of disease progression or death due to any cause, per RECIST v1.1 and as determined by local radiologist/investigator assessments. Tumor assessment assessed by central review will be also used in a supportive analysis of PFS.
- Duration of response is defined as the time from first radiographic evidence of response to the earliest documented PD or death due to underlying disease and is calculated for responders only. Responders who do not have a PD or death date by the data cutoff date will be censored for DOR at their last adequate tumor assessment of CR, PR or SD prior to the cutoff date. It will be assessed based on local radiologist/investigator review and central radiologist review.
- Time to response (CR or PR) is defined as the time from first dose until first documented radiographic evidence of response of CR or PR. Subjects who do not have a CR or PR by the cutoff date will be censored for TTR at their last adequate tumor assessment date. It will be assessed based on local radiologist/investigator review and central radiologist review.

Endpoints for Study extension period will be based on local radiologist/investigator review only

13.3. SAMPLE SIZE

The sample size is based on a two-stage design with nominal alpha=2.5% and beta=20%. The null hypothesis that the true response rate is 30% will be tested against a one-sided alternative. In the first stage, 40 subjects will be treated. In case of discordance in the results between the local assay and the central laboratory (potential false-positive local result), or lack of $BRAF^{V600E}$ confirmation, subject will be replaced. If there are 11 or fewer confirmed responses in the 40 treated subjects with a centrally confirmed BRAF $BRAF^{V600E}$ mutation, inactivity will be declared and the study will be stopped for futility.

If the study continues to the second stage, 50 additional subjects will be treated to achieve a total of 90 subjects. In case of discordance in the results between the local assay and the central laboratory (potential false-positive local result), or lack of $BRAF^{V600E}$ confirmation, subject will be replaced. The null hypothesis will be rejected if 37 or more confirmed responses are observed in 90 treated subjects with a centrally confirmed $BRAF^{V600E}$ mutation. This design yields a 1-sided type I error rate equal to 1.6% and power of 80% when the true response rate is 45%.

The sample size calculation was based on binomial probabilities calculated in R (version 3.2.3).

This binomial design matches the O'Brien-Fleming design (**O'Brien, 1979**) for one sample obtained using East software (version 6.4) with a 1-sided type I error rate equal to 2.5% and a power of 81%.

If 37 confirmed responders are observed in 90 subjects, the Clopper-Pearson (exact) binomial 95% confidence interval would be [30.8%, 52.0%] with the lower limit exceeding the clinically relevant response rate of 30%.

13.4. PROTOCOL DEVIATIONS

A protocol deviation will be considered major when it is likely to significantly bias the estimate of the primary outcome measure.

Major protocol deviations will be identified using the list of pre-defined reasons for exclusion from analysis sets for the study described in a specific document separately from the statistical analysis plan.
All deviations will be reviewed and classified as major or minor before analysis.

All protocol deviations linked to COVID-19 pandemic will be identified in the list of protocol deviations with a dedicated code and will be reviewed on a regular basis by the Study Sponsor, and by iDSMC.

Subjects with major deviations will be excluded from the Per Protocol set (see **Section 13.5**)

13.5. ANALYSIS SETS

For inclusion in any analysis set, it is required that a subject has signed his/her informed consent.
The analysis sets are defined as follows:

- The **Full Analysis Set** (FAS) is composed of all included subjects having received at least one dose of study treatment (partial or full). Unless otherwise specified, the FAS will be the default analysis set used for all analyses.

- The **Efficacy Set** (ES) is composed of all FAS subjects with a centrally confirmed *BRAF*^{V600E} mutation. The ES will be the analysis set used for the primary analysis of the main criterion and all other efficacy analyses.
- The **Per Protocol Set** (PPS) will consist of all subjects from the FAS without any major protocol deviations. The PPS will be the analysis set used for the supportive analysis of the main criterion.
- The **PK Set** will consist of all subjects who receive at least 1 dose of encorafenib, binimetinib or cetuximab and who have at least 1 post-dose PK blood collection with associated bioanalytical results.

13.6. HANDLING OF DROPOUTS AND MISSING DATA

As of the date of data-cutoff for the primary CSR for the purposes of reporting:

Subjects continuing to receive study drugs at the time of analysis will have time-to-event data (e.g., PFS, DOR) censored at the time of last tumor assessment prior to the data cut-off point used. Ongoing events (e.g., AEs, concomitant medication, etc.) will be summarized using the data cut-off date as the date of completion, with an indication that the event is ongoing.

For subjects who drop out from the study with ongoing events, the discontinuation date will be used as the completion date of the event with the appropriate censoring.

The reason for discontinuation from study will be summarized, along with the dates of first and last study drugs, duration of exposure to study drugs and date of discontinuation for each subject.

Specific details regarding the handing of missing data will be included in the statistical analysis plan.

13.7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Baseline subject characteristics including demographics and other baseline data, ECOG PS, histology, primary site of disease and medical history will be summarized using the ES and FAS.

Demographic and disease characteristics will be also summarized for the subgroup of Japanese subjects.

13.8. ANALYSIS OF OUTCOME MEASURES

Efficacy analyses will be conducted using the ES and FAS. A supportive analysis of the primary outcome will be conducted using the PPS.

13.8.1. Analysis of Primary Outcome Measure

13.8.1.1. Primary Analysis

The cORR will be provided with a corresponding Clopper-Pearson (exact) binomial 95% CI (**Clopper CJ et al, 1934**) for the ES. As detailed (in **Section 13.3**), the two-stage method will be used to test the null hypothesis with the possibility of stopping accrual earlier for futility. If the observed cORR at the end of the first stage is less than 28% (i.e., ≤ 11 confirmed CRs and/or PRs among 40 treated subjects with a centrally confirmed *BRAF*^{V600E} mutation), then insufficient efficacy will be concluded. Otherwise, at the end of stage 2, if the observed ORR is ≥41% (i.e., ≥37 confirmed responses among 90 treated subjects with a centrally confirmed *BRAF*^{V600E} mutation), the null hypothesis will be rejected.

13.8.1.2. Supportive Analysis

The cORR will be provided with a corresponding Clopper-Pearson (exact) binomial 95% CI for the PPS and FAS (see **Section 13.5**).

13.8.1.3. Exploratory Analysis

Exploratory analyses may be performed on various subgroups such as by age (< 65 vs. ≥ 65 years old), gender, CRP levels (>ULN and <ULN), MSI status (high and low), location of primary disease and possibly others. The primary endpoint and the corresponding 95% CI will be displayed using a forest plot by subgroups. Further details including the precise subgroups used will be detailed in the SAP.

cORR based on investigator-assessed tumor evaluation for the subgroup of Japanese subjects will also be examined separately.

13.8.2. Analysis of Secondary Outcome Measures

The cORR based on central review, and ORR (for confirmed + unconfirmed responses) based on local radiologist/investigator-assessed tumor evaluations and central radiologist review will be provided with a corresponding Clopper-Pearson (exact) binomial 95% CI for the ES and FAS.

The Kaplan-Meier (KM) method used to describe OS will present median time with 95% CI and estimates at several time points (including 2, 4, 6, 8, 10 and 12 months). Subjects without a death date by the data cut-off date will be censored for OS at their last contact date.

PFS will be calculated for the FAS and summarized using the KM method. The corresponding median PFS as well as PFS rates at selected time points (e.g. 3 and 6 months) will be provided with a 95% CI.

Progressive disease and death from any cause will be considered as events. If death or PD is not observed, the PFS will be censored at the date of last adequate tumor assessment prior to the cutoff date. However, if a PFS event is observed after more than 1 missing or inadequate tumor assessment, it will be censored at the last adequate tumor assessment. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used.

Subjects who received a new anti-tumoral treatment (chemotherapy, hormonotherapy, radiotherapy, surgery or other anti tumoral treatment), whatever the type of treatment before their disease progression will be censored at the last adequate assessment prior to the start date of the new antitumoral treatment.

Additional sensitivity analyses examining alternative censoring rules could be applied and will be described in the SAP.

Analysis of DOR and TTR will be summarized using KM method in a similar way.

Secondary outcomes measures in the subgroup of Japanse subjects will be examined separately.

13.9. SAFETY ANALYSIS

The FAS will be used to perform all analyses of the safety criteria.

13.9.1. Treatment exposure

Duration of study drug exposure, actual and relative dose intensity will be summarized. The number of subjects with dose changes/interruptions will be presented, along with reasons for the dose change. The actual daily doses and reasons for dose change will be listed. These analyses will be applied for each study drug individually on the FAS.

Separate summaries will be generated for the subgroup of Japanese subjects.

13.9.2. Adverse Events

Any AE reported during the study for a given subject will be classified by preferred term and corresponding system organ class using the MedDRA terminology.

The occurrence of an AE will be defined by the appearance of a new single event, the reappearance of a previously recovered event or the worsening of a continuous event (relative to its previous status).

A treatment emergent adverse event (TEAE) is defined as any event that first occurred during the treatment period (i.e. from first treatment administration date up to last administration date + 30 days) or that worsened during that study period.

Summary tables will display the number and percentage of subjects with TEAEs overall and by maximum grade, system organ class (SOC) and preferred term (PT). A subject with multiple occurrences of an AE will only be counted under the maximum NCI-CTCAE grade for this AE.

Similar analyses will also be performed for TEAEs assessed as related to study treatment by the investigator.

SAEs will also be described on an individual basis: subject's code, sex and age, Investigator's reported term, preferred term, date of the first study treatment administration, duration of each study drug, action taken regarding the study treatments administration, use of a corrective treatment, outcome and relationship to the study treatments in the Investigator's opinion.

Categories of adverse events of special interest (AESIs) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study drugs. These analyses will be specified in the SAP.

The number and percentage of subjects with at least one AE occurring before the first administration will be tabulated by MedDRA SOC and PT.

As per the EudraCT requirement: The number and percentage of subjects with at least one TEAE, and the number of occurrences of TEAEs, will be tabulated by MedDRA SOC, PT and seriousness (by descending order of frequency).

The same analysis will be performed for TEAEs assessed as related to study treatment by the investigator.

AE analyses will be generated for the subgroup of Japanese subjects.

All Adverse Events related to COVID-19 pandemic will be flagged in listings to assess any potential impact of the pandemic on the study integrity and subjects' safety. These Adverse Events will be reviewed by iDSMC.

13.9.3. Clinical Safety Laboratory Evaluation

For each hematology and chemistry laboratory parameter, data will be tabulated over time and plots of measurements over time will be generated for selected parameters.

The absolute changes in post-trial treatment administration versus baseline (the baseline value being the value measured on the last blood sample collected before the first study treatments administration) will be calculated and tabulated by parameter and post-trial treatment administration

assessment time. Results of retests performed post-trial treatment administration will not be analyzed and tabulated and will only be displayed in individual data listings.

For laboratory tests covered by the NCI-CTCAE v4.03, laboratory data will be graded accordingly. For laboratory tests covered by the NCI-CTCAE, Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. Shift tables of baseline grade vs. maximum grade on study will be presented.

For laboratory parameters that are not gradable by NCI-CTCAE, shift tables of normal-abnormal will be provided.

Analyses of laboratory data will be generated for the subgroup of Japanese subjects.

13.9.4. Other Safety Data

Vital signs, body weight, ECOG PS, ECG, dermatologic and ophthalmic examination data will be summarized descriptively over time for values and changes from baseline and/or with shift tables if applicable. Summaries of clinically notable measurements will also be provided. Definitions will be detailed in the SAP.

13.10.QUALITY OF LIFE ANALYSIS

Quality of Life will be evaluated through the EORTC QLQ-C30, EQ-5D-5L QoL and PGIC questionnaires.

Descriptive statistics will be used to summarize the scores over time on the FAS. Additionally, changes from baseline for EORTC QLQ-C30 and EQ-5D-5L scores will be described over time. Further analysis will be detailed in the SAP.

13.11.EXPLORATORY ANALYSIS

The relationship between protein levels, mutations and/or gene expression and clinical outcomes may be explored. Details of all exploratory analyses will be provided in the SAP.

13.12. CONCOMITANT THERAPIES AND THERAPEUTIC/ DIAGNOSTIC PROCEDURE

Concomitant therapies prior to and after the start of the study treatments will be tabulated from a descriptive perspective. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical (ATC) classification for the FAS.

These summaries will include medications starting on or after the start of study drugs or medications starting prior to the start of study drugs and continuing after the start of study drugs.

Any other medications starting and ending prior to the start of study drugs will be listed.

Numbers and percentages of subjects with at least one concomitant therapeutic / diagnostic procedure will be tabulated by treatment group, SOC and PT using the MedDRA terminology.

13.13. HEALTHCARE RESOURCE UTILIZATION

Type of hospital facility, reason and length of hospitalization and hospital discharge will be summarized descriptively on the FAS.

13.14. PHARMACOKINETICS ANALYSIS

Plasma concentrations of encorafenib, binimetinib and the active metabolite of binimetinib (AR00426032) and related descriptive statistics will be summarized. Serum concentrations of cetuximab and related descriptive statistics will be reported in tables.

Given the sparse PK sample collection, PK parameters for encorafenib, binimetinib and the active metabolite of binimetinib (AR00426032) and cetuximab may be generated by a compartmental approach such as a population approach, as appropriate. Details of these analyses and of the incorporation of prior information to support the model building will be provided in a specific standalone modeling plan. Analyses will be provided in a separate report.

Relationships between PK and biomarkers, clinical response and/or safety will be explored if appropriate and if data quality is adequate. Details of analyses will be included in a specific standalone modeling plan and results will be reported separately.

13.15.INTERIM ANALYSIS

The two-stage design involves an interim analysis to allow for the possibility of stopping the study early for futility.

The interim analysis of the cORR is planned and based on the 40 treated subjects from stage 1 of the study.

The time point for the futility analysis will be after all 40 treated subjects of stage1 with centrally confirmed *BRAF*^{V600E} mutation had the opportunity to complete four post baseline tumor assessment. And in case last subject required for the futility analysis has an objective response, it should be confirmed in the following tumor assessment before the futility analysis is performed.

However, it will be possible to proceed to Stage 2 as soon as 40 subjects with a centrally confirmed *BRAF*^{V600E} mutation are treated and 12 confirmed responses are observed.

Subjects data that will be analyzed during the futility analysis will be reviewed on an ongoing basis in order to determine as soon as possible (even before the inclusion of the 40th subject) whether the criteria for continuing to stage 2 (12 confirmed responses) have been met.

As it may take several treatment cycles for subjects to achieve a confirmed response, if 12 confirmed responses are not observed at the time the 40th subject is treated in Stage 1, a limited number of subjects (maximum 12) subjects from stage 2 may be treated while waiting for all subjects in the initial cohort of 40 subjects in Stage 1 to be evaluable for a confirmed response providing no safety concern was raised by the iDSMC. They will not count towards responses in Stage 1 but will be included as part of the Stage 2 cohort, should the study move forward into Stage 2.

If at any time it becomes evident that the threshold of 12 responses is unlikely to be met, then additional subjects may not be recruited (eg: 6 or fewer responses among 35 subjects with sufficient follow up [potential for at least 2 assessments]).

If 11 or fewer confirmed responses are observed in subjects with centrally confirmed *BRAF*^{V600E} mutation in stage 1, the treatment will be deemed not efficacious. Inactivity will be declared and the study will be stopped for futility.

If 12 or more confirmed responses are observed in stage 1, 50 additional subjects with a centrally confirmed *BRAF*^{V600E} mutation have to be treated. The cut-off for stage 2 analysis will be after all 90 treated subjects of stage 1 and 2 with centrally confirmed *BRAF*^{V600E} mutation had the opportunity to complete four post-baseline tumor assessments, and after subjects with an initial objective response have had an opportunity to have a confirmation scan.

An SC will review the primary outcome and safety data for the interim and final analyses (see **Section 11.4**).

An iDSMC will review the available safety information at regular interval (see **Section 11.5**). Analyses for iDSMC will be based on safety, thus this will not affect the statistical operating characteristics of the Stage 1 and Stage 2 analyses.

14. GENERAL ETHICAL CONSIDERATIONS

14.1. ETHICAL CONDITIONS

This study is performed in accordance with the principles stated in the Declaration of Helsinki and subsequent amendments and in accordance with the Good Clinical Practice Guideline (EMA/CHMP/ICH/135/1995).

14.2. INDEPENDENT ETHICS COMMITTEE AND LEGAL REQUIREMENTS

All documents required by National Regulations and any other informative documents that may be requested are submitted for review to the appropriate IEC/IRB whose procedures and operations meet national legal requirements.

Depending on national regulations, the application is submitted to the IEC/IRB by the Sponsor or by the Investigator.

A copy of the formal written approval from the IEC/IRB is provided to the Sponsor (directly by the IEC/IRB or via the Investigator) with a list of names and qualifications of its members. The request for authorization by the Competent Authority or notification (depending on national regulations) is carried out by the Sponsor.

Screening of subjects will not start before the approval of the IEC/IRB has been obtained and the study was authorized by the Competent Authority (or notified to the Competent Authority, depending on the national regulations).

14.3. SUBJECT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM

Information must be given to each subject before his/her decision to participate or abstain from participation. This information is based on the elements set out in the Declaration of Helsinki and the ICH GCP guideline. It must also describe the measures taken to safeguard subject's privacy and protection of personal data, according to EU General Data Protection Regulation (2016/679).

Restraints and risks must be explained, as well as the right to discontinue participation in the study at any stage, without affecting their further relationship with the Investigator and/or their future care.

The written information and consent form must be submitted to the subject with an oral explanation. It must be agreed and signed by the subject before any study-related procedure starts.

This information and consent procedure is under the Investigator's responsibility.

The information and consent documents are prepared in duplicate: the original copy is kept by the Investigator, and the other copy is given to the subject.

If any information becomes available during the trial that may be relevant to the subject's willingness to continue participating in the trial, an updated written informed consent must be submitted to the subject to confirm his/her agreement to continue participating.

14.4. PERSONAL DATA PROTECTION

All information from this study (excluding data from the informed consent) are captured in an electronic database into a computer under the Sponsor's responsibility in accordance with the French law, "Loi Informatique et Libertés" (January 6, 1978 and subsequent amendments) and with the EU General Data Protection Regulation (2016/679).

14.5. INSURANCE POLICY

In accordance with the provisions of the law and GCP, the Sponsor Pierre Fabre Medicament has an insurance policy intended to guarantee against possible damage resulting from the research.

The studies and/or experiments performed on behalf of the Sponsor Pierre Fabre Medicament are specifically and expressly guaranteed.

It is advisable to underline that non-compliance with the Research Legal Conditions is a cause for guarantee exclusion.

Unintentional infringements and vicarious liability are covered by our insurance**.**

14.6. FINANCIAL CONSIDERATIONS

The funding of research is provided by the Sponsor (Investigator fees, study costs, subject compensation for travel expenses, etc.).

By signing the protocol, the Investigator declares no conflicts of interest.

15. ADMINISTRATIVE PROCEDURES

15.1. PROTOCOL AMENDMENTS

Neither the Investigator nor the Sponsor may alter the protocol without the authorization of the other party. All changes to the protocol will be subject to an amendment which must be dated and signed by both parties and must appear as an amendment to the protocol.

Substantial amendments are submitted for approval/authorization to the IEC/IRB and Competent Authorities. Urgent amendments are submitted for approval/authorization to the IEC/IRB and Competent Authorities but may be implemented immediately under specific conditions defined with the Sponsor.

15.2. SOURCE DOCUMENTS, INVESTIGATOR'S FILE STORAGE

The Investigator:

- keeps all trial-related documents in appropriate file folders. Records of subjects, original ICFs, source documents, e-CRFs, treatment inventory, IEC/IRB and Sponsor correspondence pertaining to the study must be kept on file,

- retains all documents relating to the screening (consent and investigation results) of all subjects screened in the trial or not,

- retains a list of the subjects' names, addresses (and/or number of medical file), code numbers, dates of entry into and completion of the trial period, to allow checking of data reported on e-CRFs with those from source documents,

- authorizes direct access to source documents for monitoring, audits and inspections.

The trial-related documents must be retained as strictly confidential at the Investigator's site for a duration of 25 years or according to local requirements, after the completion or discontinuation of the trial.

15.3. END OF STUDY

15.3.1. Definition of the end of study

The end of the study is defined as the time point when all treated subjects will have either progressed or discontinued study treatments (including 30-day Safety Follow-Up visit) for any other reason (unacceptable toxicity, subject's decision, withdrawal of consent, initiation of subsequent anticancer therapy or death).

15.3.2. Supply of product after Main study period

After the Main study period (from first subject screened to 1 year after the start of study treatment of the last subject enrolled – 27 Dec 2020), access to study treatment will be provided through a Study extension period (from 28 Dec 2020) to all subjects whom the investigator considers are continuing to benefit from study treatment.

These subjects will receive treatment with encorafenib/binimetinib/cetuximab as long as they continue to demonstrate benefit and do not experience unacceptable toxicities and as long as none of the treatment discontinuation criteria are met or until binimetinib/encorafenib are commercially available in the first line setting of *BRAF* ^{V600E} mutated mCRC or until the binimetinib/encorafenib development program is stopped (whichever comes first).

15.4. AUDIT

The purpose of a sponsor's audit, independent of and separate from monitoring or quality control activities, is to evaluate trial conduct and compliance with the protocol, sponsor's standard operating procedures, Good Clinical Practice, and the applicable regulatory requirements.

Audits may be conducted by the sponsor's Clinical Quality Assurance Department or delegate at each relevant location where activities dedicated to clinical trial are performed: for example at sponsor's site(s), at the investigational site(s), at CRO(s) site(s) and laboratory(ies) if applicable.

All study related documentation must be directly accessible to auditors.

The practical conditions for the audit are discussed between the auditees and the sponsor's Clinical Quality Assurance Department or their delegate.

15.5. INSPECTION

The relevant Health Authorities may inspect any investigational site or the Sponsor during the course of the study or after its completion, to verify the conduct of the study and quality of the data. The Investigator must provide direct access to the respective source documents.

15.6. CONFIDENTIALITY

The study materials (protocol, e-CRF, Investigator's brochures) contain confidential information. Except if agreed to in writing with the Sponsor, the Investigators must hold such information confidential, and must not disclose it to others (except where required by applicable law).

15.7. CLINICAL STUDY REPORT

Data analysis and CSR writing are the Sponsor's responsibility. Upon completion of the data analysis, a final report including a review of the objectives and methods, a presentation and discussion of the results are drawn up according to ICH Guidelines (Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95.

The report is a clinical, (and) statistical, and pharmacokinetic integrated report. It must be signed by the sponsor's representative(s) and the coordinating Investigators.

15.8. STUDY RESULTS COMMUNICATION

Within a maximum period of 12 months after study completion global results of the research will be communicated to the Investigator.

According to the local regulations, subjects can ask the Investigator for the results.

If this study is part of a marketing authorisation application, its results will be published on the European Medicines Agency (EMA) website and on Pharmaceuticals and Medical Devices Agency

(PMDA) website (Japan). In that case, the documents will be anonymised to ensure data protection of individuals.

15.9. STUDY RESULTS PUBLICATION

The results of this study including data, reports, discoveries and inventions are the property of the Sponsor and are considered as confidential. Subject to any applicable laws in force, the Sponsor retains the right to be the first to publish or communicate the results of the study. In any case, no publication or communication relating to results of the study, in written or oral form, shall be made without Sponsor's prior written consent and shall comply with the following provisions:

- any communication or publication project must be provided to the Sponsor for review at least 60 days prior to the expected date of submission to the intended publisher or of planned presentation.

If requested by the Sponsor, the communication or publication project shall be withheld for an additional 60 days, to allow the filing of a patent application, or to allow the Sponsor to take any measures deemed appropriate to establish and preserve proprietary rights.

In case of a multicentric study, the Sponsor, in consultation with the SC, shall determine the author's list and order within the publication project according to their participation in the design of the protocol as well as their recruitment of eligible and analyzable subjects.

16. REFERENCES

Baselga J, Trigo JM, Bourhis J, et al.
Phase 2 multicenter study of the anti-epidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck.
J Clin Oncol. 2005;23:5568-77.

Benson AB 3rd, Venook AP, Cederquist L, Chan E, Chen YJ, Cooper HS, Deming D, Engstrom PF, Enzinger PC, Fichera A, et al: Colon Cancer, Version 1, 2017, NCCN
Clinical Practice Guidelines in Oncology.
J Natl Compr Canc Netw. 3: 370-398, 2017.

Binimetinib Investigator's Brochure _Current version

Bokemeyer C, Bondarenko I, Hartmann JT, et al.
Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study.
Ann Oncol. 2011;22(7):1535–46.

Bokemeyer C, Van Cutsem E, Rougier P, et al.
Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: Pooled analysis of the CRYSTAL and OPUS randomised clinical trials.
Eur J Cancer. 2012;48:1466-75.

Bonner JA, Harari PM, Giralt J, et al.
Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck.
N Engl J Med. 2006;354:567-78.

Bouchahda M, Macarulla T, Liedo G, et al.
Feasibility of cetuximab given with a simplified schedule every 2 weeks in advanced colorectal cancer: a multicenter, retrospective analysis.
Med Oncol. 2011;28(suppl 1):S253–S258.

Cetuximab Summary Of Product Characteristics

Clinical Trials Facilitation Group (CTFG)
Recommendations related to contraception and pregnancy testing in clinical trials. Final Version 2014-09-15.
http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Carneiro BA, Ramanathan RK, Fakih MG, et al.
Phase II study of irinotecan and cetuximab given every 2 weeks as second-line therapy for advanced colorectal cancer.
Clin Colorectal. 2012;11:53–59.

Clopper CJ, Pearson ES.
The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial.
Biometrika; 1934, 26(4): 404-413.

Corcoran RB, Ebi H, Turke AB, et al.
EGFR-mediated reactivation of MAPK signaling contributes to insensitivity of BRAF-mutant colorectal cancers to RA F inhibition with vemurafenib.
Cancer Discov. 2012;2(3):227-35.

Corcoran RB, Dias-Santagata D, Bergethon K, et al.
BRAF gene amplification can promote acquired resistance to MEK inhibitors in cancer cells harboring the BRAF V600E mutation.
Sci Signal.2010;3:ra84

Corcoran RB, André T, Yoshino, JC.
Efficacy and circulating tumor DNA (ctDNA) analysis of the BRAF inhibitor dabrafenib (D), MEK inhibitor trametinib (T), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAF V600E–mutated (BRAFm) metastatic colorectal cancer (mCRC).
Ann Oncol. 2016;27:abstr 455º

Cremolini C, Loupakis F, Antoniotti C, et al.
FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study.
Lancet Oncol. 2015;16:1306-1315.

Cunningham D, Humblet Y, Siena S, et al.
Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.
N Engl J Med. 2004;351:337-45.

De Roock W, Claes B, Bernasconi D, et al.
Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis.
Lancet Oncol. 2010;11:753-62.

Di Nicolantonio F, Martini M, Molinari F.
Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer.
J Clin Oncol. 2008;26:5705-12.

Douillard JY, Oliner KS, Siena S, et al.
Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer.
N Engl J Med 2013;369:1023–1034.

Dummer R, Robert C, Nyakas M, et al.
Initial results from a phase I, open-label, dose escalation study of the oral BRAF inhibitor LGX818 in patients with BRAF V600 mutant advanced or metastatic melanoma.
J Clin Oncol. 2013;31: suppl;abstr 9028.

Dummer R, Ascierto PA, Gogas H, et al
Results of COLUMBUS part 1: A phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) Versus Vemurafenib (VEM) or ENCO in BRAF-Mutant Melanoma.
Presentated at: The society for melanoma Research 2016 Congress; November 6-9, 2016; Boston Massachusetts

Dummer *R,* Ascierto *PA,* Gogas *H*, et al.
Results of COLUMBUS Part 2: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) versus ENCO in BRAF-mutant melanoma.
Annals of Oncology, Volume 28, Issue suppl_5, 1 September 2017, mdx377.002

Dummer R, Schadendorf D, Ascierto PA, et al.
Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial.
Lancet Oncol 2017; 18:435–445.

Encorafenib Investigator's Brochure _ Current version

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ERB-0005-USPI-20190423

Gomez-Roca CA, Delord J, Robert C, et al.
Encorafenib (LGX818), an oral BRAF inhibitor, in patients (pts) with BRAF V600E metastatic colorectal cancer (mCRC): Results of dose expansion in an open-label, phase 1 study.
Ann Oncol. 2014;25(suppl 4):iv167-iv209.

Ince WL, Jubb AM, Holden SN, Holmgren EB, Tobin P, Sridhar M, Hurwitz HI, Kabbinavar F, Novotny WF, Hillan KJ, et al.
Association of k-ras, b-raf, and p53 status with the treatment effect of bevacizumab.
J Natl Cancer Inst. 2005;97(13):981–989.

Kopetz S, McDonough S,Lenz HJ.
Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406).
J Clin Oncol. 2017;35:abst 3505

Lacouture ME, Anadkat MJ, Bensadoun RJ et al.
Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities.
Support Care Cancer 2011;19:1079–95

Loupakis F, Cremolini C, Salvatore L et al.
FOLFOXIRI plus bevacizumab as first-line treatment in BRAF mutant metastatic colorectal cancer
Eur J Cancer 2014; 50: 57–63.

Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, Idziaszczyk S, Harris R, Fisher D, Kenny SL, Kay E, Mitchell JK, Madi A, et al.,

and MRC COIN Trial Investigators. Addition of cetuximab to oxaliplatinbased first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial.
Lancet. 2011; 377:2103–14.

Martin-Martorell P, Rosello S, Rodriguez-Braun E, et al.
Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy:results of a phase II single institution trial.
Br J Cancer. 2008;99:455–458

Mesa AM, Gotlib J, Gupta V, et. al.
Effect of ruxolitinib therapy on myelofibrosis-related symptoms and other patient-reported outcomes in COMFORT-1: A randomized, double-blind, placebo-controlled trial.
J Clin Oncol. 2013;31:1285-92.

Morris V, Overman MJ, Jiang ZQ, et al.
Progression-free survival remains poor over sequential lines of systemic therapy in patients with BRAF-mutated colorectal cancer.
Clin Col Cancer Res. 2014;13:164-71

Mrabti H, De la Fouchardiere C, Desseigne F, et al.
Irinotecan associated with cetuximab given every 2 weeks versus cetuximab weekly in metastatic colorectal cancer.
J Cancer Res Ther. 2009;5:272–276.

Nardone B, Hensley JR, Kulik L, et al.
The effet of hand-foot skin reaction associated with the multikinase inhibitors Sorafenib and Sunitinib on health-related quality of life
JDD, 2012,Volume 11, Issue 11, article 61

(O'Brien)
A Multiple Testing Procedure for Clinical Trials
Biometrics . (1979). 35:549–556

Pfeiffer P, Bjerregaard JK, Qvortrup C.
*Every second week cetuximab (cet) and irinotecan (iri) as third line therapy in patients with advanced colorectal cancer (ACRC)***.**
Presented at the 2007 American Society of Clinical Oncology Gastrointestinal Cancers Symposium,

Pfeiffer P, Nielsen D, Bjerregaard J, et al:
Biweekly cetuximab and irinotecan as thirdline therapy in patients with advanced colorectal cancer after failure to irinotecan, oxaliplatin
and 5-fluorouracil.
Ann Oncol. 2008;19:1141–1145.

Prahallad A, Sun C, Huang S, et al.
Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR.
Nature 2012;100:100-4.

Roca JM, Alonso V, Pericay C, et al:
Cetuximab given every 2 weeks plus irinotecan is an active and safe option for previously treated patients with metastatic colorectal cancer.
Chemotherapy. 2010; 56:142–1460

Rozek LS, Herron CM, Greenson JK, Moreno V, Capella G, Rennert G, et al.
Smoking, gender, and ethnicity predict somatic BRAF mutations in colorectal cancer.
Cancer Epidemiol Biomarkers Prev. 2010;19(3):838–43.

Shaukat A, Arain M, Thaygarajan B, Bond JH, Sawhney M.
Is BRAF mutation associated with interval colorectal cancers?
Dig Dis Sci. 2010;55(8):2352–6.

Shitara K, Yuki S, Yoshida M, et al.
Phase II study of combination chemotherapy with biweekly cetuximab and irinotecan for wild-type KRAS metastatic colorectal cancer refractory to irinotecan, oxaliplatin, and fluoropyrimidines.
Invest New Drugs. 2012; 30:787–793.

Smith CG, Fisher D, Claes B et al.
Somatic profiling of the epidermal growth factor receptor pathway in tumors from patients with advanced colorectal cancer treated with chemotherapy þ/- cetuximab.
Clin Cancer Res 2013; 19: 4104–4113.

Sobrero AF, Maurel J, Fehrenbacher L, et al.
EPIC: Phase 3 trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer.
J Clin Oncol. 2008;26:2311-9.

Sorbye H, Dragomir A, Sundström M, Pfeiffer P, Thunberg U, Bergfors M et al.
High BRFA mutation frequency and marked survival differences in subgroups according to KRAS/BRAF mutation status and tumor tissue availability in a prospective population-based metastatic colorectal cancer cohort.
PLoS One 2015;10(6)e0131046.

Stintzing S, Jung A, Rossius L et al.
Mutations within the EGFR signaling pathway: influence on efficacy in FIRE-3–A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients.
J Clin Oncol 2014; 32: 445.

Tabernero J, Cervantes A, Martinelli E et al.
Optimal dose of cetuximab (C) given every 2 weeks (q2w): A phase I pharmacokinetic (PK) and pharmacodynamics (PD) study of weekly (q1w) and q2w schedules in patients (pts) with metastatic colorectal cancer (mCRC).
J Clin Oncol 2006;24(18 suppl):142s.

Tabernero J, Pfeiffer P, Cervantes A.
Administration of cetuximab every 2 weeks in the treatment of metastatic colorectal cancer: an effective, more convenient alternative to weekly administration.

Oncologist.2008;13:113–119.

Tabernero J, Ciardiello F, Rivera F, et al.
Cetuximab administered once every second week to patients with metastatic colorectal cancer: a two-part pharmacokinetic/pharmacodynamics phase I dose-escalation study.
Ann Oncol. 2010;21:1537–1545.

Tabernero J, Van Geel R, Kyrre Guren T, Rona D. Yaeger, Anna Spreafico, Jason Edward Faris, Takayuki Yoshino, Yasuhide Yamada, Tae Won Kim, Johanna C. Bendell, Martin H. Schuler, Heinz-Josef Lenz, Ferry Eskens, Jayesh Desai, Howard S. Hochster, Emin Avsar, Tim Demuth, Victor Sandor, Elena Elez, and Jan H.M. Schellens
Phase 2 results: Encorafenib (ENCO) and cetuximab (CETUX) with or without alpelisib (ALP) in patients with advanced BRAF-mutant colorectal cancer (BRAFm CRC).
Journal of Clinical Oncology 2016, 34:15_suppl, 3544-

Thakur MD and Stuart DD
Molecular pathways: Response and resistance to BRAF and MEK inhibitors in BRAFV600E tumors.
Clin Cancer Res. 2014;20:1074-80.

Tol J and Punt CJ.
Monoclonal antibodies in the treatment of metastatic colorectal cancer: a review.
Clin Ther 2010;32(3):437-53.

Tveit KM, Guren T, Glimelius B et al.
Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study.
J Clin Oncol 2012; 30: 1755–1762.

Van Cutsem E, Kohne CH, Hitre E, et al.
*Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer.*N Engl J Med 2009; 360:1408-17.

Van Cutsem E, Köhne CH, Láng I, Folprecht G, Nowacki MP, Cascinu S, et al.
Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status.
J Clin Oncol. 2011;29(15):2011–9.

Van Cutsem E, Cervantes A, Nordlinger B, et al.
Metastatic colorectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up.
Ann Oncol. 2014;25 (suppl 3):iii1-iii9.

Van Cutsem E, Atreya C, André T.
Updated results of the MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in patient (pts) with BRAF V600E mutated (BRAFm) metastatic colorectal cancer (mCRC)
Ann Oncol. 2015;26(suppl 4):iv117-iv121.

Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al.
ESMO consensus guidelines for the management of patients with metastatic colorectal cancer.
Ann Oncol. 2016;27(8):1386-1422.

Van Cutsem E., Cuyle PJ., Yaeger R., et al.
BEACON CRC Study Safety Lead-in (SLI) in Patients With BRAFV600E Metastatic Colorectal Cancer (mCRC): Efficacy and Tumor Markers.
Poster session presented at: The Annual ASCO Gastrointestinal Cancers Symposium; January 16, 2018; San Francisco, California;

Von Moos R, Thuerlimann B, Aapro M, et al.
Pegylated liposomal doxorubicin-associated hand foot syndrome: recommendations of an international panel of experts
Eur J Cancer 2008, 44(6):781-90

Vermorken JB, Mesia R, Rivera F, et al.
Platinum-based chemotherapy plus cetuximab in head and neck cancer.
N Engl J Med. 2008;359:1116-27.

Yang H, Higgins B, Kolinsky K et al.
Antitumor activity of BRAF inhibitor vemurafenib in preclinical models of BRAF-mutant colorectal cancer.
Cancer Res 2012; 72: 779–789.

Zhao B, Wang L, Qiu H, Zhang M, Sun L, Peng P et al.
Mechanisms of resistance to anti-EGFR therapy in colorectal cancer.
Oncotarget 2017;8: 14012.

Zheng Z, Hanna N, Onukwugha E, Reese ES, Seal B, Mullins CD.
Does the type of first-line regimens influence the receipt of second-line chemotherapy treatment? An analysis of 3211 metastatic colon cancer patients.
Cancer Med.2014;3(1):124–133.

17. APPENDICES

17.1. RECOMMENDED GUIDELINES FOR THE MANAGEMENT OF CETUXIMAB-INDUCED, ENCORAFENIB-INDUCED AND/OR BINIMETINIB-INDUCED SKIN TOXICITY

Clinical judgment and experience of the treating physician should guide the management plan of each subject. In general, the following interventions are in addition to the cetuximab-induced rash and the encorafenib-induced and/or binimetinib-induced rash dosing guidelines provided (in **Section 1.2**).

The Initial Rash Treatment Regimen may be initiated as prophylactic treatment 24 hours prior to the first treatment, or later as needed to treat mild rash (NCI-CTCAE Grade 1).

Initial Rash Treatment Regimen:

- Application of topical agents to the most commonly affected skin areas such as face, scalp, neck, upper chest and upper back. Topical agents include the following:

– Non-oily sunscreen (PABA-free, SPF ≥ 30, UVA/UVB protection);
– Topical steroids, preferably mometasone cream (e.g., Elocon®);
– Topical erythromycin (e.g., Eryaknen®);
– Topical pimocrolimus.

Note: Topical agents should be applied on a daily basis starting on Day 1 of study treatment or 24 hours prior to first treatment, and more often as needed.

- Possibly oral doxycycline (100 mg daily) for the first 2 to 3 weeks of study drug administration.

Other effective medications are antihistamines, other topical corticosteroids, other topical antibiotics and low-dose systemic corticosteroids.

The treatment algorithm based on NCI-CTCAE grade is as follows:

Mild Rash (CTCAE Grade 1) Treatment Regimen:

- Initiate Initial Rash Treatment Regimen, if not already started.
- Use of topical corticosteroid (e.g., mometasone cream) and/or topical antibiotic (e.g., erythromycin 2%) is recommended.
- The subject should be reassessed within a maximum of 2 weeks, or as per Investigator opinion.

Moderate Rash (CTCAE Grade 2) Treatment Regimen:

- Use of topical erythromycin or clindamycin (1%) plus topical mometasone or topical pimecrolimus (1% cream) plus oral antibiotics, such as lymecycline (408 mg QD), doxycycline (100 mg BID) or minocycline (50 to 100 mg BID).
- Although there has been no evidence of phototoxicity or photosensitivity in subjects treated with binimetinib, doxycycline (or minocycline as second-line) should be used with thorough UV protection (i.e., avoidance of direct exposure to sunlight, use of sunscreen and sunglasses, etc.).
- Use of acitretin is not recommended.

Severe Rash (CTCAE Grade 3-4) Treatment Regimen:

CTCAE Grade 3:

- In addition to the interventions recommended for moderate rash, consider oral prednisolone at a dose of 0.5 mg/kg. Upon improvement, taper the dose in a stepwise manner (25 mg for 7 days, subsequently decreasing the dose by 5 mg/day every day).
- Alternatively, in addition to the interventions recommended for moderate rash, consider oral isotretinoin (low dose, i.e., 0.3 to 0.5 mg/kg) (**Kopetz S el al, 2017**; **Lacouture ME et al, 2011**)
- Use of acitretin is not recommended.

CTCAE Grade 4 Treatment Regimen:

- Immediately discontinue the subject from study drug and treat the subject with oral or topical medications (see recommendation CTCAE Grade 3).

Symptomatic Treatment Regimen:

It is strongly recommended that subjects who develop rash/skin toxicities receive symptomatic treatment:

- For pruritic lesions: use cool compresses and oral antihistamine agents.
- For fissuring: use Monsel's solution, silver nitrate or zinc oxide cream. If not sufficient, use mild corticosteroid ointments or ointments containing a combination of corticosteroid and antibiotic such as Fucicort®.
- For desquamation: use emollients that are mild pH 5/neutral (recommended to contain 10% urea).
- For paronychia: use antiseptic bath and local potent corticosteroids, use oral antibiotics, and, if no improvement is seen, refer to a dermatologist or surgeon.
- For infected lesions: obtain bacterial and fungal cultures and treat with topical or systemic antibiotics, if indicated, based on sensitivity of culture.

17.2. RECOMMENDED GUIDELINES FOR THE MANAGEMENT OF ENCORAFENIB-INDUCED HAND-FOOT SKIN REACTIONS (HFSR)

Clinical judgment and experience of the treating physician should guide the management plan of each subject. In addition to the HFSR dosing guidelines in the protocol, the following algorithm is recommended for the management of HFSR based on the severity (CTCAE grading,) of HFSR (adapted from **Nardone B et al, 2012**). HFSR (adapted from **Nardone B et al, 2012**).

Algorithm for the Management of HFSR Based on the Severity of HFSR

HFSR severity	Intervention
No HFSR	**Maintain Frequent Contact with physician to ensure early diagnosis of HFSR**
Therapy initiation	Full body-skin examination, pedicure, evaluation by podiatrist or orthotist; wear thick cotton gloves and/or socks; avoid hot water, constrictive footwear and excessive friction
	If symptoms develop, proceed to next step
	
Grade 1	**Maintain current dose of BRAF inhibitor; monitor subject for change in severity**
Minimal skin changes or dermatitis without pain e.g.: • Numbness • Tingling • Dysesthesia • Paresthesia • Erythema • Edema • Hyperkeratosis No interference with ADL	Avoid hot water; use moisturizing cream for relief; wear thick cotton gloves and/or socks; use a 20-40% urea , salicylic acid 3-6%; ammonium lactate 12 % or lactic acid 12 % based creams to aid exfoliation.
	If symptoms worsen, proceed to next steps
	
Grade 2	**Maintain current dose of BRAF inhibitor; monitor subject for change in severity**
Skin changes with pain e.g. Peeling • Blisters • Bleeding • Edema • Hyperkeratosis Limited instrumental ADL	Treat as with Grade 1 toxicity, with the following additions: clobetasol 0.05% ointment, 2-4% lidocaine, opiates, NSAIDS, or GABA agonists for pain; follow dose modifications listed in Table 14
	If no improvement within 15 days, proceed to next steps.

Grade 3	Interrupt dose until improvement to Grade 0-1
Severe skin changes with pain e.g. Peeling • Blisters • Bleeding • Edema • Hyperkeratosis Limiting self-care ADL	Treat as for Grades 1 and 2 Follow dose modifications listed in **Table 14**

The following supportive care measures for the prevention, and/or management of HFSR summarized in the table below should be instituted along with proper subject education.

Supportive Care for the Prevention and Management of HFSR

Stage	Recommendations
Prior to initiation of study treatment	Educate the subject about the early signs and symptoms of HFSR and discuss the importance of early reporting. HFSR could start as early as 2-5 days after study drug initiation, and mostly expected to occur during the first 2 months of treatment.
Prevention of HFSR for the first 2 months of treatment with encorafenib	Monitor the subject for signs and symptoms of HFSR. Instruct the subject to: - Apply emollient cream regularly to hands and feet: use 20-40% urea , salicylic acid 3-6%; ammonium lactate 12% or lactic acid 12 % based creams - Wear cotton socks or gloves to bed to enhance the absorption of creams - Avoid tight, irritating or ill-fitting clothing and shoes - Avoid repetitive activity or staying in one position for long periods of time - Pat (do not rub) skin dry with towels - Avoid extremes of temperature, pressure and friction - Avoid performing mechanically stressful manual work - Cushioning of callused areas - Use of moisturizing and keratolytic creams to control existing palmar and plantar hyperkeratosis
Treatment of HFSR	1) Ensure that subject follows treatment interruption or dosage reduction guidelines 2) Monitor the subject for worsening/resolution of HFSR (Normal frequency monthly, except if subject has Grade 2 or 3 HFSR, where bi weekly- visits are recommended) 3) Prescribe analgesics if necessary 4) Instruct the subject to: - Continue the use of prevention strategies - Cushion sore skin - For control or relief of pain symptoms, subject may submerge hands and feet in cool water baths or apply cold compresses for relief
[a] Wear loose-fitting clothing made of soft, natural fabrics and shoes that are wide and comfortable. Avoid tight belts, panties and bras. This table is adapted from (VonMoos et al, 2008).	

17.3. RECOMMENDED GUIDELINES FOR THE MANAGEMENT OF BINIMETINIB-INDUCED DIARRHEA

Proactively Investigate for Occurrence of Diarrhea and Educate Subject:

1. Remind subjects at each visit to contact the Investigator immediately upon the first sign of loose stool or symptoms of abdominal pain. Additionally, at each study visit, each subject should be asked regarding occurrence of diarrhea or diarrhea-related symptoms. If the subject has had symptoms, the subject should be asked regarding the actions taken for these symptoms and re-instruct if indicated.

2. Subjects should be instructed on dietary modification and early warning signs of diarrhea and potentially life-threatening illnesses (e.g., severe cramping might be a sign of severe diarrhea; fever with diarrhea might be a sign of infection; fever and dizziness on standing might be a sign of shock).

3. Subjects should be educated about what to report to the Investigator (i.e., number of stools, stool composition, stool volume).

Anti-Diarrhea Therapy:

In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, subject education as outlined above, as well as proper management of diarrhea is important.

Management of diarrhea should be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. All concomitant therapies /used for treatment of diarrhea must be recorded on the e-CRF. It is recommended that subjects be provided loperamide tablets and be instructed on the use of loperamide on the first day of binimetinib dosing. In addition to the binimetinib-induced diarrhea dosing guidelines provided in **Table 14** of the protocol, these instructions should be provided at each visit and the site should ensure that the subject understood the instructions.

See **Section 7** in the protocol to explain the frequency of diarrhea and its relationship to NCI-CTCAE, v.4.03 grading and to determine if diarrhea is complicated or uncomplicated.

Rule out Other or Concomitant Causes:

These may include:

- Infection with *Candida, Salmonella, Clostridium difficile, Campylobacter. Giardia, Entamoeba* or *Cryptosporidium* species, which can lead to severe infections in immunosuppressed subjects.
- Medication-induced diarrhea.
- Malabsorption/lactose intolerance.
- Fecal impaction, partial bowel obstruction.

For Uncomplicated Grade 1/2 Diarrhea:

- Stop all lactose-containing products and alcohol, and eat frequent small meals that include bananas, rice, applesauce or toast.
- Stop laxatives, bulk fiber (e.g., Metamucil®), and stool softeners (e.g., docusate sodium, Colace®).
- Stop high-osmolar food supplements (e.g., Ensure® Plus, Jevity® Plus [with fiber]).
- Drink 8 to 10 large glasses of clear liquids per day (e.g., water, Pedialyte®, Gatorade®, broth).
- Consider administration of a standard dose of loperamide: initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.
- Discontinue loperamide after 12-hours diarrhea-free (Grade 0) interval.
- Consider temporary interruption of binimetinib until resolved to Grade ≤ 1. Re-treatment may then be resumed at current dose level.
- If uncomplicated Grade 1 to Grade 2 diarrhea persists for more than 24 hours, escalate to high-dose loperamide: 2 mg every 2 hours (maximum of 16 mg/day) or after each unformed stool.

Note: Oral antibiotics may be started as prophylaxis for infections under the discretion of the physician.

- If uncomplicated Grade 1 to Grade 2 diarrhea persists after 48 hours of treatment with loperamide, discontinue loperamide and begin a second-line agent which can be an opiate (opium tincture or paregoric), octreotide acetate or steroid (budesonide).

For Complicated Grade 1/2 Diarrhea or Any Grade 3/4 Diarrhea:

- The subject must call the Investigator immediately.
- Temporarily interrupt binimetinib treatment until resolved to Grade ≤ 1. Restart binimetinib at a reduced dose level.
- If loperamide has not been initiated, initiate loperamide immediately. Initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.
- Administer IV fluids and electrolytes as needed. In case of severe hydration, replace loperamide with octreotide acetate.
- Monitor/continue IV fluids and antibiotics as needed. Intervention should be continued until the subject is diarrhea-free for at least 24 hours.
- Hospitalization may need to be considered.

17.4. SNELLEN EQUIVALENCE (VISUAL ACUITY CONVERSION CHART)

				Distance				Near					
					Snellen Equivalent								
Line Number	Visual Angle (min)	Spatial Frequency (Cyc/deg)	LogMAR	% Central Visual Efficiency	Feet 20/	Meter 6/	Decimal	% Central Visual Efficienty	Inches (14/)	Centimeters (35/)	Revised Jaeger Standard	American Point-Type	"M" Notation
−3	0.50	60.00	0.30	100	10	3.0	2.00	100	7.0	17.5	–	–	0.20
−2	0.63	48.00	0.20	100	12.5	3.8	1.60	100	8.8	21.9	–	–	0.25
−1	0.80	37.50	0.10	100	16	4.8	1.25	100	11.2	28.0	–	–	0.32
0	1.00	30.00	0.00	100	20	6.0	1.00	100	14.0	35.0	1	3	0.40
1	1.25	24.00	−0.10	95	25	7.5	0.80	100	17.5	43.8	2	4	0.50
–	1.50	20.00	−0.18	91	30	9.0	0.67	95	21.0	52.5	3	5	0.60
2	1.60	18.75	−0.20	90	32	9.6	0.63	94	22.4	56.0	4	6	0.64
3	2.00	15.00	−0.30	85	40	12.0	0.50	90	28.0	70.0	5	7	0.80
4	2.50	12.00	−0.40	75	50	15.0	0.40	50	35.0	87.5	6	8	1.0
–	3.00	10.00	−0.48	67	60	18.0	0.33	42	42.0	105.0	7	9	1.2
5	3.15	9.52	−0.50	65	63	18.9	0.32	40	44.1	110.3	8	10	1.3
–	3.50	8.57	−0.54	63	70	21.0	0.29	32	49.0	122.5	–	–	1.4
6	4.00	7.50	−0.60	60	80	24.0	0.25	20	56.0	140.0	9	11	1.6
7	5.00	6.00	−0.70	50	100	30.0	0.20	15	70.0	175.0	10	12	2.0
–	5.70	5.26	−0.76	44	114	34.2	0.18	12	79.8	199.5	11	13	2.3
8	6.25	4.80	−0.80	40	125	37.5	0.16	10	87.5	218.8	12	14	2.5
–	7.50	4.00	−0.88	32	150	45.0	0.13	6	105.0	262.5	–	–	3.0
9	8.00	3.75	−0.90	30	160	48.0	0.13	5	112.0	280.0	13	21	3.2
10	10.00	3.00	−1.00	20	200	60.0	0.10	2	140.0	350.0	14	23	4.0
11	12.50	2.40	−1.10	17	250	75.0	0.08	0	175.0	437.5	–	–	5.0
–	15.00	2.00	−1.18	16	300	90.0	0.07	0	210.0	525.0	–	–	6.0
12	16.00	1.88	−1.20	15	320	96.0	0.06	0	224.0	560.0	–	–	6.4
13	20.00	1.50	−1.30	10	400	120.0	0.05	0	280.0	700.0	–	–	8.0
16	40.00	0.75	−1.60	5	800	240.0	0.03	0	560.0	1400.0	–	–	16.0
20	100.00	0.30	−2.00	0	2000*	600.0	0.01	0	1400.0	3500.0	–	–	40.0
30	1000.00	0.03	−3.00	0	20000†	6000.0	0.001	0	14000.0	35000.0	–	–	400.0

Bold values are standard logMAR progression.
LogMAR = logarithm of the minimum angle of resolution
*20/2000 is equivalent to counting fingers @ 2 feet
†20/20000 is equivalent to hand motion @ 2 feet

17.5. LIST OF CONCOMITANT MEDICATIONS

The following lists are not necessarily exhaustive lists of every possible substrate/inhibitor/inducer.

Table A: List of CYP450 Substrates to be Used With Caution*

CYP2C8	CYP2C9	CYP2C19	CYP3A**	
Amodiaquine	Acenocoumarol	Clopidogrel	Alfentanil [1,2]	Ergotamine [2]
Cerivastatin	Celecoxib	Diazepam	Alpha-dihydroergocryptine [1]	Everolimus [1]
Repaglinide	Diclofenac	Esoprazole	Alprazolam	Felodipine [1]
Rosiglitazone	Glipizide	Lansoprazole	Amlodipine	Fentanyl [2]
Torasemide	Irbesartan	Moclobemide	Aplaviroc	Fluticasone [1]
	Losartan	Omeprazole	Aprepitant [1]	Indinavir [1]
	Phenytoin [2]	Pantoprazole	Aripiprazole	Lopinavir [1]
	Piroxicam	Phenobarbitone	Atorvastatin	Lovastatin [1]
	S-ibuprofen	Phenytoin [2]	Boceprevir	Maraviroc [1]
	Sulfamethoxazole	Proguanil	Brecanavir	Midazolam [1]
	Tolbutamide	Rabeprazole	Brotizolam [1]	Nifedipine
	Torasemide	S-mephenytoin	Budesonide [1]	Nisoldipine
			Buspirone [1]	Nitrendipine
			capravirine	Perospirone [1]
			casopitant	Quinine
			Conivaptan [1]	Saquinavir [1]
			Cyclosporine [2]	Sildenafil [1]
			Darifenacin [1]	Simvastatin [1]
			Darunavir [1]	Sirolimus [1,2]
			Diazepam	Telaprevir
			Diergotamine [2]	Tipranavir [1]
			Diltiazem	Tolvaptan
			Ebastine [1]	Triazolam [1]
			Eletriptan [1]	Verapamil
			Eplerenone [1]	

*Table was compiled from the Indiana University School of Medicine's "Clinically Relevant" table, a list by the United States Food and Drug Administration (FDA) fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm, and the University of Washington's Drug Interaction Database.

[1] Sensitive substrates: Drugs whose plasma area under concentration-time curve (AUC) values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., TdP).

Table B: List of CYP450 Substrates to be used with Caution – CYP2B6

CYP2B6*
bupropion [1]
Cyclophosphamide
Efavirenz [1]
Ifosfamide
Methadone
Thiotepa
*Table was compiled from the Indiana University School of Medicine's "Clinically Relevant" table, a list by the FDA (http://.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm) and the University of Washington's Drug Interaction Database. [1] Sensitive substrates: The area under the concentration-time curves (AUCs) of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.

Table C: Strong/moderate CYP3A4 Inhibitors and CYP3A4 Inducers to be Prohibited or Administered with Caution when Co-administered with Encorafenib

Strong Inhibitors (prohibited)	
boceprevir	nefazodone
Clarithromycin	Nelfinavir
Conivaptan	Posaconazole
Indinavir	Ritonavir
Itraconazole	Saquinavir
Ketoconazole	Telithromycin
Lopinavir	Troleandomycin
Telaprevir	Grapefruit juice (citrus paradisi fruit juice)
Mibefradil	Voriconazole
Moderate inhibitors (use with caution)	
Ciprofloxacin	Erythromycin
Fluconazole	Amprenavir
Verapamil	Imatinib
Atazanavir	Schisandra sphenanthera
Aprepitant	Casopitant
Cyclosporine	Cimetidine
Tofisopam	Dronedarone
Fosamprenavir	Darunavir
Diltiazem	
Strong Inducers (prohibited)	
Avasimibe	Rifampin
Carbamazepine	St. John's wort
Phenytoin	
Moderate Inducers (prohibited)	
Bosentan	Efavirenz
Etravirine	Modafinil
Reproduced from fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm	

Table D: Substrates of BCRP, OCTs, OATs and OATPs to be administered with Caution

	Substrates
BCRP	Imatinib, irrinotecan, lapatinib, methotrexate, mitoxantrone, rosuvastatin, sulfasalazine, topotecan
P-gp	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
OCT2	Amantadine, amiloride, cimetidine, dopamine, famotidine, memantine, metformin, pindolol, procainamide, ranitidine, varenicline, oxaliplatin
OAT1	Adefovir, captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine, zidovudine
OAT3	Acyclovir, bumetanide, ciprofloxacin, famotidine, furosemide, methotrexate, zidovudine, oseltamivir acid, (the active metabolite of oseltamivir), penicillin G, pravastatin, rosuvastatin, sitagliptin
OATP1B1	Atrasentan, atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, SN-38 (active metabolite of irinotecan), rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, rifampin, valsartan, olmesartan
OATP1B3	Atorvastatin, rosuvastatin, pitavastatin, telmisartan, valsartan, olmesartan

Reproduced from fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Table E: Pg-P and BCRP Inhibitors/Inducers to be used with Caution

Transporter	Gene	Inhibitor [1]	Inducer [2]
P-gp	ABCB1	Amiodarone, azithromycin,captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, verapamil	Avasimibe,carbamazepine,phenytoin, rifampin, St John's wort, tipranavir/ritonavir
BCRP	ABCG2	Cyclosporine, elacridar (GF120918), eltrombopag, gefitinib	Not known

Reproduced from fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

1. Inhibitors listed for P-gp are those that showed > 25% increase in digoxin area under the concentration-time curve (AUC) or otherwise indicated if substrate is other than digoxin.
2. Inducers listed for P-gp are those that showed > 20% decrease in digoxin AUC or otherwise indicated if substrate is other than digoxin.

Table F: List of Inhibitors of UGT1A1 to be used with Caution

Inhibitors of UGT1A1	atazanavir, erlotinib, flunitrazepam, gemfibrozil, indinavir, ketoconazole, nilotinib, pazopanib, propofol, regorafenib, sorafenib

Table G: List of Potential QT Prolonging Drugs of Potential QT Prolonging Drugs[1]

Drug	QT risk[2]	Comment
Alfuzosin	possible risk	
Amantadine	possible risk	
Amiodarone	known risk	Females > Males, TdP risk regarded as low
Amitriptyline	conditional risk	Risk of TdP with overdosage. Substrate of CYP2C19
Arsenic trioxide	known risk	
Astemizole	known risk	No Longer available in U.S. Substrate for 3A4
Atazanavir	possible risk	
Azithromycin	possible risk	Rare reports
Bepridil	known risk	Females > Males
Chloral hydrate	possible risk	
Chloroquine	known risk	
Chlorpromazine	known risk	
Ciprofloxacin	conditional risk	Drug metabolism inhibitor- Risk for drug interactions
Cisapride	known risk	No longer available in the U.S.; available in Mexico. Substrate for 3A4
Citalopram	known risk	
Clarithromycin	known risk	Substrate for 3A4
Clomipramine	conditional risk	
Clozapine	possible risk	
Desipramine	conditional risk	Risk of TdP with overdosage
Diphenhydramine	conditional risk	Risk of QT increase/TdP in overdosages
Disopyramide	known risk	Females > Males
Dofetilide	known risk	
Dolasetron	possible risk	
Domperidone	known risk	Not available in the U.S.
Doxepin	conditional risk	
Dronedarone	possible risk	Substrate for 3A4
Droperidol	known risk	
Eribulin	possible risk	
Erythromycin	known risk	Females>Males. Substrate for 3A4
Escitalopram	possible risk	
Famotidine	possible risk	
Felbamate	possible risk	
Fingolimod	possible risk	
Flecainide	known risk	
Fluconazole	conditional risk	Drug metabolism inhibitor- Risk for drug interactions
Fluoxetine	conditional risk	
Foscarnet	possible risk	
Fosphenytoin	possible risk	
Galantamine	conditional risk	
Gatifloxacin	possible risk	
Gemifloxacin	possible risk	
Granisetron	possible risk	
Halofantrine	known risk	Females>Males
Haloperidol	known risk	When given intravenously or at higher-than- recommended doses, risk of sudden death, QT prolongation and torsades increases. Substrate for 3A4
Ibutilide	known risk	Females>Males
Imipramine	conditional risk	Risk of TdP in overdosage

Drug	QT risk[2]	Comment
Indapamide	possible risk	
Isradipine	possible risk	
Itraconazole	conditional risk	Drug metabolism inhibitor- Risk for drug interactions
Ketoconazole	conditional risk	Drug metabolism inhibitor
Levofloxacin	possible risk	
Levomethadyl	known risk	Not available in the U.S.
Lithium	possible risk	
Mesoridazine	known risk	
Methadone	known risk	Females>Males. Substrate for 3A4
Moexipril/HCTZ	possible risk	
Moxifloxacin	known risk	
Nicardipine	possible risk	
Nortriptyline	conditional risk	
Octreotide	possible risk	
Ofloxacin	possible risk	
Ondansetron	possible risk	
Oxytocin	possible risk	
Paliperidone	possible risk	
Paroxetine	conditional risk	
Pentamidine	known risk	Females > Males
Perflutren lipid microspheres	possible risk	
Pimozide	known risk	Females > Males. Substrate for 3A4
Probucol	known risk	No longer available in U.S.
Procainamide	known risk	
Protriptyline	conditional risk	
Quetiapine	possible risk	Substrate for 3A4
Quinidine	known risk	Females > Males. Substrate for 3A4
Ranolazine	possible risk	
Risperidone	possible risk	
Ritonavir	conditional risk	Substrate for 3A4
Roxithromycin*	possible risk	*not available in the United States
Sertindole	possible risk	
Sertraline	conditional risk	
Solifenacin	conditional risk	
Sotalol	known risk	Females > Males
Sparfloxacin	known risk	
Tacrolimus	possible risk	Substrate for 3A4
Telithromycin	possible risk	Substrate for 3A4
Terfenadine	known risk	No longer available in U.S.Substrate for 3A4
Thioridazine	known risk	
Tizanidine	possible risk	
Trazodone	conditional risk	Substrate for 3A4
Trimethoprim-Sulfa	conditional risk	
Trimipramine	conditional risk	
Vandetanib	known risk	
Vardenafil	possible risk	Substrate for 3A4
Venlafaxine	possible risk	
Voriconazole	possible risk	
Ziprasidone	possible risk	

[1] Additional agents can be found at https://www.crediblemeds.org
[2] Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT

17.6. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS RECIST VERSION 1.1

17.6.1. Measurability of Tumor at baseline

- **Definitions**

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

- **Measurable**

Tumor lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm);
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable);
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥ 15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed.

- **Non-measurable**

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, and inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses /abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

- **Special considerations regarding lesion measurability**

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

17.6.2. Specifications by methods of measurements

- **Measurement of lesions**

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

- **Method of assessment**

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials were recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers *alone* cannot be used to assess *objective* tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis.
Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds of angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

17.6.3. Tumor Response Evaluation

- **Assessment of overall tumor burden and measurable disease**

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above).

- Baseline documentation of ‘target’ and ‘non-target’ lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline (this means in instances where subjects have only one or two organ sites involved, a *maximum* of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As previously noted, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital, or coronal). The smaller of these measures is the short axis.
For example, an abdominal node which is reported as being 20 mm X 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as previously noted, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

- **Response criteria**

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- **Evaluation of target lesions**

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

- Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms (e-CRFs) or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesion.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the e-CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If

the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note*: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. If the radiologist is able to provide an actual measurement, that should be recorded, even if below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

17.6.4. Evaluation of non-target lesion

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): *Unequivocal progression* of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

- **Special notes on assessment of progression of non-target disease**

The concept of progression of non-target disease requires additional explanations as follows:

When the subject also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression *solely* on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the subject has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as previously noted, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

- **New lesions**

The appearance of new malignant lesions denotes disease progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. This is particularly important when the subject's baseline lesions show partial or complete response.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imagine can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. A 'positive' FDG-PET scan lesion is one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that time (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

- **Evaluation of best overall response**

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The subject's best overall response assignment will depend on the findings of both target and non-target

disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

17.6.5. Time point response

It is assumed that at each protocol specified time point, a response assessment occurs table 1 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

Table 1- Time point response: subjects with target (± non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	**CR**
CR	Non-CR/non-PD	No	**PR**
CR	Not evaluated	No	**PR**
PR	Non-PD or not all evaluated	No	**PR**
SD	Non-PD or not all evaluated	No	**SD**
Not all evaluated	Non-PD	No	**NE**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, NE=not evaluable

- **Missing assessments and not evaluable designation**

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

- **Best overall response: all time points**

The *best overall response* is determined once all the data for the subject is known.

Best response is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered not evaluable.

- **Special notes on response assessment**

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on the increase in size of the nodes. As noted earlier, this means that subjects with CR may not have total sum of 'zero' on the e-CRF.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete

response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesion), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45 (2):2

17.7. RECOMMENDED GUIDELINES FOR THE MANAGEMENT OF BINIMETINIB AND CETUXIMAB -ASSOCIATED INTERSTITIAL LUNG DISEASE/PNEUMONITIS

Clinical judgment and experience of the treating physician should guide the management plan of each subject. In general, the following interventions are in addition to the binimetinib-associated interstitial lung disease (ILD) dosing guidelines provided in Table 14 of the protocol and, moreover if ILD is diagnosed, cetuximab must be discontinued.

Drug-associated ILD or pneumonitis is a clinical diagnosis based on clinical signs and symptoms, radiological changes, pulmonary function tests (PFT) and exclusion of other possible etiologies of parenchymal lung disease. The most common symptoms of ILD are nonspecific and include dyspnea, dry cough, fever, fatigue, hypoxia, and occasional hemoptysis. The CTCAE v.4.03 criteria for ILD (pneumonitis) are provided below.

CTCAE v. 4.03 Criteria for Pneumonitis					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by inflammation or diffusely affecting the lung parenchyma.					

All subjects should be instructed to immediately report new or worsening respiratory symptoms. Diagnostic procedures include PFT and high-resolution CT scans. In case of ILD the subject should be treated according to the best available local practices and procedures.

The principal management of ILD consists of drug interruption and/or dose reduction and treatment with steroids (eg. as specified below). Empirical antibiotics directed at likely pathogens should also be considered while the results of diagnostic procedures and cultures are pending.

- Prednisolone 40 mg oral, daily

– Reduce dose by 10 mg every 2 weeks × 2 (until dose reduced to 20 mg oral, daily)
– Reduce dose by 5 mg weekly × 4 weeks

- Combine with empirical antimicrobial therapy while awaiting results of diagnostic procedures

Willemsen A, Gutters J, Gerritsen W, et al. mTOR inhibitor-induced interstitial lung disease in cancer patients: Comprehensive review and practical management algorithm. In J Cancer (2016):138:2312-2321.

17.8. PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Subjects will be asked the following:

Since starting treatment, my colorectal cancer symptoms are:

(1) Very much improved
(2) Much improved
(3) Minimally improved
(4) No change
(5) Minimally worse
(6) Much worse
(7) Very much worse

(Mesa AM et al, 2013).